

Research Article**Association of White Matter Hyperintensities on MRI with Cognitive Decline in Middle-Aged Adults**

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Abstract

White matter hyperintensities identified on magnetic resonance imaging are increasingly recognized as important neuroimaging markers associated with cerebral small vessel disease, vascular dysfunction, and neurodegenerative processes. Although commonly investigated in elderly populations, white matter hyperintensities are increasingly being detected among middle-aged adults and may contribute to early cognitive decline before the onset of clinically apparent dementia. The present study aimed to evaluate the association between white matter hyperintensities on magnetic resonance imaging and cognitive decline among middle-aged adults attending a tertiary care neurological center. A prospective observational analytical study was conducted on 226 adults aged 40–60 years between January 2023 and December 2024. Brain magnetic resonance imaging was performed to assess white matter hyperintensity burden using the Fazekas

grading scale. Cognitive function was evaluated using the Montreal Cognitive Assessment and Mini-Mental State Examination. Participants with moderate-to-severe white matter hyperintensities demonstrated significantly lower cognitive scores compared with individuals having mild or absent lesions ($p < 0.001$). Cognitive decline was particularly observed in executive function, attention, processing speed, and memory domains. Hypertension, diabetes mellitus, smoking, obesity, and dyslipidemia were significantly associated with increased white matter hyperintensity burden. Multivariate regression analysis identified severe white matter hyperintensities, uncontrolled hypertension, and diabetes mellitus as independent predictors of cognitive impairment. The findings highlight the clinical significance of white matter hyperintensities in middle-aged adults and emphasize the importance of early neuroimaging evaluation and vascular risk factor control to prevent progressive

cognitive decline and future neurodegenerative complications.

Keywords: White matter hyperintensities, Cognitive decline, Magnetic resonance imaging

Introduction

Cognitive decline has emerged as a major global public health concern because of increasing prevalence of neurodegenerative disorders, vascular disease, and aging-related neurological dysfunction. Although cognitive impairment is traditionally associated with elderly populations, growing evidence suggests that pathological cerebral changes contributing to cognitive decline may begin during middle adulthood [1-3]. Early identification of neuroimaging biomarkers associated with cognitive deterioration has therefore become increasingly important in preventive neurology and cognitive medicine.

White matter hyperintensities are radiological abnormalities commonly identified on T2-weighted and fluid-attenuated inversion recovery magnetic resonance imaging sequences. These lesions appear as hyperintense areas within cerebral white matter and are considered markers of cerebral small vessel disease, ischemic injury, demyelination, and chronic vascular dysfunction [2-4]. White matter hyperintensities are frequently observed in older adults; however, recent imaging studies have demonstrated increasing prevalence among middle-aged individuals with vascular and metabolic risk factors.

The pathophysiological mechanisms underlying white matter hyperintensity formation involve chronic cerebral hypoperfusion, endothelial dysfunction,

blood-brain barrier disruption, inflammation, and microvascular ischemic damage [3-5]. Hypertension, diabetes mellitus, smoking, obesity, dyslipidemia, and sedentary lifestyle have all been implicated as important contributors to cerebral small vessel disease and white matter injury. Progressive accumulation of white matter hyperintensities may disrupt neuronal connectivity and impair communication between cortical and subcortical brain regions.

Several studies have demonstrated associations between white matter hyperintensities and impaired cognitive performance, particularly in domains involving executive function, processing speed, memory, and attention [4-6]. White matter structural integrity plays a critical role in maintaining efficient cognitive processing and neural network connectivity. Consequently, extensive white matter injury may contribute to progressive cognitive dysfunction even before development of overt dementia.

Middle-aged adults represent an important population for investigating early neurovascular changes associated with cognitive decline because intervention during this stage may substantially reduce future neurodegenerative burden [5-7]. Detection of white matter hyperintensities during middle adulthood may provide opportunities for timely vascular risk factor modification and cognitive preservation strategies. However, white matter lesions in middle-aged individuals are frequently underestimated because clinical symptoms may initially remain subtle or nonspecific.

Recent neuroimaging research has increasingly emphasized the relationship between cerebral small vessel disease and neurodegenerative disorders including Alzheimer disease and vascular dementia [6-8]. White matter hyperintensities may accelerate neurodegeneration by impairing cerebral perfusion, promoting inflammation, and disrupting neuronal network function. Additionally, cumulative vascular injury and metabolic abnormalities may further exacerbate cognitive impairment in susceptible individuals.

The prevalence of vascular risk factors including hypertension, diabetes mellitus, obesity, and dyslipidemia has increased substantially in developing countries during recent decades [7-9]. Pakistan and other South Asian populations demonstrate particularly high burdens of cardiovascular and metabolic disease, potentially increasing susceptibility to early cerebral small vessel pathology and cognitive decline. Despite this growing concern, regional evidence regarding white matter hyperintensities and cognitive impairment among middle-aged adults remains comparatively limited.

