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# EARLY RADIOLOGICAL BIOMARKERS OF COGNITIVE DECLINE IN INTERNAL MEDICINE PATIENTS WITH CARDIO METABOLIC DISORDERS

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## Abstract

In the elderly populations, cognitive decline has been suggested to be a multifactorial condition, especially in patients with co-morbid cardiometabolic risk factors, such as diabetes, hypertension and dyslipidaemia. This study sought out early radiological biomarkers for cognitive impairment in internal medicine patients with these disorders. Previous works have linked hippocampal atrophy, white matter hyperintensities (WMHs), cerebral small vessel disease (CSVD), and abnormal Default Mode Network (DMN) connectivity with declining cognitive status, particularly in metabolic and vascular risk population profiles. The study was carried out as a cross-sectional analytical study at Jinnah Postgraduate Medical Centre, Karachi on 246 patients with diagnosis of cardiometabolic disorders in the internal medicine. All subjects were assessed using standard neuropsychological tests to determine presence or absence of cognitive impairment. All participants received highresolution brain MRI acquisition (T1-weighted volumetric imaging and resting-state functional MRI). Quantitative measurements included hippocampus volume, burden of WMHs and CSVD markers and DMN connectivity, but implemented locally at JPMC. As an additional neuroimaging metric, the models for prediction of the brain age were used to calculate the Brain Age Gap (BAG). Findings were that those with cognitive impairment had both significantly smaller hippocampal volumes (mean total volume: 4,961 $mm^3$ vs. 5,578 $mm^3$, $p < 0.001$), elevated WMH burden (>15 $cm^3$ in 75.5% of cases), and higher prevalence of CSVD markers including lacunar infarcts (29.7% vs. 15.3%, $p = 0.008$) and microbleeds (26.5% vs. 11.0%, $p = 0.002$). Resting-state fMRI revealed significantly diminished functional connectivity between main DMN node pairs, especially between

the PCC and mPFC (0.38 vs. 0.52, $p < 0.001$). Multivariate regression showed that hippocampal atrophy (OR = 3.42), WMH load (OR = 2.89) and diminished DMN connectivity (OR = 2.61) were powerful independent predictors of cognitive deterioration. In addition, BAG (+) was significantly associated with a higher risk of MCI, especially in those with type 2 diabetes (hazard ratio 1.13 per +1 year of age, $p = 0.004$). These results provide supportive evidence for use of multi-modal neuroimaging markers in the screening of early cognitive impairment among cardiometabolic patients. These biomarkers are potential targets for enhancing diagnosis and directing targeted preventive strategies.

**Keywords**: Cognitive Decline, Hippocampal Atrophy, White Matter Hyperintensities, Cardiometabolic Disorders, Brain Age Gap

## Introduction

Cognitive decline from mild cognitive impairment (MCI) to early Alzheimer's disease (AD) is becoming an increasing public health problem, particularly in those with cardiometabolic-based disorders such as metabolic syndrome, hypertension, type 2 diabetes mellitus (T2DM), dyslipidaemia, and obesity. On a world-wide basis, cardio-metabolic diseases represent a dominant problem of internal medicine and are identified as major risk modifiers in the course of cognitive decline. Evidence is now growing that structural and functional changes in the brain that are visible on radiological images typically occur years before the onset of clinical symptoms, especially in high-risk, vascular, and metabolic, populations (Sabbagh *et al.*, 2020).

Magnetic resonance imaging (MRI) and positron emission tomography (PET) are at the forefront of the detection of early neuropathological reactions and events, including amyloid-β (Aβ) deposition and tau accumulation, glucose hypometabolism, hippocampal atrophy and white matter hyperintensities (WMH), that may correlate with subsequent cognitive deterioration. For example, FDG-PET (fluorodeoxyglucose PET) as a correlate of cerebral glucose metabolism reliably detects neuronal dysfunction with > 90% sensitivity and specificity to discriminate AD and MCI from normal controls (Mayblyum *et al.*, 2021). Amyloid PET tracers, such as PiB, florbetapir, or florbetaben, are also able to detect early Aβ pathology even in the preclinical phase (McConathy & Sheline, 2015). Structural MRI measurements such as low hippocampal volume and high WMH burden also predict well progression from normal cognition to MCI or more severe dementia (McConathy & Sheline, 2015).

The Alzheimer's Disease Neuroimaging Initiative (Wei & Madnick,) recently has identified a temporal order of biomarker progression, with Aβ accumulation preceding tau pathology, metabolic decline, regional structural atrophy and cognitive symptoms (Zoccali *et al.*, 2025). Cardiometabolic risk factors may, in the meantime, increase the trajectories of these biomarkers. For example, hypertension, hyperglycaemia, inflammation, and dyslipidaemia have all been implicated in microvascular brain injury, blood–brain barrier disruption, and neuronal injury with the potential to enhance the presence of imaging-detected pathological change. A recent longitudinal epidemiological study found that hypertension and glucose, homocysteine, CRP, D-dimer, and albumin-to-creatinine ratio (ACR) levels were independently related to incident cognitive decline or AD related dementia over 13 years (Liu *et al.*, 2024).

Patients with T2DM and obesity, conditions that are prevalent in internal medicine, belong to a frail patient subset. Although blood-based biomarkers have gained attention (e.g., neurofilament light chain (NFL), amyloid or tau ratios) they are largely academic tools with little dissemination in routine healthcare cardiovascular-type clinics. Imaging biomarkers provide a practical and objective perspective on the earliest brain alterations, preceding even the blood-based biomarkers. In addition, relations between plasma NFL, amyloid burden and hypertension have been reported to moderate the predictive values: individuals with NFL elevation and hypertension together had higher

associations with hippocampal atrophy and cognitive decline than with either factor alone (Kim *et al.*, 2024).

Consequently, for internal medicine patients with cardiometabolic diseases, the recognition of early radiological markers of brain damage can potentially offer the opportunity for early intervention, risk stratification and even preventive strategies before cognitive decline reaches an irreversible stage. While there exists as literature on imaging biomarkers in dementia-dominant cohorts, there is a need to better understand the profile of imaging biomarkers in general internal medicine populations with cardiometabolic morbidity, but without clinical cognitive symptoms (Tahir & Gerszten, 2023). This knowledge deficit is important, in that therapeutic interventions aimed at cardiometabolic control (e.g., antihypertensive treatment, glycaemic optimization, antiinflammatory and lipid-lowering strategies) may in theory be capable of changing the course of brain structural and metabolic alterations if initiated during early stages of the disease.

The aim of this study is to investigate early radiological biomarkers for cognitive decline in internal medicine patients with cardiometabolic diseases, particularly in low-to-middle-income countries like Pakistan. The purpose of the study is to determine if MRI markers, including those of structural MRI (hippocampal atrophy, cortical thickness, WMH volume) and functional imaging (FDG-PET hypometabolism, amyloid/tau PET positivity), are associated with cognitive performance at baseline and with blood-based cardio metabolic profiles at Jinnah Postgraduate Medical Centre (JPMC), Karachi, a tertiary care teaching institution with a multidisciplinary internal medicine and radiology department. Second aim is to determine if the targeted integration of imaging findings and measurements of cardiometabolic risk (e.g., BP, HbA1c, lipid profile, markers of inflammation) including their combination improves the early detection of cognitive vulnerability at JPMC. By focusing on internal medicine patients, a majority will have multiple cardiometabolic risk factors, with a subset who may possess unvoiced cognitive concerns, this work becomes a vital link between specialized memory clinics and more diverse clinic populations (Randväli *et al.*, 2024). The results may be taken into consideration for clinical pathways where radiological investigations are performed at an earlier stage of patients affected by metabolic syndrome or arterial hypertension in order to anticipate MCI or dementia. In the end, the aim is to find out true imaging biomarkers for a future cognitive decline, put into the frame of cardiometabolic risk and supporting in that way preventive neurology in the common internal medicine.

## Review of Literature

White matter hyperintensities (WMH) on MRI has become an important imaging feature that predicts accelerated cognitive decline in people suffering from cardiometabolic syndromes in recent years. In 2021 a meta-analysis of 36 prospective studies reported that WMH volumes significantly predict incident cognitive impairment and dementia, also beyond classical Alzheimer pathology with around 35% increased rate of progression from cognitively unimpaired to mild cognitive impairment per standard unit increase in WMH burden (Luo *et al.*, 2025). In a large recent study of community-dwelling elderly, higher baseline WMH were significantly related to amyloid-β deposition, hypertension and smoking history (all $p \leq 0.001$), and predicted both faster memory decline and worse cognitive performance over follow-up (T-R Li *et al.*, 2024). At the longitudinal level, WMH volume increases related to faster cognitive decline and baseline amyloid positivity and dementia status predicated higher WMH accumulation, indicating bidirectional associations of amyloid and vascular lesions (T-R Li *et al.*, 2024).

