Effect of White Matter Hyperintensities on Daily Function via Depressive Symptoms: A Longitudinal Study in Patients With Dementia Including Alzheimer's Disease and Subcortical Ischemic Vascular Dementia

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Objective   This study aimed to investigate the mediation effect of depressive symptoms on the relationship between white matter hyperintensities and the basic activities of daily living (BADL) using an integrated approach to overcome the limitations of previous studies and examine the relationship among the three variables simultaneously.

Methods   We performed structural equation modeling using cross-sectional data from 497 Alzheimer's disease (AD), AD with small vessel disease, and subcortical ischemic vascular dementia patients enrolled in the Clinical Research for Dementia of South Korea registry who were diagnosed with mild-to-moderate dementia. Periventricular white matter hyperintensities (PWMHs) and deep white matter hyperintensities (DWMHs) were visualized separately at baseline using magnetic resonance imaging. Depressive symptoms were assessed using the Korean Form of the Geriatric Depression Scale at the follow-up assessment conducted after 1 year. BADL were assessed using the Barthel Index at the follow-up assessment conducted after 2 years.

Results   The direct and indirect effects of DWMHs on the BADL as mediated via depression were significant. However, neither the direct effect of PWMHs on the BADL nor the indirect effect of PWMHs on the BADL via depression were significant.

Conclusion   This study presented a mediation model that included a longitudinal developmental pathway from DWMHs to deterioration in the BADL mediated via depressive symptoms. Moreover, the mediation model of depressive symptoms could not be applied to the longitudinal developmental pathway from DWMHs to the deterioration in BADL.   **Psychiatry Investig 2022;19(8):687-694**

Keywords   Dementia; White matter; Depression; Activities of daily living; Cerebrovascular disease; Longitudinal study.

INTRODUCTION

Although the degree of dependence while performing daily life tasks increases with age, patients with dementia require more care than those with other age-related chronic diseases. The level of function in daily life is one of the most important measures determining disease severity and patients' independence in dementia.[1] Tools assessing the activities of daily living (ADL) vary from those evaluating basic functional levels[2-5] by grading instrumental and complex task performance abilities.[1,6] The severity of dementia is the most important variable influencing the decline in the level of daily function, but other factors such as age, sex, education level, and depression also have a substantial influence on ADL.[1] Additionally, white matter changes have been mentioned in previous studies as an important variable related to the ADL.[1,7-9]

Several previous studies have already proven that late-life depression bears a substantial correlation with the decline in cognitive and daily life functions.[8,10,11] However, the underlying causal pathological relationship is highly complex. Depression in old age can cause several disabilities and the associated factors, and the nature of this relationship is highly variable.[8,10,11] Akin to ADL, cerebrovascular disease is an important factor related to depression from amongst several po-

tential common pathological factors.[8]

White matter hyperintensities (WMHs), which are amongst the most important factors in cerebrovascular disease, are known to be associated with depression, cognitive decline, and deterioration in daily life function.[12-14] Several studies have shown that WMHs are significantly associated with the severity of depressive symptoms (DEP); the greater the severity of the WMHs at baseline, the higher the probability of the risk of depression during follow-up.[8] Additionally, WMHs acts as preceding factors that significantly predict depression and deterioration in daily life function.[14,15] A study of older patients with depression found an association between subcortical WMHs and functional impairment.[16] Moreover, a longitudinal study of patients with white matter lesions also found a significant decline in daily life function after one year, based on a 3-year follow-up.[12,17]

WMHs can be classified as periventricular WMHs (PWMHs) and deep WMHs (DWMHs). PWMHs are attached to the brain ventricles, while DWMHs are located in the subcortical white matter far from the ventricle.[18] PWMHs and DWMHs are different, and stratification of WMHs can provide valuable information on important pathological aging processes.[19] In particular, previous studies have shown that PWMHs showed a stronger association with cognitive function compared to DWMHs, while DWMHs showed a stronger association with depression compared to PWMHs.[14,20,21] As observed by previous studies, it is necessary to treat DWMHs and PWMHs as separate entities, because they occur in different areas. To the best of our knowledge, none of the previous studies that investigated WMHs with respect to ADL divided the former into DWMHs and PWMHs. In this study, we examined the long-term effects of DWMHs and PWMHs on ADL deterioration.

