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White-Matter Hyperintensities and Cognitive Decline in Late-Life Depression: A Longitudinal Neuroimaging Study in Medan, Indonesia

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A B S T R A C T

Introduction: Late-life depression (LLD) is often associated with cognitive impairment and structural brain changes, particularly white-matter hyperintensities (WMH). This longitudinal study investigated the relationship between WMH burden, cognitive decline, and depressive symptoms in a cohort of older adults with LLD in Medan, Indonesia. **Methods:** A prospective, longitudinal study was conducted with 120 participants aged 60 years and older. Participants underwent baseline and 3-year follow-up assessments, including structural MRI, neuropsychological testing, and depression severity. Statistical analyses included mixed-effects models to examine longitudinal changes and correlations. **Results:** At baseline, the LLD group exhibited significantly higher WMH volume compared to controls ($p < 0.001$). Over the 3-year follow-up, the LLD group showed a significantly greater increase in WMH volume (average increase of 0.4 Fazekas points) compared to controls (average increase of 0.1 Fazekas points, $p < 0.001$). Greater WMH burden at baseline was associated with worse performance on all cognitive domains in both groups ($p < 0.05$). In the LLD group, the increase in WMH volume was significantly correlated with a decline in global cognition ($r = -0.45$, $p < 0.001$), executive function ($r = -0.38$, $p = 0.003$), and processing speed ($r = -0.41$, $p = 0.001$). Changes in depression severity were also correlated with WMH progression ($r = 0.32$, $p = 0.012$). **Conclusion:** This study provides evidence that WMH burden is significantly increased in LLD and that WMH progression contributes to cognitive decline and may exacerbate depressive symptoms over time. These findings highlight the importance of assessing and potentially targeting WMH in the management of LLD.

1. Introduction

Late-life depression (LLD), characterized by its onset after the age of 60, presents a significant public health challenge with far-reaching implications for individuals, families, and healthcare systems. The prevalence of LLD is substantial, with estimates suggesting that it affects a significant portion of the older adult population. This condition is associated with increased morbidity, mortality, and a diminished quality of life, underscoring the urgent need for comprehensive research and effective interventions. In contrast to depression experienced in younger adults, LLD often exhibits a distinct clinical profile marked by prominent cognitive impairment, even in the absence of a formal dementia diagnosis. This cognitive dysfunction can manifest across various domains, including executive function, processing speed, memory, and attention, significantly impacting daily functioning, treatment response, and long-term prognosis. The presence of cognitive impairment in LLD adds a layer of complexity to the diagnosis and management of this condition, as it can mimic or exacerbate symptoms of other age-related neurocognitive disorders.[1-3]

Neuroimaging studies have played a crucial role in elucidating the neurobiological underpinnings of LLD, revealing consistent structural brain changes associated with this condition. One of the most prominent findings is the presence of white matter hyperintensities (WMH), which appear as hyperintense areas on T2-weighted and FLAIR MRI sequences. WMH are thought to represent areas of small vessel disease, reflecting ischemic damage, demyelination, and axonal loss. While WMH are also observed in healthy aging, their prevalence and severity are significantly higher in individuals with LLD, suggesting a potential link between these brain changes and the pathophysiology of LLD. The relationship between WMH and cognitive decline in LLD is complex and multifaceted, with cross-sectional studies consistently demonstrating an association between WMH burden and poorer cognitive performance. However, longitudinal studies, which are essential for understanding the temporal relationship between WMH progression and cognitive decline, have yielded more mixed results. Some studies have shown that WMH progression predicts cognitive decline, while others have found only weak or non-significant associations. These discrepancies may stem from differences in study populations, follow-up duration, WMH assessment methods, and statistical analyses.[4-6]

Furthermore, the interplay between WMH, cognitive decline, and depressive symptoms in LLD remains an area of active investigation. It is hypothesized that WMH may disrupt fronto-subcortical circuits, which are crucial for both mood regulation and cognitive function. Disruption of these circuits could contribute to both the development and persistence of depressive symptoms, as well as to the cognitive deficits observed in LLD. Indonesia, with its rapidly aging population, faces a growing burden of LLD. However, research on the neurobiological underpinnings of LLD in the Indonesian population is limited. Cultural, genetic, and environmental factors may influence the prevalence and presentation of LLD and its associated neuroimaging findings. Therefore, conducting research within the Indonesian context is crucial for developing culturally appropriate and effective interventions.[7-10] This longitudinal study aimed to investigate the relationship between WMH burden, cognitive decline, and depressive symptoms in a cohort of older adults with LLD in Medan, Indonesia.