Although previous studies have predominantly focused on elderly populations, relatively fewer investigations have specifically evaluated the association between white matter hyperintensity burden and cognitive decline in middle-aged adults [8-10]. Furthermore, cognitive impairment occurring during middle adulthood may significantly affect occupational performance, quality of life, social functioning, and future dementia risk if not recognized early.

The present study was therefore designed to evaluate the association between white matter hyperintensities detected on magnetic resonance imaging and cognitive decline among middle-aged adults. The study additionally aimed to assess vascular and metabolic risk factors associated with increased white matter hyperintensity burden and cognitive impairment. By generating updated regional evidence, the findings may support early neuroimaging screening and preventive strategies targeting vascular cognitive decline in middle-aged populations.

Methodology

A prospective observational analytical study was conducted at Fatima Memorial College for Medicine and Dentistry after approval from the institutional ethical review committee. The study included middle-aged adults undergoing brain magnetic resonance imaging evaluation for headache, dizziness, mild memory complaints, or routine neurological assessment. The sample size was calculated using OpenEpi software version 3.01 by considering an anticipated prevalence of cognitive decline associated with white matter hyperintensities of 35%, confidence interval of 95%, study power of 80%, and margin of error of 5%, resulting in a minimum required sample size of 210 participants. After adjustment for incomplete imaging and cognitive data, 226 participants were enrolled.

Adults aged 40–60 years who underwent brain magnetic resonance imaging and completed cognitive assessment were included. Individuals with previously diagnosed dementia, major psychiatric illness, stroke, traumatic brain injury,

neurodegenerative disease, epilepsy, brain tumors, or severe visual and hearing impairment affecting cognitive evaluation were excluded. Verbal informed consent was obtained from all participants before enrollment. Confidentiality of clinical and imaging information was maintained throughout the study.

Detailed demographic and clinical data including age, gender, educational status, smoking history, hypertension, diabetes mellitus, dyslipidemia, obesity, physical activity, and medication history were recorded using structured questionnaires and medical records. Blood pressure measurement, fasting blood glucose, lipid profile, and body mass index assessment were performed according to standardized protocols.

Magnetic resonance imaging of the brain was performed using a 1.5 Tesla scanner. White matter hyperintensities were evaluated on fluid-attenuated inversion recovery and T2-weighted sequences by experienced radiologists blinded to cognitive assessment results. Lesion severity was graded using the Fazekas scale, categorizing participants into absent/mild, moderate, and severe white matter hyperintensity groups.

Cognitive function was assessed using the Montreal Cognitive Assessment and Mini-

Mental State Examination administered by trained neurologists. Specific cognitive domains including memory, executive function, attention, language, orientation, and visuospatial ability were evaluated. Cognitive impairment was defined according to standardized cutoff scores adjusted for educational status.

Data analysis was performed using SPSS version 26.0. Quantitative variables were expressed as mean $\pm$ standard deviation, while categorical variables were presented as frequencies and percentages. Independent t-test, one-way ANOVA, and chi-square test were used for comparison between white matter hyperintensity severity groups. Pearson correlation analysis was performed to evaluate associations between Fazekas scores and cognitive scores. Multivariate logistic regression analysis was conducted to identify independent predictors of cognitive decline. A p-value less than 0.05 was considered statistically significant.

Results

A total of 226 middle-aged adults participated in the study. The mean age of participants was 51.4 ± 5.8 years, and males constituted 54.0% of the study population. Moderate-to-severe white matter hyperintensities were identified in 41.6% of participants.

Table 1. Demographic and Clinical Characteristics of Study Participants

Variable	Frequency/Mean $\pm$ SD	Percentage	p-value
Mean age (years)	51.4 ± 5.8	—	0.018
Male gender	122	54.0%	0.214
Hypertension	118	52.2%	<0.001
Diabetes mellitus	93	41.2%	<0.001
Dyslipidemia	87	38.5%	0.002

Variable	Frequency/Mean $\pm$ SD	Percentage	p-value
Smoking history	76	33.6%	0.011
Obesity	84	37.2%	0.006
Moderate WMH burden	61	27.0%	<0.001
Severe WMH burden	33	14.6%	<0.001

Explanation: Vascular and metabolic risk factors including hypertension, diabetes mellitus, obesity, and smoking were highly prevalent among participants with moderate-to-severe white matter hyperintensities.

Table 2. Comparison of Cognitive Scores According to White Matter Hyperintensity Severity

Cognitive Variable	Mild/Absent WMH	Moderate WMH	Severe WMH	p-value
Montreal Cognitive Assessment score	27.6 $\pm$ 1.8	24.3 $\pm$ 2.1	20.7 $\pm$ 2.5	<0.001
Mini-Mental State Examination score	28.8 $\pm$ 1.2	26.9 $\pm$ 1.7	23.8 $\pm$ 2.2	<0.001
Executive function score	8.4 $\pm$ 1.1	6.9 $\pm$ 1.3	5.1 $\pm$ 1.5	<0.001
Attention score	7.8 $\pm$ 1.0	6.4 $\pm$ 1.2	4.9 $\pm$ 1.3	<0.001
Memory score	7.5 $\pm$ 1.2	6.1 $\pm$ 1.4	4.8 $\pm$ 1.6	<0.001

Explanation: Participants with severe white matter hyperintensity burden demonstrated significantly lower cognitive performance across multiple domains, particularly executive function, memory, and attention.