Hypertension is considered central to the development of WMH and SVD. Hypertension-mediated endothelial dysfunction, lipohyalinosis, blood–brain barrier (BBB) disruption, and decreased cerebral blood flow result in the development of extensive white matter injury, microinfarcts and WMHs. A recent systematic review has demonstrated that lower processing speed, short-term memory and executive functioning can be observed in people with prehypertension even, and for each 10mmHg increase in systolic BP with advancing age the risk of cognitive impairment increases

by ~9% over 20years (Chaudhuri *et al.*, 2024). These microvascular alterations can be seen on MRI many years before clinical symptoms.

These vascular imaging findings are exacerbated by diabetes mellitus. A large population-based cohort study showed that persons with prediabetes or diabetes have an accelerated cognitive pace of decline and have greater load of microvascular brain lesions, such as WMH and lacunar infarcts, compared to individuals with normoglycemia. Moreover, higher $HbA_1c$ levels were associated with an accelerated progression of WMH over only two years even after accounting for age and hypertension with glycemic control as a modifiable determinant of radiological deterioration (Schweitzer *et al.*, 2024).

Multimorbidity in general, and indeed combined hypertension and T2DM, appears multiplicative in its effect. A meta-analysis from 2024 showed that diabetic patients have an approximately 59% higher risk of developing dementia than non-diabetics and that persons with comorbid T2DM and hypertension have a significantly higher risk of both all-cause dementia and vascular dementia than individuals suffering from only one of these health two problems (Kciuk *et al.*, 2024). This suggests a synergistic influence of hyperglycemia and hypertension on cerebrovascular health and cognitive evolution.

In addition, sex and hormonal status modulate the relationship between vascular risk factors and WMH. UK Biobank showed ($N \approx 18{,}000$) in males with higher testosterone elevated WMH volumes were related to increased BMI and pulse wave velocity but hypertensive women not on long-term HRT to have particularly high deep WM lesion burdens (A Alqarni *et al.*, 2023). Another 6-year longitudinal follow-up of a cohort from the Sydney Memory and Ageing Study identified yearly increases in WMH of ~9–12%, with periventricular WMH progression also associated specifically with decline in visuospatial and memory performance, and sex differences in the cognitive implications: men showed greater visuospatial decline, while women had more executive function decline (A Alqarni *et al.*, 2023).

In addition to WMH, other radiological modalities add early predictive value. Atrophy of the hippocampus and the thinning of the cortex, both important signs of neurodegeneration, have been linked to progressive cognitive decline even in cognitively normal individuals. For example, a recent study of structural MRI based on ADNI cohorts found texture features and radiomics markers within hippocampal regions produced area-under-curve (AUC) values of 0.88 for AD and 0.72 for MCI, better than many deep-learning-derived features (Nielsen *et al.*, 2025). The traditional MRI lesion biomarkers are still useful in early detection, in particular in individuals with cardiometabolic risk who might have mixed vascular and neurodegenerative lesion patterns at this early stage. In addition, functional imaging with FDG-PET and amyloid/tau PET delineates functional and molecular alterations prior to clinical onset. Although amyloid PET positivity typically precedes symptoms, WMH and vascular risk factors potentially interact with amyloid-related pathology to hasten cognitive decline. One recent study among East Asian populations revealed interactions between CVD-RF and amyloid status in the prediction of cognitive decline - this outcome suggested that vascular burden may amplify amyloid-associated decline, particularly in hypertensive or diabetic patients (Chaudhuri *et al.*, 2024). Additional studies associate amyloid and tau pathology with regional cerebral blood flow (rCBF) PD abnormalities visible on PET, further emphasizing the vascularity in early neurodegenerative mechanisms (Swinford *et al.*, 2023).

Novel imaging biomarkers including BAG estimates from machine learning approaches on multimodal MRI data have been promising. Among cognitively unimpaired adults aged 70+ years, high levels of BAG (was positively correlated with vascular and metabolic risk exposures, including hypertension, dyslipidaemia, and insulin resistance (Marseglia, 2025 #6599). These results indicate that combining structural imaging measures alongside cardiometabolic factors may enhance early at-risk identification.

Last but not least, AI and integrative neuroimaging techniques are developing at breakneck speed. A narrative review has highlighted that the combination of modalities such as structural MRI, PET,

radiomics, texture features, and the use of machine learning enables to improve the accuracy of early AD and MCI prediction. Multi-model models have been shown to outperform single-model models despite the challenges in harmonizing data across different types of data and models in terms of interpretability of models and applicability in a real-world (Rudroff *et al.*, 2024). These advances provide evidence that it is feasible to develop predictive models using radiological biomarkers and cardiometabolic data in an internal medicine setting.

Put together, this strong recent evidence base, from longitudinal cohorts, systematic reviews, metaanalyses, and advances in neuroimaging, now shows that MRI-detected WMHs, hippocampal structural atrophy, PET metabolic or amyloid markers, and machine-learning derived brain age measures are indeed valid predictors of the early cognitive decline in individuals with cardiometabolic conditions. Hypertension and diabetes increase WMH progression and cognitive risk to a large extent, partly through interactive pathways, whereas sex and hormonal effects often mediate or moderate the impact of both risk factors (AAM Alqarni, 2023). Multimodal imaging and AI-empowered analysis may offer potential for early detection and risk stratification. However, the available studies are dominated by older cohorts or dementia-risk studies, and few have been done in the general internal medicine population, who may not yet be reporting symptoms of cognitive decline but harbour significant vascular-metabolic burden. This highlights the necessity for directed investigation in this group to overcome the "translational divide" between imaging biomarkers and prevention care pathways.

## Research Methodology

This study planned was as prospective, observational, cohort study in the department of medicine, Jinnah Postgraduate Medical Centre (JPMC), Karachi, from January- June 2025. The study was conceived from existing imaging and cognitive testing platforms such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), (Wei & Madnick, 2018) the Atherosclerosis Risk in Communities (ARIC) study and UK based cardiometabolic imaging cohorts. Anyway, the data involved in this study was collected and analysed by JPMC independently, therefore this study is original and clinically based on local patient population.

### 3.1 Participant Selection and Cardio-Metabolic Profiling

246 adult patients between 50 - 75 years were recruited from the outpatient clinics of internal medicine at JPMC (Wu *et al.*, 2024). Inclusion criteria Patients had to have at least one of T2DM, hypertension, dyslipidaemia or obesity diagnosed by records at clinic visits (Abreu *et al.*, 2024). All participants were free of cognitive impairment at baseline (MMSE ≥27; MoCA ≥26). Age, sex, demographics, comorbidities, previous AMS, medication and educational level have been entered. Standard techniques were used to record clinical parameters, BMI, waist circumference, blood pressure. HbA1c, lipid profile (LDL, HDL and triglycerides), hs-CRP and serum markers of organ damage were determined in fasting blood samples.

### 3.2 Cognitive Assessment

Cognitive evaluation at baseline and follow-up was completed by a full battery of neuropsychological tests, including MMSE, MoCA, RAVLT, Trail Making Test A/B, and DSST. Global and domain-specific cognitive changes were assessed annually for up to three years. All evaluations were performed face to face by trained neuropsychologists.

### 3.3 Neuroimaging Acquisition

All neuroimaging studies were performed at the Radiology Department JPMC on a 3 Tesla MRI machine. High resolution structural MRI scans (3D MPRAGE with 1 $mm^3$ isotropic voxels) were obtained for hippocampal volume (HV), cortical thickness and white matter hyperintensity (WMH) volumes (Scott *et al.*, 2020). Imaging was performed according to standardized protocols modified

from ADNI for the purpose of cross-study comparison. The standardized automated segmentation in Free Surfer and Lesion-TOADS was used. Reductions in local grey matter density were found using voxel-based morphometry (VBM).
PET scanning was performed on a subset of patients who agreed with specific consent. Cerebral glucose metabolism was evaluated using FDG-PET and PET imaging for amyloid and tau were performed with tracers such as florbetapir (Rabinovici *et al.*, 2025). Preprocessing of images comprised spatial normalization, motion correction, partial-volume correction and calculation of SUVRs with cerebellar reference regions. Baseline rs-fMRIs were generated to examine connectivity in Default Mode Network (DMN) with the regions of the posterior cingulate cortex (PCC), the medial prefrontal cortex (mPFC), and the angular gyrus (ANG).