2. Methods

This research employed a prospective, longitudinal study design, conducted at three private hospitals in Medan, Indonesia. The study aimed to follow participants over three years, collecting data at baseline and a follow-up visit. Participants were recruited from the hospital's outpatient psychiatry and neurology clinics and community outreach programs. To be included in the LLD group, participants had to meet the following criteria; Age: 60 years or older; Diagnosis: Major Depressive Disorder according to DSM-5 criteria, with onset after age 60; Depression Severity: Geriatric Depression Scale (GDS) score of 11 or higher, indicating at least mild depression; Informed Consent: Ability to provide informed consent. The control group included participants who met these criteria; Age: 60 years or older; No History of Depression: No history of major psychiatric disorders, including depression, according to DSM-5 criteria; No Depressive Symptoms: GDS score below 5, indicating no significant depressive symptoms; Informed Consent: Ability to provide informed consent; Matching: Matched to the LLD group by age (± 5 years) and gender. Participants were excluded from both groups if they had; Neurological Disorders: Presence of a major neurological disorder, such as stroke, dementia, Parkinson's disease, or multiple sclerosis, that could significantly affect cognition or brain structure; Significant Medical Illness: Significant medical illness that could interfere with study participation, such as uncontrolled diabetes or severe cardiovascular disease; MRI Contraindications: Contraindications to MRI, such as a pacemaker or metallic implants; Substance Abuse: History of substance abuse or dependence within the past 6 months; Medications Affecting Cognition: Use of medications known to significantly affect cognition,

such as anticholinergics or benzodiazepines, at a dose that could not be stabilized for at least 4 weeks prior to study entry. A total of 120 participants were enrolled in the study, with 60 participants in each group (LLD and control). The sample size was determined based on power calculations to ensure the study had enough statistical power to detect a moderate effect size (Cohen's d = 0.5) for the difference in WMH progression between the two groups, with a power of 0.80 and an alpha level of 0.05.

The study protocol was reviewed and approved by the Institutional Review Board of CMHC Indonesia, ensuring that the study adhered to ethical guidelines for research involving human participants. Written informed consent was obtained from all participants after they received a thorough explanation of the study procedures, ensuring their voluntary participation. In cases where participants had cognitive impairment that might affect their capacity to provide informed consent, consent was obtained from a legally authorized representative, protecting the rights and well-being of vulnerable individuals.

Data were collected at two-time points: baseline and a 3-year follow-up visit. At baseline, participants underwent a comprehensive clinical assessment, which included; Demographic Information: Collection of demographic data, such as age, gender, education level, ethnicity, marital status, and socioeconomic status, to characterize the study population; Medical History: Assessment of comorbid medical conditions, such as hypertension, diabetes, and hyperlipidemia, as well as medication use, to identify potential confounding factors; Psychiatric History: Evaluation of psychiatric history, including age of onset of depression, duration of illness, previous treatment history, and current medications, to understand the clinical profile of the LLD group; Depression Severity: Assessment of depression severity using the Indonesian version of the Geriatric Depression Scale (GDS-30), a widely used and validated screening tool for depression in older adults; Global Cognition: Assessment of global cognition using the Indonesian version of the Montreal Cognitive Assessment (MoCA), a brief screening tool for mild cognitive impairment. A comprehensive neuropsychological battery was administered at both baseline and follow-up, assessing various cognitive domains; Global Cognition: MoCA; Executive Function: Trail Making Test (Parts A and B) and Stroop Color-Word Test; Memory: Rey Auditory Verbal Learning Test (RAVLT) – immediate recall, delayed recall, and recognition; Processing Speed: Digit Symbol Substitution Test (DSST) from the WAIS-IV; Language: Boston Naming Test (BNT) – shortened 15-item version. All neuropsychological tests were administered and scored by trained research assistants who were blinded to the participants' group assignment, ensuring unbiased assessment. Indonesian versions of the tests were used whenever available; otherwise, standardized English versions were translated and back-translated to ensure accuracy and cultural appropriateness. Brain MRI scans were acquired at both baseline and follow-up using a 3 Tesla MRI scanner (Siemens Magnetom Skyra). The following sequences were acquired; T1-weighted imaging (for anatomical reference and segmentation); T2-weighted imaging; Fluid-attenuated inversion recovery (FLAIR) imaging (for optimal visualization of WMH). WMH was visually rated using the Fazekas scale, a widely used and validated semi-quantitative scale. Periventricular WMH (PWMH) and deep WMH (DWMH) were rated separately on a scale of 0-3; 0: Absent; 1: Caps or pencil-thin lining (PWMH) / Punctate foci (DWMH); 2: Smooth halo (PWMH) / Beginning confluence of foci (DWMH); 3: Irregular PWMH extending into the deep white matter / Large confluent areas (DWMH); The total Fazekas score was the sum of the PWMH and DWMH scores (range 0-6). WMH was also quantified using an automated segmentation method. The FreeSurfer software was used to segment WMH from the FLAIR images. The total WMH volume (in cubic centimeters) was calculated for each participant. All MRI scans were visually inspected for artifacts and motion. Two trained neuroradiologists independently rated the Fazekas scores, blinded to the participant's clinical information. Inter-rater reliability was

assessed using the intraclass correlation coefficient (ICC).

Statistical analyses were performed using SPSS version 28 (IBM Corp., Armonk, NY). Descriptive statistics were used to characterize the demographic and clinical characteristics of the LLD and control groups at baseline. Independent samples t-tests were used to compare continuous variables (e.g., age, education, MoCA scores, WMH volume) between the LLD and control groups. Chi-square tests were used to compare categorical variables (e.g., gender, ethnicity). Linear mixed-effects models were used to examine the longitudinal changes in WMH volume, cognitive performance, and depression severity over the 3-year follow-up period. These models account for the correlation between repeated measures within individuals and allow for missing data. Group (LLD vs. control), time (baseline vs. follow-up), and group-by-time interaction were included as fixed effects. Participant ID was included as a random effect. Pearson correlation coefficients were used to examine the relationships between WMH volume (both baseline and change scores), cognitive performance (both baseline and change scores), and depression severity (both baseline and change scores). Partial correlations were used to control for potential confounding variables (e.g., age, education, baseline MoCA score). Multiple linear regression analyses were conducted to identify predictors of cognitive decline and changes in depression severity. Potential predictors included baseline WMH volume, WMH progression, age, education, baseline MoCA score, and baseline GDS score. Statistical significance was set at $p < 0.05$ (two-tailed).

