Higher HbA_{1c} is Associated with Greater Two-Year Progression of White Matter Hyperintensities

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Running title: WMH and HbA_{1c}

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Abstract

White matter hyperintensity (WMH) lesions on brain MRI images are surrogate markers of cerebral small vessel disease (CSVD). Longitudinal studies examining the association between diabetes and WMH progression have yielded mixed results. Thus, in this study we investigated the association between HbA_{1c}, a biomarker for the presence and severity of hyperglycemia, and longitudinal WMH change after adjusting for known risk factors for WMH progression. We recruited 64 participants from South Korean memory clinics to undergo brain MRI at the baseline and a two-year follow-up. We found: First, higher HbA_{1c} was associated with greater global WMH volume (WMHV) changes after adjusting for known risk factors (B = 7.7E-04, $p = 0.025$); Second, the association between baseline WMHV and WMHV progression was only significant at diabetic levels of HbA_{1c} ($p < 0.05$, when $HbA_{1c} > 6.51\%$), and non-APOE ε4 carriers showed a stronger association between HbA_{1c} and WMHV progression (B = -2.59E-03, $p = 0.004$); Third, associations of WMHV progression with HbA_{1c} were particularly apparent for deep WMHV change (B = 7.17E-04, $p < 0.01$) compared to periventricular WMHV change, and for frontal (B = 5.00E-04, $p < 0.001$) and parietal (B = 1.534-04, $p < 0.05$) WMHV change compared to occipital and temporal WMHV change. In conclusion, higher HbA_{1c} levels were associated with greater two-year WMHV progression, especially in non-APOE ε4 participants or those with diabetic levels of HbA_{1c}. These findings demonstrate that diabetes may potentially exacerbate cerebrovascular and white matter disease.

Article Highlights

- How diabetes contributes to cerebral small vessel disease (CSVD) and dementia has not yet been fully clarified.
- We investigated the association between HbA_{1c}, a biomarker for the presence and severity of hyperglycemia, and longitudinal WMH change after adjusting for known risk factors for WMH progression.
- Higher HbA_{1c} levels were associated with greater two-year WMHV progression.

Cerebral small vessel disease (CSVD) is a leading cause of cognitive decline, functional loss, and disability in older adults. White matter hyperintensity (WMH) lesions on brain MRI are surrogate markers of CSVD. It is necessary to examine the factors associated with longitudinal WMH growth in order to better understand the disease mechanisms and inform the strategy to prevent and/or treat cognitive decline (1). Diabetes is a chronic macrovascular risk factor for white matter change (2). Diabetes can be a target for intervention because it may induce changes in vascular integrity and function and brain structure. However, not every person with diabetes has WMH, suggesting that WMH burden might also be related to other vascular factors and genetic variations. Vascular factors affecting WMH growth include thyroid function (3), hypertension (4), obesity (5), and amyloid burden (6). Apolipoprotein E (APOE) ε4 allele, the strongest genetic risk factor for Alzheimer's disease (AD), also affects the pathomechanistic pathways of CSVD and likely shares common mechanisms with diabetes (7). However, how the relationship between diabetes and APOE contributes to CSVD and even dementia has not yet been fully clarified, despite some clinical observations (7-10).

Thus, it's necessary to examine the effects of diabetes on CSVD while considering other vascular and genetic factors to inform the precise approach for the prevention and treatment of dementia. In this study, we investigated the association between HbA_{1c}, a glycemic status marker of diabetes, and longitudinal WMH changes after controlling for other cardiovascular factors. As an exploratory analysis, we also evaluated how this relationship could be affected by the APOE genotype and how it differed according to the baseline WMH lesions.

Research Design and Methods

Participants

This study was a part of the ongoing Biobank Innovations for Chronic Cerebrovascular Disease With ALZheimer's Disease Study (BICWALZS) and the Centre for Convergence Research of Neurological Disorders (Clinical Research Information Service; identifier, KCT0003391). More information on the BICWALZS can be found in the supplemental material. Participants from the BICWALZS were recruited at the memory clinics of Ajou University Hospital and Suwon Community Geriatric Centers in South Korea. The presence or absence of diabetes, hypertension, and hyperlipidemia were based on the clinical history of being treated under the diagnosis by a physician. Patients with a history of neurological or medical conditions, such as territorial cerebral infarction, intracranial hemorrhage, Parkinson's disease, heart failure, renal failure, or other conditions that could interfere with the study, were excluded. Information on the methods for clinical diagnosis criteria, blood sampling and laboratory assessments, and APOE genotyping used for this study can be found in Expanded Methods in the supplemental material. Among the individuals in the above cohort, we used data from 64 participants including brain MRI, APOE, and blood laboratory assessments, including HbA_{1c}.

Amyloid PET acquisition and measurement of amyloid deposition

The participants underwent the same protocol for ^{18}F-flutemetamol PET scanning using a Discovery STE/690 PET/CT scanner (GE, Milwaukee, WI, USA). ^{18}F-flutemetamol was injected into the antecubital vein as a bolus (mean dose, 185 MBq). After 90 min, a 20-min PET scan (4 × 5 min dynamic frames) was performed. Information on the methods to quantify ^{18}F-flutemetamol

retention based on the standard uptake value ratio (SUVR) can be found in the Expanded Methods in the supplemental material.