Furthermore, the significant correlation and causal relationships between the ADL and depression are well known.[8] Mograbi et al.[22] (2018) also found that dementia was significantly related to all types of ADLs, and that the depression group showed a decrease in ADL. A study with elderly individuals aged above 60 years found that depression was a significant predictor of the decline in the ADL.[23]

Meanwhile, the relationship between vascular lesions, depression, and dysfunction is complex. Katz[24] (2004) suggested that each of these conditions may be the cause or result of different conditions and may be part of related syndromic spectrum. Not only do these conditions share common risk factors but they can also be a part of vascular lesion, depression, ADL function diseases development. However, to the best of our knowledge, no study has investigated the mediation effects of depressive symptoms by simultaneously considering all three variables (WMHs, depressive symptoms, and ADL)

in an integrated manner. This is because previous studies have focused on verifying the relationship between any two variables instead of using a comprehensive approach, which has led to limitations in identifying the pathological development of impairment in daily function mediated by depressive symptoms.[16,20,21] In addition, large-scale longitudinal studies that determined the possible mediation of WMHs and ADL by depressive symptoms in a dementia-specific clinical group are rare. Therefore, in this study, WMHs, depressive symptoms, and ADL, which were measured at different time intervals, were included in the mediation model. This study attempted to verify causality more rigorously, since cross-sectional studies are ill-suited for this purpose. The goal of this study was to explore whether the increase in the severity of WMHs would also increase the severity of depression and daily life dysfunctions. Examining this aspect in a clinical dementia cohort will be meaningful in expanding the understanding of the developmental pathology of dementia beyond currently available evidence, to emphasize the direct effect of depression on daily life function.

METHODS

Participants

The Clinical Research for Dementia of South Korea (CREDOS) is a comprehensive epidemiological study of dementia in Korea. It is a multicenter nationwide cohort study spanning 30 hospitals throughout South Korea, which is funded by the Ministry of Health, Welfare, and Family Affairs. Consecutive outpatients who visited the clinics at the CREDOS-affiliated centers for memory disorders between September 2005 and June 2010 were included in the study. We included 497 patients diagnosed with mild-to-moderate dementia from the CREDOS cohort in the present study. The diagnoses of mild cognitive impairment and Alzheimer's disease (AD) were performed on the basis of diagnostic interviews conducted by neurologists and psychiatrists. The severity of dementia was determined using the Clinical Dementia Rating (CDR) scale, which was assessed by neuropsychologists after obtaining consent to participate in the study. Patients with a CDR score <3 (0.5, 1, and 2) were included, and those with a CDR score ≥3 (3, 4, and 5) were excluded because of the difficulty to adequately determine the depressive symptoms in such patients owing to the severe impairment in cognitive function. All variables were evaluated at baseline, 1-year follow-up, and 2-year follow-up. This study was approved by the Institutional Review Boards of all participating hospitals (IRB no. 2012-26), and written informed consent was obtained from all participants and their caregivers after providing a full description of the study.

We excluded patients with other degenerative etiologies including idiopathic Parkinson's disease, diffuse Lewy body disease, corticobasal degeneration, and progressive supranuclear palsy. Patients with clinical evidence of stroke, territory or strategic infarction, and those exhibiting high-signal abnormalities on magnetic resonance imaging (MRI) related to radiation injury, multiple sclerosis, vasculitis, or leukodystrophy were also excluded. The other exclusion criteria were as follows: 1) patients whose age did not fall within the range of 60 to 85 years; 2) presence of mental retardation; 3) presence of disorders that could have confounded the participants' cognitive state, such as untreated thyroid dysfunction, syphilis, or metabolic encephalopathy; 4) current or past history of neurological or psychiatric illnesses such as schizophrenia, epilepsy, brain tumors, encephalitis, or severe head trauma; and 5) physical illnesses or disorders that could interfere with the clinical study, such as hearing or vision loss, aphasia, uncontrolled diabetes, hypertension, malignancy, or renal disorders.