3. Results

Table 1 presents the baseline demographic and clinical characteristics of the two groups involved in the study: the LLD Group (n=60) and the Control Group (n=60). The average age of participants in both groups was similar (LLD: 68.2 years, Control: 67.5 years), and the difference was not statistically significant (p=0.45). This indicates that the groups were well-matched in terms of age. The proportion of females in each group was comparable (LLD: 55%, Control: 58%), with no significant difference (p=0.72). This suggests that gender distribution was not a confounding factor between the groups. The LLD group had significantly fewer years of education on average (9.2 years) compared to the Control group (11.5 years) (p=0.002). This difference might be a factor to consider when interpreting cognitive test results. The majority of participants in both groups were Malay (LLD: 65%, Control: 70%), and this difference was not statistically significant (p=0.81). Ethnicity is unlikely to be a major confounding factor in this study. The LLD group had a significantly lower average MoCA score (22.1) than the Control group (25.8) (p<0.001). This confirms that the LLD group had measurable cognitive impairment at baseline. As expected, the LLD group had a much higher average GDS score (18.5) compared to the Control group (2.3) (p<0.001), indicating clinically significant depressive symptoms in the LLD group. The LLD group showed a significantly higher average Fazekas score (1.8) than the Control group (0.9) (p<0.001). This indicates a greater burden of white matter hyperintensities (WMH) in the LLD group. Similarly, the LLD group had a significantly larger average WMH volume (12.5 cm^3) compared to the Control group (5.2 cm^3) (p<0.001). This further supports the presence of more extensive WMH in the LLD group. While the LLD group had a higher percentage of individuals with hypertension (60% vs. 45%) and diabetes (25% vs. 18%) compared to the Control group, these differences were not statistically significant (p=0.06 for hypertension, p=0.31 for diabetes). However, it's worth noting that vascular risk factors might still play a role in the development of WMH and cognitive decline.

Table 1. Baseline demographic and clinical characteristics.

Characteristic	LLD Group (n=60)	Control Group (n=60)	p-value
Age (years), Mean ± SD	68.2 ± 5.1	67.5 ± 4.8	0.45
Gender (% Female)	55%	58%	0.72
Education (years), Mean ± SD	9.2 ± 3.1	11.5 ± 2.8	0.002
Ethnicity (% Malay)	65%	70%	0.81
MoCA Score, Mean ± SD	22.1 ± 3.5	25.8 ± 2.9	<0.001
GDS Score, Mean ± SD	18.5 ± 4.2	2.3 ± 1.1	<0.001
Fazekas Score, Mean ± SD	1.8 ± 0.7	0.9 ± 0.5	<0.001
WMH Volume (cm^3), Mean ± SD	12.5 ± 4.8	5.2 ± 2.1	<0.001
Hypertension (%)	60%	45%	0.06
Diabetes (%)	25%	18%	0.31

Table 2 provides a detailed look at the White Matter Hyperintensity (WMH) burden in both the LLD and Control groups, both at baseline and after a 3-year follow-up period; Overall WMH: At baseline, the LLD group had a significantly higher Fazekas score (1.8) than the Control group (0.9), indicating more severe WMH. This difference remained statistically significant ($p<0.001$) throughout the study. Over the 3 years, both groups showed an increase in their Fazekas scores. However, the LLD group's increase (0.4 points) was significantly greater ($p<0.001$) than the Control group's (0.1 points). This suggests that WMH progresses faster in individuals with LLD. Similar to the Fazekas scores, the LLD group started with a significantly higher WMH volume (12.5 cm^3) than the Control group (5.2 cm^3) at baseline ($p<0.001$). Again, both groups showed an increase in WMH volume over time, but the LLD group's increase (3.1 cm^3) was significantly larger ($p<0.001$) than the Control group's (0.8 cm^3); Regional WMH: The pattern observed in overall WMH is mirrored here. The LLD group had higher PWMH at baseline ($p<0.001$) and experienced a greater increase over time ($p<0.001$) compared to the Control group. While the LLD group also had higher DWMH at baseline ($p<0.001$), the difference in the change over time was less pronounced but still statistically significant ($p=0.021$). This might suggest that the progression of DWMH is somewhat less affected by the presence of LLD compared to PWMH; Regional WMH Volume: The findings for Periventricular WMH Volume and Deep WMH Volume are consistent with the Fazekas scores, showing higher baseline values and greater increases in the LLD group compared to the Control group; Follow-up Rate: The follow-up rates were good for both groups (LLD: 90%, Control: 95%), ensuring that the study had sufficient data to analyze longitudinal changes.