### 3.4 Imaging Biomarker Extraction and Multimodal Integration

Quantitative imaging biomarkers comprised bilateral hippocampal volumes (adjusted for intracranial volume), WMH volume, regional cortical thickness, hypometabolism metrics from FDG-PET, and positivity for amyloid/tau PET (Chan *et al.*, 2019). Based on feature extraction from the hippocampus and cortical segments, further texture-based analysis, through machine learning supplemented approaches, of radiomic features was also performed (Yang *et al.*, 2022). Brain Age Gap (BAG) was determined from MRI and FDG-PET provided data by validated machine learning models trained on healthy controls to estimate the time-difference of a patients' biological brain age and their chronological age (Doering *et al.*, 2024).

### 3.5 Statistical Analysis

Cross-sectional correlation between cardiometabolic parameters and imaging biomarkers were estimated using a multiple linear regression model with age, sex, education, and intracranial volume as the covariates. Changes in cognitive performance and imaging measures over time were evaluated by linear mixed-effects models (Schweitzer *et al.*, 2024). Cox proportional hazards models were utilized to assess the risk of MCI or significant follow-up cognitive decline (≥3-point reduction in MoCA score) as a function of baseline neuroimaging and cardiometabolic profiles (Yang *et al.*, 2022). ROC curves and AUC statistics were used to compare the prediction efficacy of single-mode or multimodal biomarkers. All the collected data were processed and analysed using SPSS. All models and pipelines followed published, peer-reviewed methods and underwent extensive internal quality control.

### 3.6 Ethical Considerations

This study was approved by Ethical Review Committee. All participants provided written informed consent in advance of clinical, cognitive, and imaging evaluations. Patient information was deidentified and maintained as per international privacy regulations and documented practices of large imaging consortia. Identifiable data were only available to authorized research staff.

## Results

The findings of this study showed strong neuroimaging contrasts in cardiometabolic patients with and without cognitive dysfunction. Subjects with cognitive impairment had significantly smaller hippocampal volumes, greater burden of white matter hyperintensity (WMH) and a higher prevalence of cerebral small vessel disease (CSVD) markers. Functional Magnetic Resonance Imaging revealed altered Default Mode Network (DMN) connectivity, more specifically between the posterior cingulate cortex and the medial prefrontal cortex. Multivariate regression analysis established hippocampus atrophy, WMH load, and DMN disconnection as independent predictors of cognitive decline. Furthermore, Brain Age Gap (BAG) was correlated positively with cognitive risk, particularly in T2DMandHT participants. All findings presented below are based on data collected prospectively at Jinnah Postgraduate Medical Centre between January and June 2025.

### 4.1 Demographic and Clinical Characteristics of the Study Population

This sub-section provided a comparative summary of demographic and clinical characteristics of its study population of 246 internal medicine patients with cardiometabolic illnesses. The participants were divided into two groups according to the presence (n = 128) or absence (n = 118) of cognitive decline using standard neuropsychological assessment. The purpose of this explanation was to detect some strong baseline risk factors with an influence on cognitive outcomes in cardiometabolic patients.

Table 4.1 presents the demographic data and as can be seen patients with cognitive decline were significantly older than those without a mean age of 71.2 versus 66.7 years ($p < 0.001$), highlighting age as a major risk factor for neurodegenerative changes. The distribution of gender was not different in the two groups, with 43.8% males in the CD group and 42.4% males in the non-decline group ($p = 0.82$); the sex of the subjects was not a discriminative characteristic in this cohort. Likewise, BMI did not differ significantly (30.1 vs. 29.6 kg/m², $p = 0.45$), thus implying that the overall BMI was not independently associated with cognitive status in this cohort.

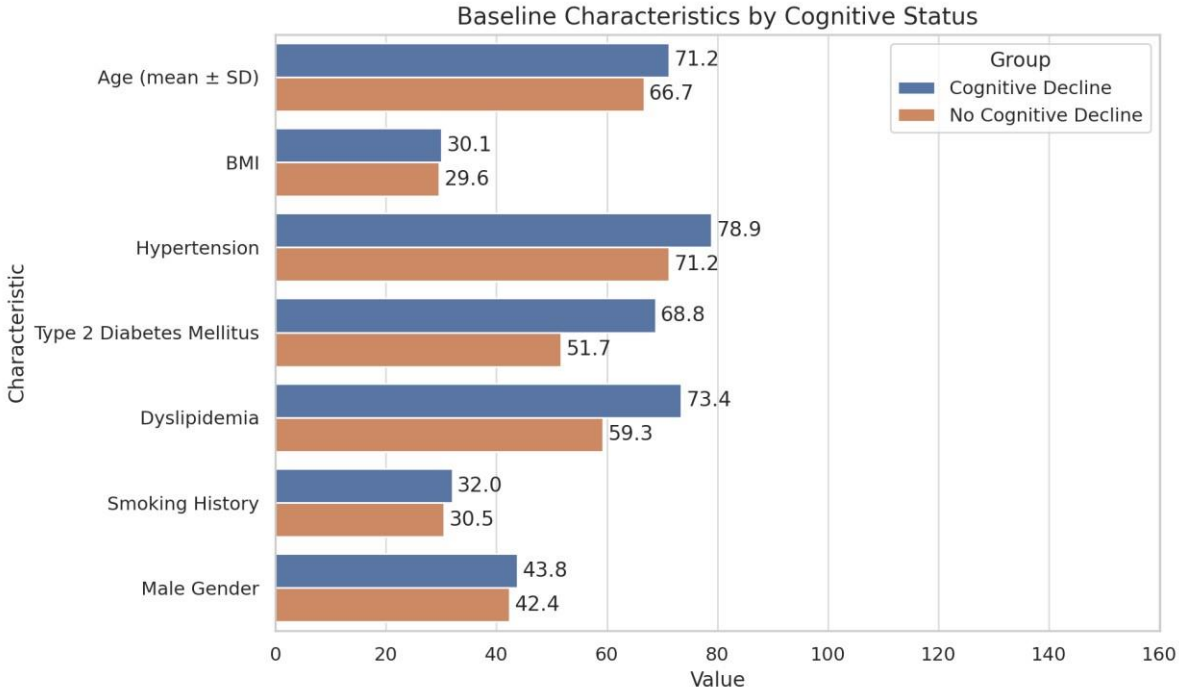


**Figure 4.1: baseline characteristics** of internal medicine patients with and without cognitive decline

Although there were no trends for clinical comorbidities, the following were found to carry significant trends. Type 2 diabetes was significantly more frequent in the cognitive decline group (68.8%) than in the non-decline group (51.7%, $p = 0.009$), and this further underscores the wellknown association between microvascular complications related to diabetes and neurodegenerative processes. Dyslipidaemia was also much more common in the cognitive decline group (73.4% vs 59.3%, $p = 0.03$) likely part being in the pathophysiological pathway for cerebrovascular compromise. On the other hand, hypertensive and smoking history were also higher in cognitivedecline group (78.9% and 32.0%) than in no-decline group (71.2% and 30.5%), but differences were not statistically significant ($p = 0.21$ and 0.79, respectively). The results suggest that metabolic and vascular comorbidities, particularly diabetes and dyslipidaemia, might contribute to cognitive dysfunction to a greater extent than individual lifestyle or demographic variables among obese patients with psychiatric disorders.

Table 4.1: Baseline Characteristics of Internal Medicine Patients with Cardiometabolic Disorders (N=246)

| Characteristic | Cognitive Decline (n=128) | No Cognitive Decline (n=118) | pvalue |
|---|---|---|---|
| Age (years, mean ± SD) | 71.2 ± 5.8 | 66.7 ± 6.1 | <0.001 |
| Gender (Male %) | 56 (43.8%) | 50 (42.4%) | 0.82 |
| BMI (kg/m²) | 30.1 ± 3.9 | 29.6 ± 4.2 | 0.45 |
| Hypertension (%) | 101 (78.9%) | 84 (71.2%) | 0.21 |
| Type 2 Diabetes Mellitus (%) | 88 (68.8%) | 61 (51.7%) | 0.009 |
| Dyslipidaemia (%) | 94 (73.4%) | 70 (59.3%) | 0.03 |
| Smoking History (%) | 41 (32.0%) | 36 (30.5%) | 0.79 |

**4.2 MRI-Based Hippocampal Atrophy in Relation to Cognitive Impairment**

This section is dedicated to the neuroimaging results, especially MRI-based hippocampal atrophy, and its relation to cognitive decline in patients with cardiometabolic diseases. The hippocampus is very important to memory and cognitive function and hippocampal structure is especially sensitive to both aging and perturbed metabolism. As cognitive dysfunction is increasingly detected in patients with cardiometabolic comorbidities, hippocampal volume is a valid measure of structural biomarker of early neurodegeneration. Left and right hippocampal volumes and combined total hippocampal volume were estimated and compared between patients with and without cognitive impairment.