We included patients with AD and subcortical ischemic vascular dementia (SIVD). Patients with AD met the probable AD criteria proposed by the National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder Association.[25] Patients with vascular dementia (VD) met the Diagnostic and Statistical Manual of Mental Disorders-IV criteria.[26] AD and VD were diagnosed using interviews conducted by neurologists and psychiatrists. AD and VD share vascular risk factors,[27] and the dichotomization of AD and VD has received considerable criticism owing to its simplistic nature.[7] Thus, instead of stratifying patients into the AD or SIVD group, the CREDOS study devised its own classification system. We reclassified all patients using two criteria: the degree of cognitive impairment and subcortical vascular ischemic lesions observed on MRI. Cognitive impairment was defined using the CDR score. Subcortical ischemic lesion severity was categorized as minimal, moderate, or severe according to the subcortical ischemic lesion rating criteria by combining the DWMH and PWMH scores. Based on these criteria, patients with CDR scores of 0.5, 1, and 2 were classified into three categories according to the severity of small vessel disease observed on MRI as follows: AD, AD with small vessel disease (AD with SVD), and SIVD, respectively.

Measures

MRI was conducted based on protocol for CREDOS registration. WMHs were rated using the Fazekas scale.[28] Grading was performed on a three-point scale, such that DWMHs were rated as 1 (maximum diameter <10 mm), 2 (≥10 mm, <25 mm), or 3 (≥25 mm). Three trained neurologists rated all scans from all participating centers. The inter-rater reliability of the

CREDOS WMHs visual rating scale was very high (intraclass correlation coefficient, 0.726 to 0.905).

Activities of daily living scales

We used the Barthel Index (rating scale: 0–20, the higher the score the lesser the degree of dependence) for the evaluation of the basic activities of daily living (BADL)[29] at baseline and 1-year and 2-year follow-up visits. This caregiver-administered instrument is designed to measure the BADL. The Barthel Index consists of 10 items, i.e., feeding, personal toilet, self-bathing, dressing and undressing, getting on and off toilet, controlling bladder, controlling bowel, moving from wheelchair to bed and returning, walking on a level surface (or propelling a wheelchair if unable to walk), and ascending and descending stairs. All items were scored on a 3-point Likert scale ranging from 0 to 3, with higher scores indicating lower function.

Depression scales

DEP was assessed at baseline and 1-year and 2-year follow-up visits using the Korean version of the Geriatric Depression Scale (KGDS).[30] The KGDS is a valid and reliable tool for the assessment of geriatric depression, for which it was designed specifically. The area under the curve for the KGDS is 0.902 and Cronbach's alpha is 0.921. In a validation study, 88 outpatients or inpatients aged ≥55 years or older were assessed using the KGDS. Depression was diagnosed through a diagnostic interview by two psychiatrists, and the optimal cut-off was determined to be 17 points, based on the diagnosis.

Statistical analysis

SPSS 22.0 and SPSS Macro Process (IBM Co., Armonk, NY, USA) were used for statistical analyses. First, Spearman's correlation analysis was performed to confirm the relationships between the variables. Subsequently, a four-step regression analysis method proposed by Baron and Kenny[31] (1986) was employed to indirectly confirm the mediation effect of the mediator variable to verify whether the independent variable indirectly affected the dependent variable via the mediator variable. Thereafter, the statistical significance of the mediation effect was directly verified using process model 4, and the mediation effect was verified using the bootstrap method. In this study, we adopted the bootstrap method to verify the mediation effect based on empirical distribution, where the number of bootstrap samples was 10,000. A bias-corrected bootstrap confidence interval was used for the bootstrap confidence interval. Conceptually, this method is the same as the percentile bootstrap confidence interval; however, it is a relatively simple method of modifying the confidence interval by considering the proportion of estimates whose value is small-

er than that of the point estimate of the original sample among the k-mediated effect estimates representing indirect effects. This method is superior to the bootstrap confidence interval method. The confidence interval was set to 95%. Based on the results, if 0 was not included in the 95% confidence interval, the mediation effect was considered to be significant at a significance level of 5%.