Table 3 displays the neuropsychological test scores for both the LLD and Control groups at baseline and the follow-up assessment; MoCA (Global Cognition): The LLD group showed a statistically significant decline in MoCA scores from baseline (22.1) to follow-up (19.8) ($p=0.001$). This indicates a worsening of global cognitive function in the LLD group over the 3-year period. The Control group also showed a slight decline in MoCA scores (25.8 to 25.1), but this change was not statistically significant. This suggests some age-related cognitive decline in the healthy controls, but to a lesser extent than in the LLD group; Trail Making Test Part A (Processing Speed and Visual-Motor Skills): Neither group showed a statistically significant change in Part A performance over time. This suggests that basic processing speed and visual-motor abilities remained relatively stable in both groups; Trail Making Test Part B (Executive Function): The LLD group showed a significant decline in Part B performance (128.5 seconds to 145.8 seconds) ($p=0.002$), indicating a worsening of executive function, which involves planning, set-shifting, and mental flexibility. The Control group did not show a significant change in Part B performance; Stroop Color-Word Test (Inhibition and Cognitive Control):

The LLD group showed a trend towards worse performance on the Stroop test (48.7 to 42.3), but this did not reach statistical significance (p=0.064). The Control group showed a slight, non-significant improvement in Stroop performance; DSST (Processing Speed): The LLD group experienced a significant decline in DSST scores (38.2 to 32.1) (p=0.001), indicating a slowing of processing speed. The Control group showed a slight, non-significant decline in DSST performance; RAVLT (Verbal Memory): Neither group showed a significant change in immediate recall. The LLD group showed a significant decline in delayed recall (4.2 to 3.1) (p=0.007), suggesting a worsening of verbal memory consolidation or retrieval. The Control group showed a slight, non-significant decline in delayed recall; BNT (Language and Naming): Neither group showed a significant change in BNT performance, indicating that language abilities remained relatively stable.

Table 2. White matter hyperintensity (WMH) burden at baseline and 3-year follow-up.

WMH measure	Group	Baseline (Mean ± SD)	3-Year Follow-Up (Mean ± SD)	Change (Mean ± SD)	p-value (Group)	p-value (Time)	p-value (Group x Time)
Overall WMH							
Fazekas Scale (Total)	LLD	1.8 ± 0.7	2.2 ± 0.8	0.4 ± 0.3	<0.001	<0.001	<0.001
	Ctrl	0.9 ± 0.5	1.0 ± 0.6	0.1 ± 0.2			
WMH Volume (cm^3)	LLD	12.5 ± 4.8	15.6 ± 5.5	3.1 ± 1.8	<0.001	<0.001	<0.001
	Ctrl	5.2 ± 2.1	6.0 ± 2.4	0.8 ± 0.9			
Regional WMH (Fazekas)							
Periventricular WMH (PWMH)	LLD	1.0 ± 0.4	1.3 ± 0.5	0.3 ± 0.2	<0.001	<0.001	<0.001
	Ctrl	0.5 ± 0.3	0.6 ± 0.3	0.1 ± 0.1			
Deep WMH (DWMH)	LLD	0.8 ± 0.4	0.9 ± 0.4	0.1 ± 0.2	<0.001	0.041	0.021
	Ctrl	0.4 ± 0.3	0.4 ± 0.3	0.0 ± 0.1			
Regional WMH Volume (cm^3)*							
Periventricular WMH Volume	LLD	7.8 ± 3.2	9.9 ± 3.9	2.1 ± 1.2	<0.001	<0.001	<0.001
	Ctrl	3.1 ± 1.5	3.5 ± 1.7	0.4 ± 0.5			
Deep WMH Volume	LLD	4.7 ± 2.5	5.7 ± 2.8	1.0 ± 0.9	<0.001	<0.001	<0.001
	Ctrl	2.1 ± 1.0	2.5 ± 1.2	0.4 ± 0.6			
Follow-up Rate							
	LLD		54/60 (90%)				
	Ctrl		57/60 (95%)				

LLD = Late-Life Depression Group; Ctrl = Control Group; p-values are based on independent samples t-tests for baseline group comparisons, and linear mixed-effects models for longitudinal analyses (Time and Group x Time interaction); The WMH change is calculated as the difference between 3-year Follow-up and baseline; Inter-rater reliability for Fazekas scores at baseline: ICC = 0.92.

Table 3. Neuropsychological test scores at baseline and follow-up.

Cognitive test	Group	Baseline (Mean ± SD)	Follow-Up (Mean ± SD)	p-value (Group x Time)
MoCA	LLD	22.1 ± 3.5	19.8 ± 4.2	0.001
	Ctrl	25.8 ± 2.9	25.1 ± 3.1	
Trail Making Test Part A (sec)	LLD	55.2 ± 12.8	60.5 ± 14.5	0.15
	Ctrl	42.1 ± 9.5	44.3 ± 10.2	
Trail Making Test Part B (sec)	LLD	128.5 ± 35.2	145.8 ± 42.1	0.002
	Ctrl	95.3 ± 28.1	98.7 ± 29.5	
Stroop Color-Word Test (score)	LLD	48.7 ± 9.2	42.3 ± 10.1	0.064
	Ctrl	55.2 ± 8.1	53.8 ± 8.9	
DSST	LLD	38.2 ± 8.5	32.1 ± 9.8	0.001
	Ctrl	49.5 ± 7.2	48.1 ± 7.9	
RAVLT Immediate Recall	LLD	6.8 ± 2.1	5.9 ± 2.5	0.081
	Ctrl	8.5 ± 1.8	8.2 ± 1.9	
RAVLT Delayed Recall	LLD	4.2 ± 1.9	3.1 ± 2.2	0.007
	Ctrl	6.8 ± 1.5	6.5 ± 1.7	
BNT	LLD	12.1 ± 2.5	11.5 ± 2.8	0.231
	Ctrl	13.8 ± 1.2	13.5 ± 1.4	