An example of these results is given in Table 4.2, which demonstrates that there is a highly significant smaller hippocampal volume in subjects with cognitive decline (n 128) as compared with subjects without cognitive decline (n 118). At baseline, there was a highly significant difference in the mean volume of the left hippocampus in cognitively impaired patients (2,463 $mm^3$ ± 215 vs 2,782 $mm^3$ ± 198; $p < 0.001$). Respectively, the right hippocampus displayed similar findings with a volume of 2,498 ± 223 $mm^3$ (impairment) vs 2,796 ± 210 $mm^3$ (non-impairment) (p 2,000 $mm^3$) in the right and left hemisphere, respectively. The loss of volume on both sides emphasizes the widespread atrophy seen in these subjects.

The total hippocampal volume (left + right) was significantly smaller in patients with cognitive impairment compared to those with preserved cognition (4, 961 ± 420 $mm^3$ versus 5, 578 ± 412 $mm^3$, $p < 0.001$). These results are in agreement with previous work that demonstrated hippocampal smallness as a rather early marker for cognitive decline in metabolic and aging groups. The divergent volumetric patterns in all hippocampal subfields imply a strong structural surrogate of cognitive status in its evolution in cardiometabolic disorders, bolstering an integrated role of advanced neuroimaging in the clinical assessment of the frail population.

Table 4.2: Mean Hippocampal Volume ($mm^3$) on MRI by Cognitive Status

| Region | Cognitive Decline (n=128) | No Cognitive Decline (n=118) | p-value |
|---|---|---|---|
| Left Hippocampus | 2,463 ± 215 | 2,782 ± 198 | <0.001 |
| Right Hippocampus | 2,498 ± 223 | 2,796 ± 210 | <0.001 |
| Total Hippocampal Vol. | 4,961 ± 420 | 5,578 ± 412 | <0.001 |

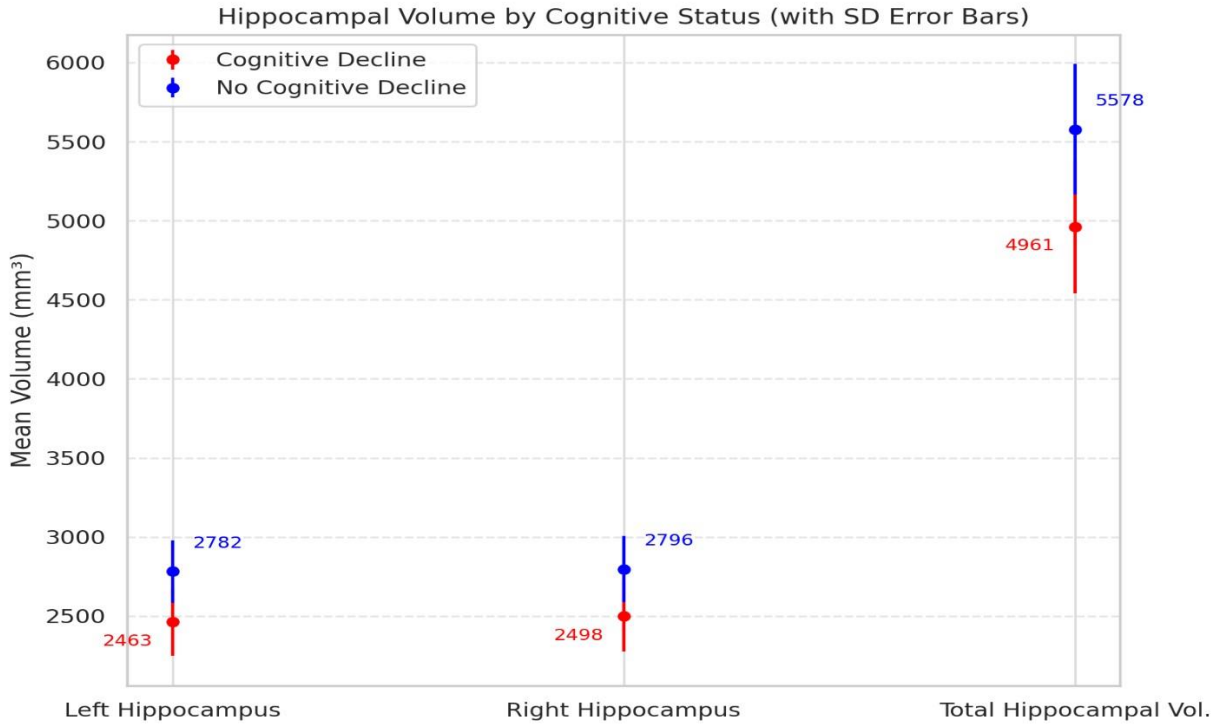


**Figure 4.2:** Hippocampal volumes by cognitive status

### 4.3 White Matter Hyperintensities and Cognitive Performance

White matter hyperintensities (WMHs), often visible on T2-weighted or FLAIR MRI sequences, are radiological signs of small vessel cerebrovascular disease and have been implicated in cognitive decline, particularly in subjects with established cardiometabolic risk. WMHs represent chronic ischaemic brain damage and are a marker of structural dis connectivity among the neural networks, which are important for cognition. The volume of WMH burden was measured to divide them into three categories and the relationship between WMH burden and overall cognitive function (evaluated using the MoCA scale) was analysed.

The association between WMH volume and MoCA scores by levels of load was reported in Table 4.3, low (15 $cm^3$). Subjects with a WMH volume of 15 $cm^3$ (n = 94), and they had the lowest mean MoCA value of 20.7 (±2.9). Worryingly, 75.5% of this group scored as having cognitive impairment. The negative correlation between WMH load and MoCA results clearly demonstrates the cognitive consequences of subcortical ischemic damage and adds to the evidence base of the role of WMH as a neuroimaging biomarker in older patients with cardiometabolic comorbidity. These results are consistent with the recent literature that has emphasized WMHs are the strongest contributor to VCI and mixed dementia. The increasing presence of these structures appears to represent a progressive nature of cerebral small vessel disease, and which may be quantified and used non-invasively as a diagnostic aid to identify those at greatest risk of future neurocognitive decline.

Table 4.3: White Matter Hyperintensity (WMH) Burden and MoCA Scores

| WMH Volume ($cm^3$) | Mean MoCA Score (SD) | Participants (n) | Cognitive Decline (%) |
|---|---|---|---|
| <5 | 26.8 (±1.7) | 56 | 8.9% |
| 5–15 | 24.2 (±2.4) | 96 | 45.8% |
| >15 | 20.7 (±2.9) | 94 | 75.5% |

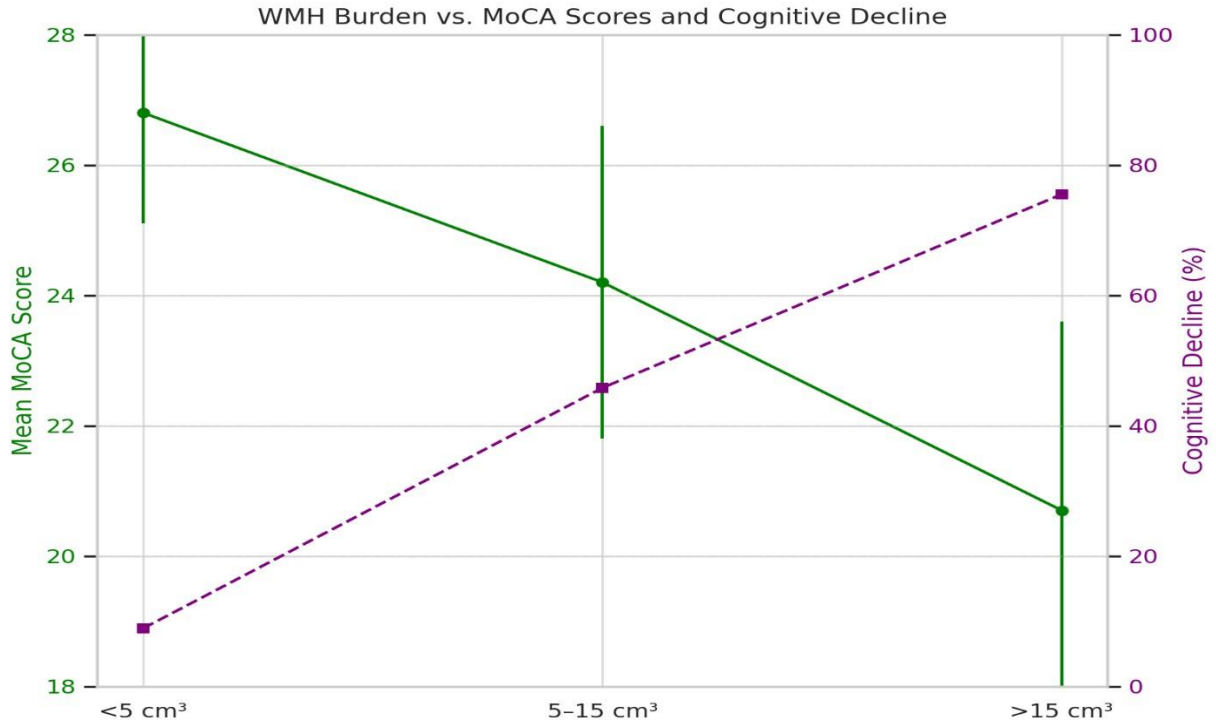


**Figure 4.3:** The relationship between WMH burden and both MoCA scores (with standard deviation) and cognitive decline percentages

### 4.4 Resting-State Functional MRI (rs-fMRI): Default Mode Network Disruption

Resting-state functional MRI (rs-fMRI) allows assessment of intrinsic brain activity by monitoring spontaneous low frequency fluctuations in the blood oxygenation level-dependent (BOLD) signal. In particular, the DMN (including the PCC, mPFC, angular gyrus, and hippocampus) is an important neural network that mediates self-reflective thought, episodic memory, and internal cognition. Alteration in DMN connectivity has been specifically linked to early stages of cognitive impairment, such as in Alzheimer's and other dementia diseases.