RESULTS

Demographics and baseline clinical characteristics are shown in Table 1. Approximately 60% of the group population was

Table 1. Demographic and clinical characteristics of participants at baseline (N=497)

	Value
Sex	
Male	197 (39.6)
Female	300 (60.4)
Age (yr)	70.45±7.28
Education years	9.84±4.98
CDR	
0.5	422 (84.9)
1	68 (13.7)
2	7 (1.4)
AD	39 (7.8)
AD w/SVD	268 (53.9)
SIVD	190 (38.2)
PWMHs	
Baseline	1.80±0.88
1y F/U	1.81±0.89
2y F/U	1.84±0.90
DWMHs	
Baseline	1.40±0.69
1y F/U	1.41±0.70
2y F/U	1.47±0.75
BADL	
Baseline	19.82±0.86
1y F/U	19.71±1.40
2y F/U	19.55±1.57
DEP	
Baseline	13.15±7.24
1y F/U	12.38±7.34
2y F/U	11.98±7.54

Values are presented as mean±standard deviation or number (%). CDR, Clinical Dementia Rating; AD, Alzheimer's disease; AD w/ SVD, AD with small vessel disease; SIVD, subcortical ischemic vascular disease; PWMHs, periventricular white matter hyperintensities; DWMHs, deep white matter hyperintensities; BADL, the basic activities of daily living; DEP, the severity of depressive symptoms; F/U, follow-up

female. The mean±standard deviation age in the group was 70.45±7.28 years. The mean±standard deviation year of education was 9.84±4.98 years. The mean±standard deviation baseline score of PWMHs was 1.80±0.88, DWMHs was 1.40± 0.69, BADL was 19.82±0.86, and DEP was 13.15±7.24. The mean±standard deviation 1-year follow-up score of PWMHs was 1.81±0.89, DWMHs was 1.41±0.70, BADL was 19.71±1.40, and DEP was 12.38±7.34. The mean±standard deviation 2-year follow-up score of PWMHs was 1.84±0.90, DWMHs was 1.47±0.75, BADL was 19.55±1.57, and DEP was 11.98±7.54.

Correlation analysis between variables

The assumption of normality is satisfied when the absolute values of skewness and kurtosis do not exceed 2 and 7, respectively.[32] As shown in Table 2, the variables used in this study satisfied the assumption for normality. The Spearman correlation coefficient was calculated, since the WMHs were rated on an ordinal scale.

Mediation effects of the severity of depressive symptoms on the relationship between white matter hyperintensities and basic activities of daily living

Deep white matter hyperintensities

The effects of DWMHs and DEP on the BADL and the combined effects of both variables on BADL were verified (see Figure 1 and Table 3). First, regression analysis was conducted with DWMHs as the predictor variable and DEP as the criterion variable, to examine the effect of DWMHs on DEP. The regression coefficient β for this analysis equaled 0.147 ($p<0.01$); thus, DWMHs exerted a significant influence on DEP. Second, regression analysis was conducted with DWMHs as the predictor variable and BADL as the criterion variable, to examine the effect of DWMHs on the BADL. The regression coefficient β for this analysis was -0.121 ($p<0.01$); thus, the effect of DWMHs on the BADL was statistically significant. Third, the effect of DEP on BADL retained statistical

Table 2. Spearman correlation between measurement variables (N=497)

	1	2	3	4
1. DWMHs	-			
2. PWMHs	0.599**	-		
3. DEP	0.147**	0.084	-	
4. BADL	-0.121**	-0.016	-0.123**	-
Skewness	1.451	0.390	0.411	-1.354
Kurtosis	0.590	-1.592	-0.839	3.092

**p<0.01. DWMHs, deep white matter hyperintensities; PWMHs, periventricular white matter hyperintensities; DEP, the severity of depressive symptoms; BADL, the basic activities of daily living

significance, while controlling for the effect of DWMHs on BADL (β=-0.107, p<0.05). Fourth, the effect of DWMHs on BADL retained statistical significance, even after controlling for the effect of DEP (β=-0.105, p<0.05).