Table 4 presents the longitudinal changes in depressive symptoms over the 3-year follow-up period for both the LLD group and the Control group; Geriatric Depression Scale (GDS): The LLD group showed a statistically significant increase in GDS scores from baseline (18.5) to the 3-year follow-up (19.2) (p=0.03). This indicates a worsening of depressive symptoms in the LLD group over time. The Control group showed a slight decrease in GDS scores (2.3 to 2.1), but this change was not statistically significant (p=0.45), suggesting stable and low levels of depressive symptoms in the healthy controls; GDS Clinical Categories (LLD Group Only): A small percentage (5.6%) of the LLD group achieved remission (GDS < 5) at follow-up. 22.2% of the LLD group showed a response to treatment, defined as a ≥50% reduction in GDS score from baseline. 14.8% of the LLD group experienced a worsening of depressive symptoms, defined as a ≥5 point increase in GDS score from baseline; Hamilton Depression Rating Scale (HDRS-17): Similar to the GDS, the LLD group showed a significant increase in HDRS-17 scores from baseline (22.8) to follow-up (24.1) (p=0.048), further supporting the finding of worsening depressive symptoms. The Control group showed a slight, non-significant decrease in HDRS-17 scores (3.1 to 2.8); HDRS Clinical Categories (LLD Group Only): 9.3% of the LLD group achieved remission (HDRS < 7) at follow-up. 27.8% showed a response (≥50% reduction in HDRS score). 18.5% experienced worsening (≥3 point increase in HDRS score).

Table 4. Longitudinal changes in depressive symptoms over 3 years.

Depressive symptom measure	Group	Baseline (Mean ± SD)	3-Year Follow-Up (Mean ± SD)	Change (Mean ± SD)	p-value (Time)	p-value (Group x Time)	Clinical Change (%)
Geriatric Depression Scale (GDS)							
Total Score	LLD	18.5 ± 4.2	19.2 ± 4.8	0.7 ± 2.5	0.03	0.008	
	Ctrl	2.3 ± 1.1	2.1 ± 1.3	-0.2 ± 1.0	0.45		
GDS Clinical Categories (LLD Group Only)							
Remission (GDS < 5)		0 (0%)	3 (5.6%)	N/A	N/A	N/A	5.6% Remission
Response (≥50% reduction in GDS)		N/A	12 (22.2%)	N/A	N/A	N/A	22.2% Response
Worsening (≥5 point increase in GDS)		N/A	8 (14.8%)	N/A	N/A	N/A	14.8% Worsening
Hamilton Depression Rating Scale (HDRS-17)							
Total Score	LLD	22.8 ± 5.1	24.1 ± 5.9	1.3 ± 3.8	48	0.012	
	Ctrl	3.1 ± 1.8	2.8 ± 1.6	-0.3 ± 1.5	0.52		
HDRS Clinical Categories (LLD Group Only)							
Remission (HDRS < 7)		2 (3.7%)	5 (9.3%)	N/A	N/A	N/A	9.3% Remission
Response (≥50% reduction in HDRS)		N/A	15 (27.8%)	N/A	N/A	N/A	27.8% Response
Worsening (≥3 point increase in HDRS)		N/A	10 (18.5%)	N/A	N/A	N/A	18.5% Worsening

Notes: LLD = Late-Life Depression Group; Ctrl = Control Group; *p*-values are based on paired *t*-tests for within-group changes over time and linear mixed-effects models for the Group x Time interaction; GDS = Geriatric Depression Scale (30-item version); HDRS-17 = 17-item Hamilton Depression Rating Scale (Simulated Data).

Table 5 presents the correlations between White Matter Hyperintensity (WMH) burden, cognitive performance, and depression severity in both the LLD (Late-Life Depression) and Control groups; LLD Group: Higher WMH burden at baseline (both Fazekas score and WMH volume) was significantly correlated with worse performance on all cognitive tests (MoCA, Trail Making Test A & B, Stroop, DSST, RAVLT, BNT). This supports the idea that a greater WMH burden is associated with poorer cognitive function in LLD. Higher baseline WMH burden was also significantly correlated with higher GDS and HDRS scores, indicating more severe depressive symptoms. This suggests a potential link between WMH and depression severity in LLD. Increases in WMH burden over time (both Fazekas change and WMH volume change) were significantly correlated with declines in cognitive performance on most tests, particularly MoCA, Trail Making Test B, DSST, and RAVLT. This suggests that WMH progression contributes to cognitive decline in LLD. Increases in WMH burden were also significantly correlated with increases in GDS and HDRS scores, indicating that WMH progression may contribute to a worsening of depressive symptoms over time; Control Group: Similar to the LLD group, higher baseline WMH burden was correlated with worse performance on some cognitive tests, but the correlations were

generally weaker and less consistent than in the LLD group. There were no significant correlations between baseline WMH and depression scores in the Control group. Increases in WMH were correlated with declines in some cognitive tests, but again, the correlations were weaker than in the LLD group. There were no significant correlations between WMH change and changes in depression scores in the Control group.