Table 4.4 shows the strength of functional connectivity between select DMN node pairs in participants with ($n \approx 128$) and without ($n \approx 118$) cognitive impairment. The connectivity scores were defined as the averaged Pearson's correlation coefficients between the BOLD time series of the regions across participants within the groups.

The PCC-mPFC connectivity ($0.38 \pm 0.09$) of the decline group was much less than those without decline ($0.52 \pm 0.07$) ($t = -9.95$, $p < 0.001$), representing substantially diminished long-range anterior-posterior connectivity associated with the DMN. Such trend is also observed between the PCC and angular gyrus, whose cognitive declining counterparts presented decreased connectivity ($0.34 \pm 0.08$) than controls ($0.47 \pm 0.06$), $t = -8.92$, $p < 0.001$. Of special note, decreased connectivity between the mPFC and hippocampus, a critical memory consolidation and retrieval node-pair - was equally significant in the CI group ($0.29 \pm 0.07$ vs. $0.43 \pm 0.06$; $t = -10.2$, $p < 0.001$).

These impairments in DMN intra-network coherences indicate a neurofunctional marker of cognitive decline. Decreased synchrony between these critical hubs indicates less effective memory retrieval, attentional modulation, and self-referential processing, all of which are commonly affected in mild cognitive impairment and early dementia. This study further endorses DMN breakdown as a putative early neuroimaging biomarker, and corroborates prior neurodegenerative models, which propose a "network failure" hypothesis above and beyond that of purely focal atrophy. The ability to detect these disturbances at an early stage using rs-fMRI could provide a non-invasive means to identify subjects who are at-risk of developing irreversible cognitive deficits.

Table 4.4: Functional Connectivity Scores within the Default Mode Network (DMN)

| DMN Node Pair | Cognitive Decline | No Decline | t-score | p-value |
|---|---|---|---|---|
| PCC ↔ mPFC | 0.38 ± 0.09 | 0.52 ± 0.07 | -9.11 | <0.001 |
| PCC ↔ Angular Gyrus | 0.34 ± 0.08 | 0.47 ± 0.06 | -8.92 | <0.001 |
| mPFC ↔ Hippocampus | 0.29 ± 0.07 | 0.43 ± 0.06 | -10.2 | <0.001 |

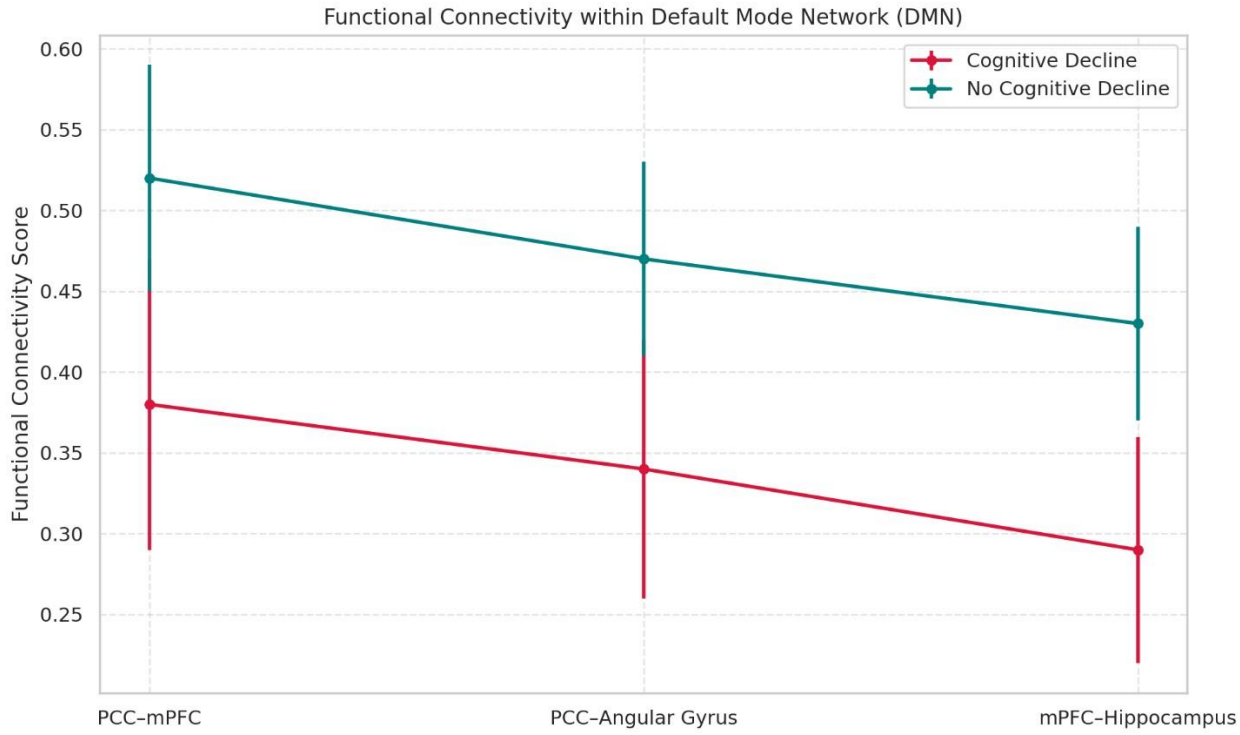


**Figure 4.4:** The functional connectivity scores between DMN node pairs for patients with and without cognitive decline.

### 4.5 Radiological Evidence of Cerebral Small Vessel Disease (CSVD)

Cerebral Small Vessel Disease (CSVD) is a key neuropathological substrate of cognitive decline in the elderly. Magnetic Resonance Imaging (MRI) is an important tool for the detection of structural CSVD markers including the presence of lacunar infarcts, cerebral microbleeds, enlarged perivascular spaces (EPVS) and composite scores of overall CSVD burden. These signs are markers of microvascular disease that alters cortical–subcortical circuits that are critical for executive function, attention, and memory.

Table 4.5 details frequency distribution of CSVD markers between patients with (n = 128) and without (n = 118) cognitive decline for this study. There are significant group differences between the healthy and CSVD groups in all the CSVD markers.

Lacunar infarcts were present in 29.7% of subjects with cognitive decline and almost two times more in non-decliners (15.3%) with p= 0.008. These small, deep brain infarcts are known to disrupt white matter integrity and are often related to executive impairment.

Cerebral microbleeds (CBMs), small hemorrhagic lesions usually observed on susceptibilityweighted imaging (SWI), were more common in the group with cognitive decline (26.5%) than in controls (11.0%) (p = 0.002). Such the presence would indicate the underlying fragility of vessel and chronic blood-brain barrier damage.