Subsequently, the mediation effect of DEP on the relationship between DWMHs and BADL was verified directly using the bootstrap method (Table 4). The analysis revealed that the non-standardized estimate of the indirect effect was -0.004, which means that an increase in 1 point in the original DWMH score increased the original BADL score by -0.004 points via DEP. Moreover, the lower and upper limits of the
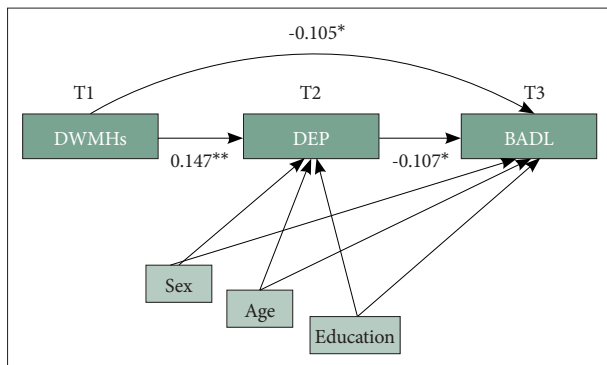
Figure 1. Mediation model of the effect of depressive symptoms on the relationship between DWMHs and cognitive function. The dotted line represents the covariance between the variables. T1 represents the baseline measurement, T2 the follow-up measurement after 1 year, and T3 the follow-up measurement after 2 years. The severity of DWMHs in T1, the severity of depression in T2, and the BADL in T3 were put into the mediated model. *p<0.05; **p<0.01. DWMHs, deep white matter hyperintensities; DEP, the severity of depressive symptoms; BADL, the basic activities of daily living.

95% confidence interval of the indirect effect non-standardized estimate were -0.042 and -0.002, respectively, and 0 was not included in the bootstrap confidence interval. This suggests that the indirect effect of DWMHs on the BADL was statistically significant.

Periventricular white matter hyperintensities

The effects of PWMHs and DEP on BADL and the combined effects of both variables on the BADL were verified (see Figure 2 and Table 3). First, regression analysis was conducted with PWMHs as the predictor variable and DEP as the criterion variable, to examine the effect of PWMHs on DEP. The regression coefficient β for this analysis was 0.120 (p<0.01); thus, PWMHs exerted a significant influence on DEP. Second, regression analysis was conducted with PWMHs as the predictor variable and BADL as the criterion variable to examine the effect of PWMHs on the BADL. The regression coefficient β for this analysis was 0.002 (not significant), and the

Table 4. Indirect effects of depressive symptoms (N=497)

| Path	Effect	Boot S.E.	95% CI	
			LLCI	ULCI
DWMHs → BADL	-0.004	0.002	-0.042	-0.002
PWMHs → BADL	-0.028	0.017	-0.078	0.005

All coefficients are non-standardized coefficient estimates. The effect size of indirect effect represents the ratio of indirect effect to total effect. DWMHs, deep white matter hyperintensities; BADL, the basic activities of daily living; PWMHs, periventricular white matter hyperintensities; S.E., standard error; CI, confidence interval; LLCI, ULCI, lower and upper bounds within the 95% CI

Table 3. Regression analysis results (N=497)

	IV	DV	B	S.E.	β	t	R²	F
1	Sex		1.309	0.699	0.087	1.873		
	Age	DEP	-0.102	0.044	-0.101	-2.312*	0.073	12.947***
	Education		-0.294	0.069	-0.199	-4.284***		
2	Sex		0.213	0.155	0.067	1.375	0.009	1.501
	Age	BADL	-0.010	0.010	-0.046	-1.011		
	Education		0.025	0.015	0.080	1.647		
3	DWMHs	DEP	1.549	0.468	0.147	3.306**	0.022	10.932***
	PWMHs		1.008	0.377	0.120	2.674**	0.086	11.618
	DWMHs	BADL	-0.270	0.100	-0.121	-2.690**	0.015	7.237***
	PWMHs		0.003	0.084	0.002	0.037	0.009	1.123
	DWMHs		-0.235	0.101	-0.105	-2.326*	0.026	6.478***
	DEP	BADL	-0.023	0.010	-0.107	-2.377*		
	PWMHs		0.031	0.084	0.017	0.370	0.025	2.495*
	DEP		-0.028	0.010	-0.131	-2.814**		