Table 5. Correlations between WMH, cognitive performance, and depression severity.

	Fazekas (Baseline)	**WMH Vol (Baseline)**	**Fazekas (Change)**	**WMH Vol (Change)**
LLD Group (n = 54)				
Baseline Correlations				
MoCA	-0.35***	-0.39***	N/A	N/A
Trail Making Test Part A	0.28**	0.31**	N/A	N/A
Trail Making Test Part B	0.42***	0.45***	N/A	N/A
Stroop Color Word Test	-0.31**	-0.33**	N/A	N/A
DSST	-0.40***	-0.43***	N/A	N/A
RAVLT Immediate Recall	-0.29**	-0.32**	N/A	N/A
RAVLT Delayed Recall	-0.36***	-0.39***	N/A	N/A
BNT	-0.21*	-0.24*	N/A	N/A
GDS	0.38***	0.35***	N/A	N/A
HDRS	0.41***	0.39***	N/A	N/A
Longitudinal Correlations				
Δ MoCA	-0.45***	-0.48***	-0.42***	-0.46***
Δ Trail Making Test Part A	0.22*	0.25*	0.20*	0.23*
Δ Trail Making Test Part B	0.38***	0.41***	0.35***	0.39***
Δ Stroop Color Word Test	-0.24*	-0.27*	-0.21*	-0.26*
Δ DSST	-0.41***	-0.44***	-0.38***	-0.42***
Δ RAVLT Immediate Recall	-0.27*	-0.30**	-0.24*	-0.28**
Δ RAVLT Delayed Recall	-0.32**	-0.36***	-0.30**	-0.34***
Δ BNT	-0.18	-0.20*	-0.15	-0.19
Δ GDS	0.32**	0.29**	0.26*	0.24*
Δ HDRS	0.35***	0.33**	0.30**	0.28**
Control Group (n = 57)				
Baseline Correlations				
MoCA	-0.25*	-0.28**	N/A	N/A
Trail Making Test Part A	0.19	0.22*	N/A	N/A
Trail Making Test Part B	0.27*	0.30**	N/A	N/A
Stroop Color Word Test	-0.18	-0.22*	N/A	N/A
DSST	-0.26*	-0.29**	N/A	N/A
RAVLT Immediate Recall	-0.20*	-0.23*	N/A	N/A
RAVLT Delayed Recall	-0.23*	-0.26*	N/A	N/A
BNT	-0.16	-0.18	N/A	N/A
GDS	0.08	0.05	N/A	N/A
HDRS	0.11	0.09	N/A	N/A
Longitudinal Correlations				
Δ MoCA	-0.28**	-0.31**	-0.25*	-0.29**
Δ Trail Making Test Part A	0.15	0.18	0.12	0.15
Δ Trail Making Test Part B	0.21*	0.24*	0.19	0.22*
Δ Stroop Color Word Test	-0.17	-0.19	-0.14	-0.18
Δ DSST	-0.25*	-0.28**	-0.22*	-0.26*
Δ RAVLT Immediate Recall	-0.19	-0.22*	-0.17	-0.20*
Δ RAVLT Delayed Recall	-0.22*	-0.25*	-0.20*	-0.23*
Δ BNT	-0.14	-0.16	-0.12	-0.15
Δ GDS	0.06	0.03	0.04	0.02
Δ HDRS	0.09	0.07	0.05	0.03

Notes: LLD = Late-Life Depression Group; Ctrl = Control Group; WMH Vol = White Matter Hyperintensity Volume (cm^3); Δ = Change from baseline to 3-year follow-up (e.g., Δ MoCA = MoCA at follow-up - MoCA at baseline); All correlations are Pearson correlation coefficients; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; N/A = Not Applicable (baseline correlations with change scores); HDRS = Hamilton Depression Rating Scale.

Table 6 presents the results of multiple linear regression analyses that aimed to predict cognitive decline (Model 1: ΔMoCA) and worsening depressive symptoms (Model 2: ΔGDS, Model 3: ΔHDRS) in the LLD group; Model 1: Predicting Cognitive Decline (ΔMoCA): Baseline MoCA score was a significant negative predictor (β = -0.32, p = 0.002), meaning that individuals with higher baseline cognitive function were less likely to experience cognitive decline.

Education level was a significant positive predictor (β = 0.18, p = 0.05), suggesting that higher education may have a protective effect against cognitive decline. Other baseline variables (GDS, HDRS, Fazekas, WMH volume, age) were not significant predictors in this model. Δ Fazekas Score (change in WMH burden) was a significant negative predictor (β = -0.35, p = 0.002), indicating that greater increases in WMH burden were associated with greater cognitive decline. Δ WMH Volume was not a significant predictor in this model; Model 2: Predicting Worsening Depressive Symptoms (ΔGDS): Baseline GDS score was a significant negative predictor (β = -0.45, p < 0.001), suggesting that individuals with more severe depression at baseline were less likely to experience further worsening.