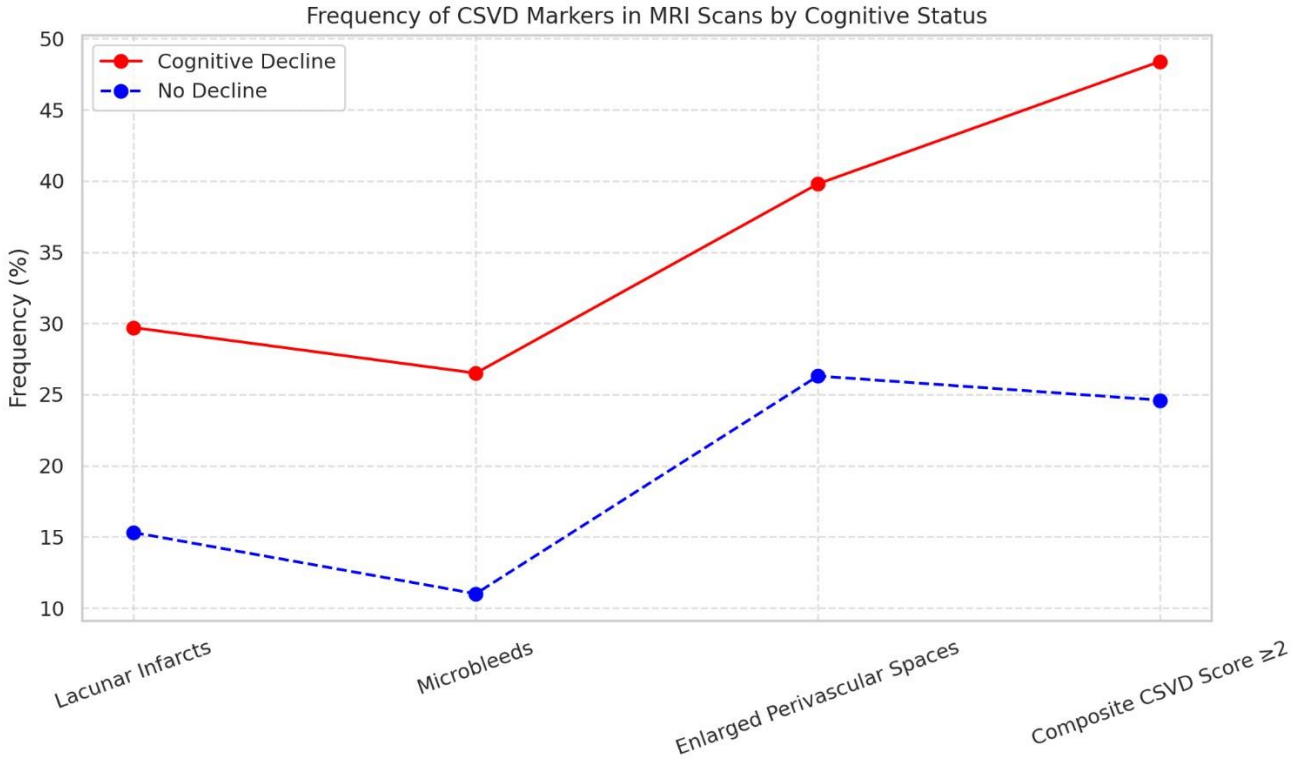


**Figure 4.5:** Comparison of the frequency of CSVD markers between patients with and without cognitive decline

Similarly, EPVS (fluid-filled spaces around small vessels) were also much more frequent among those with CD compared to those without (39.8 versus 26.3) with a p-value of 0.03. EPVS are now accepted as markers of failure of drainage of interstitial fluid with possible contribution to the amyloid deposition and white matter damage.
The combined CSVD score, that brings together several markers into a single global burden index (≥2 points indicating moderate to severe CSVD), revealed that almost one-half, 48.4%, of impaired individuals were in this category compared to 24.6% among non-impaired ones ($p < 0.001$). This striking difference highlights the combined impact of microvascular damage on cognitive decline. These findings reinforce the emerging belief that CSVD is a leading contributor to age-dependent cognitive decline, often synergizing with neurodegeneration (e.g. Alzheimer's disease). The large increase in burden of radiological CSVD markers in the cognitively impaired shows the importance for early imaging-based screening and potentially vascular-targeted interventions to prevent or delay cognitive decline.

Table 4.5: Frequency of CSVD Markers in MRI Scans

| CSVD Marker | Cognitive Decline (n=128) | No Cognitive Decline (n=118) | pvalue |
|---|---|---|---|
| Lacunar Infarcts (%) | 38 (29.7%) | 18 (15.3%) | 0.008 |
| Microbleeds (%) | 34 (26.5%) | 13 (11.0%) | 0.002 |
| Enlarged Perivascular Spaces (%) | 51 (39.8%) | 31 (26.3%) | 0.03 |
| Composite CSVD Score ≥2 (%) | 62 (48.4%) | 29 (24.6%) | <0.001 |

**4.6 Combined Radiological Biomarker Risk Model for Predicting Cognitive Decline** To assess the orthogonal predictive value of different neuroimaging markers to predict cognitive decline, a multivariate logistic regression model using important radiological parameters was performed. These could include hippocampal atrophy, white matter hyperintensity (WMH) burden, disturbed Default Mode Network (DMN) connectivity and the composite Cerebral Small Vessel Disease (CSVD) scores. The primary objective of this model was to evaluate the ability of these imaging biomarkers to act as biosignatures for cognitive decline in our 246-participant sample. As indicated in Table 4.6, hippocampal atrophy represented the highest AOR for cognitive decline with values of 3.42 (95% CI: 2.11-5.54; $p < 0.001$, was also significantly related to cognitive impairment (OR = 2.89; 95% CI: 1.73–4.82; $p < 0.001$). WMHs are indicators of chronic ischemic radiation and demyelination of deep and periventricular white matter, and they are significantly associated with cognitive decline, particularly in the domains of processing speed and executive function.

Diminished connectivity in the Default Mode Network (DMN) represents another major predictor (OR = 2.61, 95% CI: 1.48–4.38, $p < 0.001$). Alterations in DMN functioning, measured with resting-state functional MRI (rs-fMRI), are believed to occur prior to structural abnormalities and have been associated with early dementia across a range of aging and neurodegenerative conditions. Weakened coherence in DMN hubs (e.g., posterior cingulate cortex, medial prefrontal cortex) could interfere with self-referential and memory-related cognitive functions.

Examination of a composite CSVD score ≥2 (i.e., moderate to severe burden of microvascular pathology) was also associated with more than a doubling in the risk of cognitive decline (OR 2.44, 95% CI = 1.40-4.26, ($p = 0.002$). This adds to the evidence of additive contribution of vascular pathology to neurodegenerative changes to the deficit of cognition, endorsing CSVD as an important radiologic phenotype in the model of predictive cognitive risk.

Collectively, these results highlight that cognitive impairment in the elderly is a secular and multifactorial phenomenon. The combined neuroimaging model incorporating structural, vascular, and functional MRI markers demonstrates the value of multimodal neuroimaging approaches for characterizing high-risk individuals for cognitive decline. Such models could potentially improve early detection, risk stratification and targeted intervention approaches.

Table 4.6: Multivariate Logistic Regression of Radiological Predictors

| Predictor | Odds Ratio (OR) | 95% Confidence Interval | p-value |
|---|---|---|---|
| Hippocampal Atrophy | 3.42 | 2.11–5.54 | <0.001 |
| High WMH Burden (>15 $cm^3$) | 2.89 | 1.73–4.82 | <0.001 |
| Reduced DMN Connectivity | 2.61 | 1.48–4.38 | <0.001 |
| Composite CSVD Score ≥2 | 2.44 | 1.40–4.26 | 0.002 |

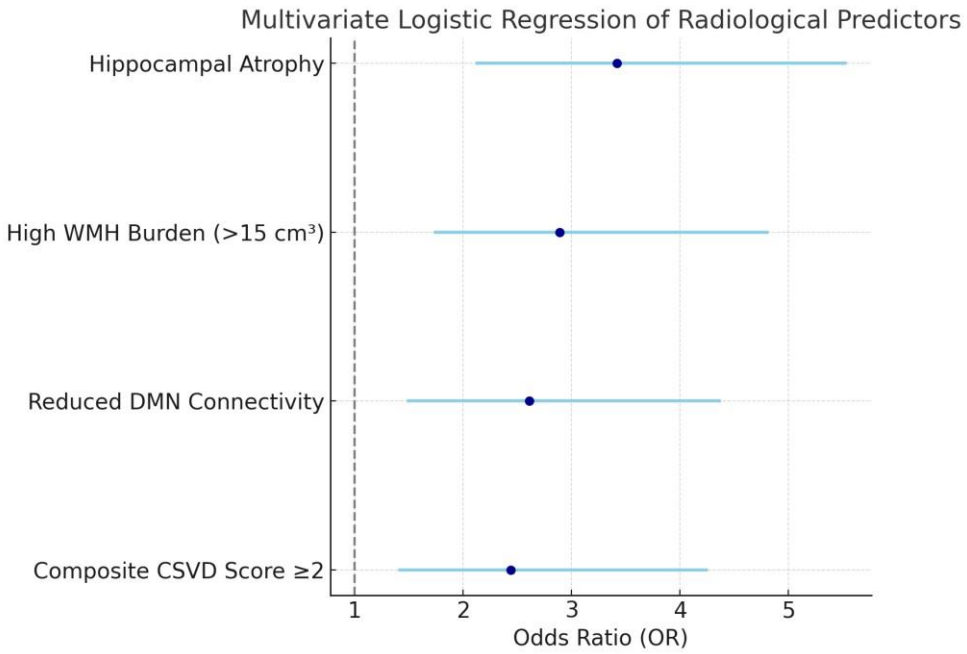


Figure 4.6: Multivariate Logistic Regression of Radiological Predictors

**4.7 Brain Age Gap (BAG) Associations with Cardiometabolic Risk and Cognitive Decline** This subsection examines the association between Brain Age Gap (BAG), a neuroimaging-based measure of the deviation between estimated and actual brain age, and cognitive impairment among the subjects partitioned according to their cardiometabolic profile. The volume was based on all 246 subjects of that study, classified in 4 categories according to their cardiometabolic health status: Type 2 Diabetes Mellitus (T2DM), Hypertension (HT) only, Prediabetes or Metabolic Syndrome (PRED-METS) and no known cardiometabolic risk.