*p<0.05; **p<0.01; ***p<0.001. IV, independent variable; DV, dependent variable; B, non-standardized coefficient estimates; S.E., standard error; β, standardized coefficient estimates; DEP, the severity of depressive symptoms; BADL, the basic activities of daily living; DWMHs, deep white matter hyperintensities; PWMHs, periventricular white matter hyperintensities
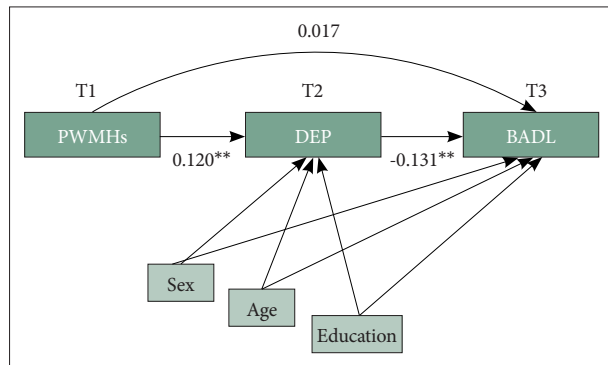
Figure 2. Mediation model of the effect of depressive symptoms on the relationship between PWMHs and cognitive function. The dotted line represents the covariance between the variables. T1 represents the baseline measurement, T2 the follow-up measurement after 1 year, and T3 the follow-up measurement after 2 years. The severity of PWMHs in T1, the severity of depression in T2, and the BADL in T3 were put into the mediated model. **p<0.01. PWMHs, periventricular white matter hyperintensities; DEP, the severity of depressive symptoms; BADL, the basic activities of daily living.

effect of PWMHs on BADL was not significant. Third, the effect of DEP on the BADL was significant, while controlling for the effect of PWMHs on BADL (β=-0.131, p<0.01). Fourth, the effect of PWMHs on the BADL was not significant, after controlling for the effect of DEP (β=0.017, not significant).

Subsequently, the bootstrap method was employed to directly verify the mediation effect of DEP on the relationship between PWMHs and BADL (Table 4). The non-standardized estimate of the indirect effect was -0.028 according to this analysis, which means that an increase in 1 point in the original PWMH score raised the original BADL score by -0.028 points via the severity of depressive symptoms. Additionally, the lower and upper limits of the 95% confidence interval of the indirect effect non-standardized estimate were -0.078 and 0.005, respectively, and 0 was included in the bootstrap confidence interval. This suggests that the indirect effect of PWMHs on the BADL was not significant.

DISCUSSION

The purpose of this study was to ascertain the relationship among the two types of WMHs (DWMHs and PWMHs), depressive symptoms, and BADL using mediation models and identify the mediation effects of depression. We generated a model of both direct and indirect pathways (via depressive symptoms) between DWMHs/PWMHs and BADL function using a process model.

To the best of our knowledge, the current study, unlike its predecessors, was not limited to exploring the relationship between two variables (e.g., WMHs−depression or WMHs−BADL). It is the first study to longitudinally examine the relationship among three variables and the role of depression as a mediator. This current study verified that depression mediates the development of dysfunction in the BADL in patients with WMHs and dementia, suggesting a pathway that can predict the pathogenesis of severe depression. Additionally, this suggests that patients with white matter lesions are likely to experience depression at some point during the process of deterioration in daily living function.

Interestingly, the direct effect of DWMHs on the BADL and their indirect effect via depressive symptoms were both significant, and both were insignificant in the case of PWMHs. Specifically, the indirect effect of DWMHs on the BADL via depression was significant, whereas the indirect effect of PWMHs on the BADL via depression was not significant. First, the significant indirect effect of DWMHs on the BADL mediated via depression suggests that patients undergoing alterations in the DWMHs leading to worsening of the BADL may experience depressive symptoms. The results of this study, which showed that depressive symptoms mediate the pathway leading to functional impairment due to DWMHs, provide an understanding of the nature of the depressive symptoms experienced by patients with dementia. In other words, considering that impairment in daily living function is an important component of dementia, and the results of this study are in line with the argument that depressive symptoms should be considered as prodromal symptoms for dementia.[33,34] On the other hand, our results suggest that the problems of patients with depression are not limited to emotional distress, but may also include the possibility that depression may lead to impairment in the performance of daily activities. This indicates the need to consider the possibility that elderly patients suffering from depressive symptoms in clinical settings have dementia with imminent functional impairment. Furthermore, after 2 years of follow-up, the direct effect of DWMH on the BADL retained statistical significance, after controlling for the effect of depressive symptoms on the BADL. This suggests the possibility that not only depressive symptoms but other mediator variables can also sufficiently contribute to the decline in basic daily life function. In other words, variables not considered in this study, such as decreased memory and cognitive function, including impaired concentration (as observed in previous studies), can also be predictive factors for the decline in the BADL in elderly patients with dementia.[35] Second, this study showed that both the direct effect of PWMHs on the BADL and indirect effect of PWMHs on the BADL, as mediated via depression, were not significant. Since little is known about the differential effects of specific WMHs on BADL, these results, which showed that only the pathway from DWMHs to BADL, and not PWMHs, had a significant mediation effect on depression, may not be explained adequately. Nevertheless, the analysis of these results from a neu-