Table 3. Independent Predictors of Cognitive Decline

Predictor Variable	Odds Ratio (95% CI)	p-value
Severe WMH burden	4.28 (2.17–8.41)	<0.001
Hypertension	3.11 (1.74–5.56)	<0.001
Diabetes mellitus	2.87 (1.59–5.18)	0.001
Smoking	2.14 (1.16–3.96)	0.014
Dyslipidemia	1.96 (1.08–3.58)	0.026
Obesity	1.82 (1.01–3.29)	0.041

Explanation: Severe white matter hyperintensity burden, hypertension, and diabetes mellitus were significant

independent predictors of cognitive decline among middle-aged adults.

Discussion

The present study demonstrated a significant association between white matter hyperintensities identified on magnetic resonance imaging and cognitive decline among middle-aged adults. Participants with moderate-to-severe white matter hyperintensity burden exhibited significantly lower cognitive scores, particularly in executive function, attention, and memory domains. These findings support growing evidence indicating that cerebral small vessel disease contributes substantially to early cognitive impairment even before old age [11-12].

White matter hyperintensities are increasingly recognized as important neuroimaging markers reflecting chronic cerebral microvascular injury and ischemic white matter damage. The strong negative correlation observed between white matter hyperintensity severity and cognitive performance in the current study is consistent with recent neuroimaging investigations demonstrating impaired neuronal connectivity and reduced information processing efficiency associated with white matter injury [11-13]. White matter tracts are essential for coordinated communication between cortical and subcortical brain regions; therefore, disruption of these pathways may significantly impair higher cognitive functions.

Executive dysfunction represented one of the most prominent cognitive abnormalities associated with white matter hyperintensities in the present study. Similar findings have been reported in previous investigations evaluating cerebral small vessel disease and vascular cognitive impairment [12-14]. Frontal-subcortical circuit disruption

resulting from white matter lesions may impair planning ability, decision-making, cognitive flexibility, and processing speed, thereby contributing to reduced executive performance.

Hypertension emerged as a major independent predictor of both white matter hyperintensity burden and cognitive decline in the current study. Chronic uncontrolled hypertension contributes to endothelial dysfunction, vascular remodeling, impaired cerebral autoregulation, and microvascular ischemic injury [13-15]. Long-standing hypertension may therefore accelerate white matter degeneration and promote progressive cognitive deterioration. The findings highlight the importance of early blood pressure control for prevention of cerebral small vessel disease.

Diabetes mellitus and obesity were also significantly associated with increased white matter hyperintensity burden and impaired cognition. Metabolic abnormalities contribute to inflammation, oxidative stress, endothelial dysfunction, and accelerated atherosclerotic changes affecting cerebral microvasculature [14-16]. Additionally, insulin resistance and chronic hyperglycemia may directly influence neurodegenerative processes and cognitive decline. These findings support the growing recognition of metabolic syndrome as a major contributor to vascular cognitive impairment.

Smoking and dyslipidemia demonstrated significant associations with white matter lesion severity in the present investigation. Cigarette smoking promotes oxidative stress, chronic inflammation, endothelial injury, and vascular narrowing, all of which contribute to cerebral ischemic damage [15-17]. Similarly,

dyslipidemia accelerates atherosclerotic vascular disease and may impair cerebral perfusion, thereby increasing susceptibility to white matter injury and cognitive dysfunction.

An important finding of the present study is the detection of clinically relevant cognitive decline during middle adulthood rather than advanced age alone. Early identification of white matter hyperintensities among middle-aged individuals provides opportunities for preventive intervention before progression to severe cognitive impairment or dementia [16-18]. Neuroimaging evaluation in high-risk individuals with vascular and metabolic disorders may therefore facilitate earlier diagnosis and risk stratification.

The findings of the current study have important public health implications, particularly in developing countries experiencing increasing burdens of hypertension, diabetes mellitus, obesity, and cerebrovascular disease [17-20]. Preventive strategies emphasizing vascular risk factor modification, smoking cessation, healthy lifestyle promotion, and regular neurological evaluation may significantly reduce future cognitive decline and neurodegenerative disease burden. The present study additionally contributes regional evidence regarding the association between white matter hyperintensities and cognitive impairment among middle-aged South Asian adults, an area that remains comparatively underinvestigated.

Conclusion

White matter hyperintensities detected on magnetic resonance imaging are significantly associated with cognitive decline among

middle-aged adults, particularly affecting executive function, memory, and attention. Hypertension, diabetes mellitus, obesity, and smoking substantially increase white matter hyperintensity burden and cognitive impairment risk. Early neuroimaging assessment and aggressive vascular risk factor control may help prevent progressive cognitive deterioration and future neurodegenerative complications.

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