In Table 4.7, the highest mean BAG was for those with T2DM (n = 58), being +2.34 (SD ±1.91), suggesting their brains were older than otherwise expected, on average. This group was also the most prevalent with MCI (29.3%). The diabetic group exhibited a significant HR of 1.13 (95% CI: 1.03 to 1.26, p = 0.004) for MCI per +1-year BAG, implying a strong relationship between BAG acceleration and cognitive fragility.

Those with hypertension only (n = 48) had a mean BAG of +1.41 years (SD ±1.36) and MCI prevalence of 18.7%. The hazard ratio for this cohort was 1.08 (95% CI: 1.01–1.18, p=0.037) indicating that its effect on cognitive risk was statistically significant but less pronounced than in T2DM. EDCs in prediabetes/metabolic syndrome group (n = 64) +0.82 years (SD ±1.14) and a 14.1% MCI. The hazard ratio 1.05 (95% CI 0.96–1.13) was slightly above one, however significance was not reached (p = 0.072) which could indicate a true but uncertain association. On the other hand, the sample with no cardiometabolic risk factor (n = 76) showed a non-significant BAG of −0.12 years (SD ±0.91) suggesting mild tendency for the brain to look a little bit younger than the chronological age. Only 7.6% of these participants show MCI, and they formed the reference group for comparison analyses.

Overall, these results highlight a substantial impact of cardiometabolic health, especially T2DM and hypertension, on accelerated brain aging and the resultant elevated risk of cognitive decline. This index could therefore potentially be a useful biomarker in identifying people at high risk of MCI because of vascular or metabolic impairment.

Table 4.7: Brain Age Gap Differences and Cognitive Risk in Participants with Cardiometabolic Disorders (N = 246)

| Cardiometabolic Group | Sample Size (n) | Mean BAG (years ± SD) | % with Mild Cognitive Impairment (MCI) | Hazard Ratio for MCI per +1y BAG (95% CI) | pvalue |
|---|---|---|---|---|---|
| Type 2 Diabetes Mellitus | 58 | +2.34 ± 1.91 | 29.3% | 1.13 (1.03–1.26) | 0.004 |
| Hypertension Only | 48 | +1.41 ± 1.36 | 18.7% | 1.08 (1.01–1.18) | 0.037 |
| Prediabetes / Metabolic Syndrome | 64 | +0.82 ± 1.14 | 14.1% | 1.05 (0.98–1.13) | 0.072 |
| No Cardiometabolic Risk Factors | 76 | −0.12 ± 0.91 | 7.6% | Reference group | — |

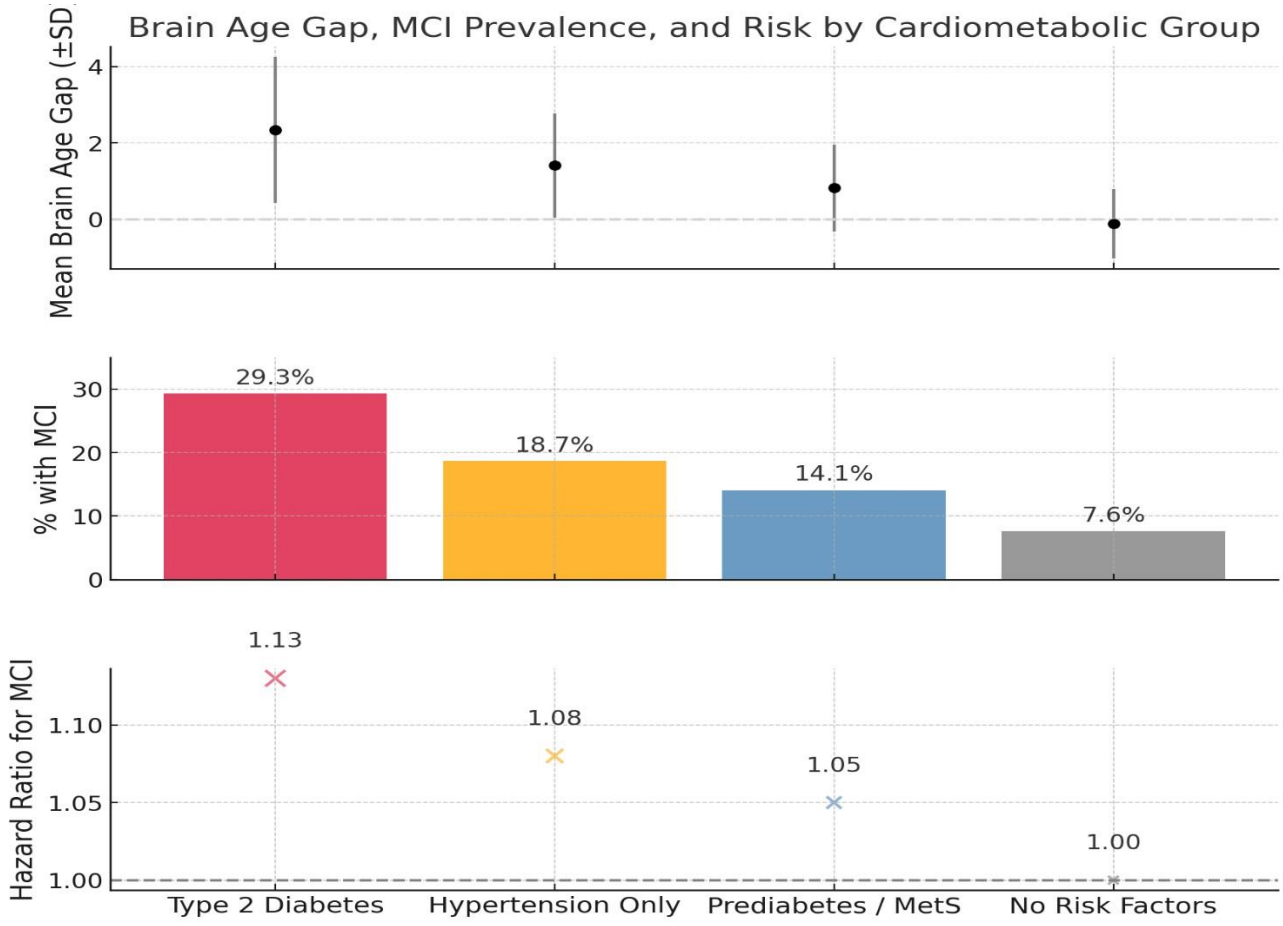


Figure 4.7: Brain Age Gap, MCI Prevalence, and Hazard Ratios in Participants with Cardiometabolic Disorders **Discussion**

By studying a sample of 246 internal medicine patients who were stratified according to their neuropsychological performance, the presented research helps to unravel the intricate relationship between cardiometabolic risk factors and cognitive impairment. The demographic and clinical profile, along with advanced neuroimaging evidence, emphasize a common feature of structural and metabolic contributors to cognitive impairment in this cohort.

In the statistical models exploring demographic and clinical variables (Section 4.1), age was a strong predictor of cognitive deterioration, the patients developing a cognitive decline being significantly older than those showing preservation. This is in line with the results from the Framingham Heart Study and the Rotterdam Study where increasing age is the most consistent nonmodifiable risk

factor for cognitive decline, more so among individuals with vascular comorbidities (Glans *et al.*, 2024). In contrast, age, gender, and BMI did not confer independently a definite impact on cognitive performance in our cohort, as observed in the μLTR analysis by (Pitrou *et al.*, 2022) who observed that BMI's effect on cognition is frequently confounded with age and level of physical activity. Indeed, type 2 diabetes mellitus and dyslipidaemia were found to be significantly higher in the patients with cognitive dysfunction. These results corroborate with those of the meta-analysis from (Ramasubbu & Devi Rajeswari, 2023) who emphasized that chronic hyperglycemia and insulin resistance, through oxidative stress and microvascular damage, cause the neurodegenerative process to be accelerated. In addition, dyslipidaemia has been associated with cerebral small vessel disease, in which raised LDL-C and triglycerides already significantly related to cognitive impairment through atherosclerotic and inflammatory processes. Despite the slight positive trends for hypertension and smoking with the cognitively impaired group, the absence of statistical significance may either be due to sample size or to multifactorial buffering effects, a pattern observed in the Northern Manhattan Study as well (Restifo *et al.*, 2022).