rostructural perspective reveals that ischemic SVD, a known risk factor for depression, possesses a stronger association with DWMHs than that with PWMHs. On the other hand, PWMHs are known to be mainly affected by chronic hemodynamic insufficiency, including hypotension and atrophy. This suggests that DWMHs have a stronger association with depressive symptoms originating from SVD than PWMHs. Therefore, although it may be difficult to consider that impairment in daily living function is directly related to specific areas of the brain, it is plausible that only the pathway from DWMHs to BADL is mediated significantly via depressive symptoms. However, further studies focusing on specific neural pathways and regions are needed to elucidate the effect of region-specific WMH on BADL.

Although previous studies have shown that WMHs have a significant effect on the decline in daily living function, no study has investigated whether it is longitudinally associated with depressive mediation for BADL. Moreover, only a few studies have examined both lesions by classifying WMHs into two subtypes. This study is the first to report that not only DWMHs but PWMHs also longitudinally affect the BADL through depressive symptoms. On the other hand, this study found that the indirect effect of PWMHs on the BADL mediated by depression was not significant, which is in line with the results of previous studies that found that the mediation effect of depression on PWMHs and cognitive function was not significant.[7,35] Previous studies have only investigated the direct effect or relevance of DWMHs or PWMHs with respect to depression, or depression with respect to BADL; however, this study also examined the indirect effects mediated by depression. Moreover, it sought and verified a clear developmental pathway by accumulating two years of longitudinal data. Previous studies set independent variables as a single factor without dividing WMHs into subtypes. In this study, not only DWMHs but also PWMHs were set as independent variables to explore various relationships between the variables.[8,15] Our study also investigated whether white matter lesions mediated depressive symptoms in the process of affecting the BADL, whereas previous studies only investigated whether the effects of white matter lesions on BADL were modulated by depressive symptoms.[8,15] In other words, the current study found that white matter lesions were predictive of BADL dysfunction, akin to previous studies, while offering an important and new perspective supported by a longitudinal investigation of the role of depressive symptoms (which was not reported by any prior study). By discovering a longitudinal pathway from white matter lesions through depressive symptoms to the development of dementia, the findings of this study expand the understanding of the developmental pathology of dementia beyond existing evidence. Furthermore,

since the sample population of this study was relatively large, including those with AD and AD with SVD, its results can be applied to patients with VD. Further studies focusing on specific routes and regions are needed to explain the effects of specific WMHs.

This study has several limitations. First, cognitive decline, another key feature of dementia, was not evaluated in this study. Studies involving variables such as cognitive dysfunction and ADL decline are warranted to accurately verify the pathogenetic pathway from the WMHs to dementia through depression. Second, although the large sample size can be considered to have contributed to the significance of the current results, it may overestimate the actual effect. To compensate for this overestimation, the significance and effect size were calculated. It should also be considered that large sample sizes can improve statistical power and provide reliable and repeatable results. Finally, this study assessed the severity of depression on a continuous basis instead of a diagnosis of major depressive disorder. Therefore, further research is needed to determine whether these results are also applicable to patients with clinical depression.

This study presented a mediation model that yielded important information on the respective pathological pathways connecting two types of WMHs with depressive symptoms, and BADL function beyond the framework of previous research. This study presented a mediation model including a longitudinal developmental pathway from DWMHs to BADL through depressive symptoms. It also found that the mediation model via depressive symptoms could not be applied to the longitudinal developmental pathway from DWMHs to BADL.

Availability of Data and Material
The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Do Hoon Kim. Formal analysis: Chang Hyun Lee. Supervision: Do Hoon Kim. Writing—original draft: Hye Won Jeong, Chang Hyun Lee. Writing—review & editing: Hye Won Jeong.

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