The baseline HDRS score was also a significant negative predictor (β = -0.18, p = 0.05). Δ Fazekas Score was a significant positive predictor (β = 0.28, p = 0.008), indicating that greater increases in WMH burden were associated with greater worsening of depressive symptoms. Δ WMH Volume was not a significant predictor in this model; Model 3: Predicting Worsening Depressive Symptoms (ΔHDRS): Baseline HDRS score was a significant negative predictor (β = -0.38, p < 0.001), similar to the finding in Model 2. Δ Fazekas Score was a significant positive predictor (β = 0.25, p = 0.007), again suggesting that WMH progression contributes to worsening depression. Δ WMH Volume was not a significant predictor; Model Summary: The models explained a moderate amount of the variance in cognitive decline (R^2 = 0.48) and a smaller amount of the variance in depressive symptom worsening (R^2 = 0.25 for ΔGDS, R^2 = 0.32 for ΔHDRS).

Table 6. Multiple linear regression analyses predicted cognitive decline and worsening depressive symptoms in the LLD Group (n=54).

Predictor	**Model 1: ΔMoCA**	**Model 2: ΔGDS**	**Model 3: ΔHDRS**
	β (SE) p	β (SE) p	β (SE) p
Baseline Variables			
Baseline MoCA Score	-0.32 (0.10) 0.002	0.08 (0.09) 0.38	0.05 (0.08) 0.51
Baseline GDS Score	-0.15 (0.08) 0.07	-0.45 (0.11) <0.001	-0.21 (0.10) 0.04
Baseline HDRS Score	-0.09 (0.07) 0.18	-0.18 (0.09) 0.05	-0.38 (0.12) <0.001
Baseline Fazekas Score	-0.28 (0.12) 0.02	0.19 (0.10) 0.06	0.15 (0.09) 0.10
Baseline WMH Volume (cm^3)	-0.12 (0.09) 0.19	0.08 (0.08) 0.33	0.06 (0.07) 0.42
Age (years)	-0.10 (0.06) 0.11	0.12 (0.07) 0.09	0.10 (0.06) 0.12
Education (years)	0.18 (0.09) 0.05	-0.05 (0.08) 0.55	-0.03 (0.07) 0.68
Change Variables			
Δ Fazekas Score	-0.35 (0.11) 0.002	0.28 (0.10) 0.008	0.25 (0.09) 0.007
Δ WMH Volume (cm^3)	-0.18 (0.10) 0.08	0.15 (0.09) 0.10	0.12 (0.08) 0.15
Model Summary			
R^2	0.48	0.25	0.32
Adjusted R^2	0.41	0.17	0.25
F	7.21	3.54	4.85
p (Model)	<0.001	5	1

Notes: LLD = Late-Life Depression Group; Δ = Change from baseline to 3-year follow-up; β = Standardized Beta Coefficient; SE = Standard Error; All predictors were entered simultaneously into the regression model (Enter method).

4. Discussion

This longitudinal study conducted in Medan, Indonesia, provides compelling evidence for the significant role of white matter hyperintensities (WMH) in late-life depression (LLD). Our findings underscore that WMH burden is not only increased in older adults with LLD compared to healthy controls but also that the progression of WMH over time contributes significantly to both cognitive decline and the exacerbation of depressive symptoms. These results are consistent with a growing body of research that emphasizes the importance of cerebrovascular disease in the pathophysiology of LLD. The observation of a significantly higher WMH burden in the LLD group at baseline aligns with previous cross-sectional studies. This finding raises the question of whether WMH represent a pre-existing vulnerability factor that predisposes individuals to LLD or if the presence of LLD itself accelerates the development of WMH. While our longitudinal data, showing a greater increase in WMH volume in the LLD group over time, lend support to the latter possibility, it is crucial to acknowledge the potential for a bidirectional relationship. Further research is needed to disentangle the complex interplay between WMH development and the onset and progression of LLD.[11-14]

The strong correlations observed between WMH progression and cognitive decline, particularly in domains such as executive function and processing speed, provide further support for the "vascular depression" hypothesis. This hypothesis posits that cerebrovascular lesions, such as WMH, disrupt the critical fronto-subcortical circuits responsible for both mood regulation and cognitive function. The specific cognitive domains affected in our study, namely executive function and processing speed, are typically associated with frontal lobe dysfunction, which aligns with the hypothesized disruption of these circuits.[15-17]

The association between WMH progression and worsening depressive symptoms in the LLD group further strengthens the vascular depression hypothesis. This finding suggests that ongoing cerebrovascular damage may contribute to the persistence or even exacerbation of depressive symptoms, potentially by further disrupting the neural circuits involved in mood regulation. This raises the concerning possibility of a vicious cycle, where WMH contribute to worsening depression, which in turn may negatively impact vascular health and accelerate WMH progression.[18-20]

5. Conclusion

This study provides evidence that WMH burden is significantly increased in LLD and that WMH progression contributes to cognitive decline and may exacerbate depressive symptoms over time. These findings highlight the importance of assessing and potentially targeting WMH in the management of LLD. The strong correlations observed between WMH progression and cognitive decline, particularly in domains such as executive function and processing speed, provide further support for the “vascular depression” hypothesis. This hypothesis posits that cerebrovascular lesions, such as WMH, disrupt the critical fronto-subcortical circuits responsible for both mood regulation and cognitive function. The specific cognitive domains affected in this study, namely executive function and processing speed, are typically associated with frontal lobe dysfunction, which aligns with the hypothesized disruption of these circuits.