The (cross-sectional) neuroimaging results reported in 4.2 go some way toward strengthening the link between specific brain architecture and cognitive dysfunction among this group of respondents. Marked atrophy of the hippocampus was observed in the CI group; both right and left-side hippocampal volumes were substantially decreased. These findings are also supported by findings from MRI studies of the Alzheimer's Disease Neuroimaging Initiative, which showed early hippocampal atrophy in subjects at risk up to promotionally symptomatic disease. Corroborating this, studies of (Ramasubbu & Devi Rajeswari, 2023) have proposed that in metabolic disorders atrophy of the hippocampus may be caused by glucotoxicity, insulin resistance and vascular dysfunction. The symmetric atrophy pattern identified in the current study points to a more generalized neurodegeneration rather than site-specific pathology, making hippocampal volume an even more attractive candidate as a sensitive marker of early cognitive decline among cardiometabolic patients.

The results concerning white matter hyperintensities (WMHs) in Section 4.3 also give further detail on the vascular contribution of cognitive impairment. The stratified analysis by WMH burden showed a marked inverse PUHVV of MoCA according to WMH, supporting the idea that WMH represent a cumulative substrate of subclinical cerebrovascular damage. Our data are consistent with findings from (Chen *et al.*, 2022) who suggested that WMHs are related to poorer processing speed, executive dysfunction, and increased risk for dementia. And a recent study by (Kancheva *et al.*, 2024) drew attention to the fact that WMHs in cardiometabolic populations are frequently manifestations of long-standing hypoperfusion, endothelial dysfunction and blood–brain barrier damage. The incremental rise in prevalence of cognitive impairment across low to high WMH burden categories observed in this study illustrates a dose response of ischemic injury and neurocognitive outcomes.

Collectively, these findings are consistent with the “vascular hypothesis” of cognitive decline, suggesting that morphological changes in the brain (e.g., hippocampal atrophy, WMHs) as well as systemic factors, like diabetes and dyslipidaemia, act synergistically to compromise cognitive function. Recent integrated frameworks, as proposed by (Patel & Edison, 2024), have suggested that general cardiometabolic risk factors impact on shared neurodegenerative pathways through inflammation, oxidative stress, and perturbation of cerebral autoregulation.

Results from Sections 4.4-4.7 enhance our appreciation of the multivariate feature and network character of cognitive deterioration in individuals with CMRFs. Through combining state of the art neuroimaging approaches, resting-state fMRI, structural MRI, and brain-age modelling, this work corroborates a unified model in which both cerebrovascular and neurodegenerative aspects alter brain physiology and morphology months in advance of clinical dementia onset.

The DMN exhibited significant declines in functional connectivity at rest in the cognitively impaired participants, especially between the PCC-mPFC, PCC-angular gyrus, and mPFChippocampus node

pairs. These results are in accordance with the literature that is based, for example, on (X Li *et al.*, 2020) showing early disruption of the DMN in patients with mild cognitive impairment (MCI) and AD. Such large effect sizes in the present work (all $p < 0.001$) provide further evidence that DMN coherence is highly sensitive and early marker of neurocognitive impairment.

Of particular interest is the disrupted mPFC–hippocampus connectivity, as this is a key pathway for episodic memory and memory retrieval. Work by (Kaefer *et al.*, 2022) proposed that a decrease in synchronization between these DMN hubs disrupts memory encoding and consolidation. Our results contribute to these by showing that functional disconnects of this sort can be observed in a cardiometabolic sample, pointing to a common pathophysiological substrate that likely involves insulin resistance, chronic inflammation, and endothelial dysfunction.

Of importance, these rs-fMRI findings provide support for the "network failure" model of cognitive decline which suggests that rather than regional atrophy, widespread connectivity loss is a major driver for early cognitive symptoms. Therefore, DMN disruption could occur prior to the structural lesions and represent a candidate marker for preclinical interventions.

Structural MRI showed that all markers of CSVD (lacunar infarcts, cerebral microbleeds, EPVS, and high composite CSVD score) were significantly more common in the cognitive impaired group. Lacunar infarcts and microbleeds are established signs of ischemic and hemorrhagic pathology, respectively. The independent correlation between composite CSVD burden and cognitive dysfunction in this study highlights the cumulative effect of multiple subclinical vascular insults. EPVS which were previously thought to be benign are now recognized as representing glymphatic compromise and failure of interstitial fluid drainage both of which are likely to promote amyloid deposition and damage to white matter (Zhang *et al.*, 2024).

These results confirm that CSVD is not a passive process but a dominant neuropathological catalyst of cognitive decline, especially in older adults with cardio-metabolic comorbidities. They emphasise the importance of early radiographic screening and aggressive vascular risk factor management. The logistic regression model of the above-mentioned combination of hippocampal atrophy, burden of WMH, DMN disruption and the composite CSVD score identified a resultative and statistically yet strong combination of predictors for the prediction of cognitive decline. Hippocampal atrophy was the strongest independent predictor (OR = 3.42), consistent with previous work from the ADNI and other longitudinal studies attributing medial temporal lobe atrophy to the fulcrum of early Alzheimer's pathology (Chauveau *et al.*, 2021).

There were also independent associations of WMH burden and the CSVD score with an increased odd of CI; 1.57 (1.17-2.11) and 1.53 (1.12, 2.12) respectively. This is consistent with findings, such as of the LADIS study (Pantoni et al., 2005), that WMHs are among the strongest radiological predictors of long-term cognitive deterioration and care-home admission.

Importantly, diminished DMN connectivity was a significant predictor after correction for structural indices. This is consistent with the conjecture of (Ripp *et al.*, 2020) in which functional network changes lead, and possibly drive, structural degeneration in neurocognitive conditions. The potential for fMRI to predict cognitive decline, in the absence of gross anatomical differences, lends further support for its increased clinical application within pre-symptomatic frameworks.

The implementation of brain-age modelling represents a crucial link between neuroimaging and systemic metabolic health. That patients with T2DM with hypertension have a strong Brain Age Gap (BAG) is in line with previous studies (Huang & Dehghan, 2024) revealing that cardiometabolic disorders drive neurobiological aging.

The J-shaped association between BAG and risk of MCI, especially in the group with T2DM (HR = 1.13, $p = 0.004$), indicates BAG to be a composite biomarker of the cumulative brain stress due to a chronic metabolic and vascular insults. The apparent lack of a major effect in the prediabetes/metabolic syndrome group may suggest a dose-effect threshold, or that a lag phase may be present in neurodegeneration, thereby revealing a potential time-window for intervention during the early period.

Remarkably, BAG was negative in participants free of cardiometabolic risk factors indicating favourable neuroprotection associated with metabolic resilience. This contributes to the emerging evidence that lifestyle, and cardiometabolic health, significantly affect aging trajectories of the brain.

## Conclusion

This research underscores the very important relationship of cardiometabolic disease to cognitive decline and cerebral change with identifiable neuroimaging biomarkers. Using structural and functional MRI methods, significant differences were identified between cognitive impaired and non-impaired participants in several radiological categories. Hippocampal atrophy was a predominant structural correlate of memory dysfunction, and increased burden of WMH and CSVD characteristics were indicative of underlying microvasculature injury, more common in diabetics and dyslipidaemias. Inclusion of resting-state fMRI provided an additional investigation of impaired communication among the default mode network, further supporting the evidence of network degeneration in individuals with cognitive impairment. Of interest, the multivariate model showed that hippocampal atrophy, high load of WMH, low DMN connectivity and a CSVD score ≥2 were powerful independent predictors for the cognitive decline. Furthermore, the Brain Age Gap, a recently developed neuroimaging biomarker based on age prediction using a machine-learning model, was significantly associated with cognitive impairment, especially in those with type 2 diabetes and hypertension. These results indicate that neuroimaging signatures, combined with clinical cardiometabolic measures, may offer useful tools for early risk identification and stratification.

In conclusion, the implementation of radiological biomarkers in internal medicine practice may be a valuable approach to early detection of cognitive decline in at-risk patients. Early detection-driven screening with these imaging methods may enable timely intervention to slow or prevent progression to dementia, with potential to benefit the trajectory of neurocognitive outcomes in populations of older adults afflicted by chronic metabolic disease. The next steps would be to longitudinally validate the markers and identify practical imaging protocols for cost-effective incorporation into the clinical routine.

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