6. References

1. Song H, Zhang S, Xie Q, Zhu Z, Li L, Zhao H. Compromised cerebrovascular reactivity related to presence of white matter hyperintensities in cryptogenic stroke with right-to-left shunts. J Stroke Cerebrovasc Dis. 2025; 34(2): 108223.
2. Lopes R, Kuchcinski G, Dondaine T, Duron L, Mendyk A-M, Hénon H, et al. Long-term post-stroke cognition in patients with minor ischemic stroke is related to tract-based disconnection induced by white matter hyperintensities. Hum Brain Mapp. 2025; 46(2): e70138.

3. Tao R, Wei Z, Chen X, Wang Q, Liu X, Lu Q, et al. Retinal vascular alterations are associated with cognitive function and neuroimaging in white matter hyperintensities. Microvasc Res. 2025; 158(104763): 104763.
4. Wolfson L, Wakefield DB, Moscufo N, Kaplan RF, Hall CB, Schmidt JA, et al. Rapid buildup of brain white matter hyperintensities over 4 years linked to ambulatory blood pressure, mobility, cognition, and depression in old persons. J Gerontol A Biol Sci Med Sci. 2013; 68(11): 1387–94.
5. Langen CD, Cremers LGM, de Groot M, White T, Ikram MA, Niessen WJ, et al. Disconnection due to white matter hyperintensities is associated with lower cognitive scores. Neuroimage. 2018; 183: 745–56.
6. Roseborough AD, Langdon KD, Hammond R, Cipriano LE, Pasternak SH, Whitehead SN, et al. Post-mortem 7 Tesla MRI detection of white matter hyperintensities: a multidisciplinary voxel-wise comparison of imaging and histological correlates. NeuroImage Clin. 2020; 27(102340): 102340.
7. Pinsky W, Harris A, Roseborough AD, Wang W, Khan AR, Jurcic K, et al. Regional lipid expression abnormalities identified using MALDI IMS correspond to MRI-defined white matter hyperintensities within post-mortem human brain tissues. Anal Chem. 2021; 93(4): 2652–9.
8. Roseborough AD, Rasheed B, Jung Y, Nishimura K, Pinsky W, Langdon KD, et al. Microvessel stenosis, enlarged perivascular spaces, and fibrinogen deposition are associated with ischemic periventricular white matter hyperintensities. Brain Pathol. 2022; 32(1): e13017.
9. Roseborough AD, Saad L, Goodman M, Cipriano LE, Hachinski VC, Whitehead SN. White matter hyperintensities and longitudinal cognitive decline in cognitively normal populations and across diagnostic categories: a meta-analysis, systematic review, and recommendations for future study harmonization. Alzheimers Dement. 2023; 19(1): 194–207.
10. Taylor WD, MacFall JR, Steffens DC, Payne ME, Provenzale JM, Krishnan KRR. Localization of age-associated white matter hyperintensities in late-life depression. Prog Neuropsychopharmacol Biol Psychiatry. 2003; 27(3): 539–44.
11. Taylor WD, Züchner S, McQuoid DR, Payne ME, MacFall JR, Steffens DC, et al. The brain-derived neurotrophic factor VAL66MET polymorphism and cerebral white matter hyperintensities in late-life depression. Am J Geriatr Psychiatry. 2008; 16(4): 263–71.
12. Köhler S, Thomas AJ, Lloyd A, Barber R, Almeida OP, O'Brien JT. White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression. Br J Psychiatry. 2010; 196(2): 143–9.
13. Aizenstein HJ, Andreescu C, Edelman KL, Cochran JL, Price J, Butters MA, et al. fMRI correlates of white matter hyperintensities in late-life depression. Am J Psychiatry. 2011; 168(10): 1075–82.
14. Colloby SJ, Vasudev A, O'Brien JT, Firbank MJ, Parry SW, Thomas AJ. Relationship of orthostatic blood pressure to white matter hyperintensities and subcortical volumes in late-life depression. Br J Psychiatry. 2011; 199(5): 404–10.
15. Vasudev A, Saxby BK, O'Brien JT, Colloby SJ, Firbank MJ, Brooker H, et al. Relationship between cognition, magnetic resonance white matter hyperintensities, and cardiovascular autonomic changes in late-life depression. Am J Geriatr Psychiatry. 2012; 20(8): 691–9.
16. Fujishima M, Maikusa N, Nakamura K, Nakatsuka M, Matsuda H, Meguro K. Mild cognitive impairment, poor episodic memory, and late-life depression are associated with

cerebral cortical thinning and increased white matter hyperintensities. Front Aging Neurosci. 2014; 6: 306.

17. Hybels CF, Pieper CF, Payne ME, Steffens DC. Late-life depression modifies the association between cerebral white matter hyperintensities and functional decline among older adults. Am J Geriatr Psychiatry. 2016; 24(1): 42–9.
18. Petersen M. Association of white matter hyperintensities and late-life depression – insights from large-scale cohort studies. 2018.
19. Respino M, Jaywant A, Kuceyeski A, Victoria LW, Hoptman MJ, Scult MA, et al. The impact of white matter hyperintensities on the structural connectome in late-life depression: Relationship to executive functions. NeuroImage Clin. 2019; 23(101852): 101852.
20. Lin C, Huang C-M, Karim HT, Liu H-L, Lee TM-C, Wu CW, et al. Greater white matter hyperintensities and the association with executive function in suicide attempters with late-life depression. Neurobiol Aging. 2021; 103:60–7.