MRI data acquisition and processing for white matter hyperintensities

Participants completed MRI scans on GE Discovery MR750w 3T scanners, including the following two sequences: a three-dimensional (3D) magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted sequence and a T2-weighted (T2w) fluid-attenuated inversion recovery (FLAIR) sequence. The MRI sequence parameters are listed in Supplemental Table S1. An automated method to segment WMH on T2w FLAIR images was used based on our previous studies (11; 12). We generated regional cortical white matter masks for the frontal, parietal, occipital, and temporal lobes. We investigated additional models of regional WMHs using lobular cortical and deep/periventricular masks. The total WMH volume (WMHV) and regional WMHV was normalized by the intracranial volume and log-transformed for analysis. WMHV change was calculated as the difference between the normalized, log-transformed WMHV at the follow-up and baseline. Extended information on the methods for automated WMH segmentation and generation of regional white matter masks can be found in the supplemental material.

Statistical analysis

The relationship between HbA_{1c} and WMHV changes was tested using linear regression models. Covariates included demographics (age and sex), body mass index (BMI), and cardiovascular risks (systolic and diastolic blood pressure, low-density and high-density lipid

levels, smoking status). Given the collinearity among blood pressure and lipid variables, one blood pressure variable and one lipid variable (selected based upon its association with WMHV change) were included in the models. Age, BMI, baseline WMHV, and HbA_{1c} were included in the models as covariates *a priori*. The main analysis included three models: main effects associated with diabetes plus baseline WMHV, main effects of diabetes plus baseline WMHV and cardiovascular risk factors, and an exploratory model examining covariates strongly associated with diabetes: APOE ε4 status, baseline WMHV, and their interaction effects on HbA_{1c}. We then applied the Johnson–Neyman technique and generated a Johnson–Neyman plot to probe and visualize the conditional effect of HbA_{1c} on WMHV change versus baseline WMHV (13). For regional WMHV change analysis, we analyzed model 1 (diabetes main effects) and the exploratory model (diabetes main effects + APOE ε4 status, baseline WMHV). Secondary analyses were conducted to consider the effect of thyroid-stimulating hormone (TSH), amyloid burden (global ^{18}F-flutemetamol SUVR) and scanner site on WMHV change, respectively. Statistical analyses were performed using R (https://www.R-project.org).

Data and resource availability

The datasets generated during and/or analyzed in the current study are available from the corresponding author upon request.

Results

The characteristics of our participants are listed in Table 1. Among the 64 participants, 73.02% were female. Participants' average age was 72.13 years old, and the average number of years of education was 8.20 years. Regarding underlying diseases, 50% had hypertension, 18.75% had diabetes mellitus (all of which were on diabetes medication), and 32.18% had hyperlipidemia. The proportion of the participants with clinical diagnoses of MCI or dementia (AD or other) was 75.00% or 21.88%, respectively.

We tested the relationship between HbA_{1c} levels and WMHV changes (Fig. 1). We first tested the relation between HbA_{1c} and WMHV change in a model of diabetes main effects, and observed that higher HbA_{1c} was associated with larger WMHV change (Model 1, p=0.004) (Table 2). We then tested an additional model for diabetes main effects controlling for cardiovascular risk factors, and found that HbA_{1c} maintained a significant positive correlation with WMHV change (p=0.0023). In our secondary analyses, we considered two models that tested diabetes main effects while controlling for TSH, amyloid burden, or scanner site, respectively. In each model we observed that HbA_{1c} maintained a significant effect (p=0.0013, 0.025, 0.0042, respectively) (data not shown).

In our exploratory model examining HbA_{1c} in relation to WMHV change, we tested for the main covariates associated with diabetes, and HbA_{1c}'s interaction effect with APOE ε4 status and baseline WMHV (Table 2). We observed a significant interaction between HbA_{1c} and APOE ε4 status (p=0.0042) and baseline WMHV (p=0.013). APOE ε4 non-carriers were observed to have a stronger correlation between HbA_{1c} and WMHV changes than APOE ε4 carriers (Supplemental Figure S1). The Johnson–Neyman analysis (Fig. 2) indicated that the association between WMHV change and baseline WMHV became stronger as HbA_{1c} levels increased, becoming significant (p<0.05) at an HbA_{1c} of 6.51%.

Several additional analyses were conducted to observe how HbA_{1c} spatially correlates with WMHV change (Supplemental Table S2) using Model 1 (diabetes main effects) and exploratory model (diabetes main effects + interactions between HbA_{1c} and APOE ε4 status, baseline WMHV). Deep WMHV change showed a significant, positive correlation in both models with HbA_{1c} (p=0.0024 for Model 1 and p=0.0004 for final model). Meanwhile, periventricular WMHV change was not significantly correlated with HbA_{1c} in either model (p=0.0721 for Model 1 and p=0.1511 for exploratory model). In the exploratory model, the interaction between HbA_{1c} and APOE ε4 status was significant for both deep (p=0.0037) and periventricular (p=0.031) WMHV changes. The interaction between HbA_{1c} and baseline WMHV was only significant for deep WMHV changes (p=0.0026, in contrast to p=0.3131 for periventricular). When testing the spatial relationship in each lobe, we observed that the frontal and parietal WMHV changes were significantly correlated with HbA_{1c} and its interaction with APOE ε4 status and baseline WMHV, while no correlation or effects were observed in the occipital and temporal lobes.

Discussion

This study has three main findings. First, a higher HbA_{1c} was associated with greater global WMHV expansion. This association persisted after adjusting for a range of covariates including cardiovascular risk factors, thyroid health measures, and amyloid burden. Second, HbA_{1c} had a significant interaction with the baseline WMHV and APOE ε4 allele status. The association of baseline WMHV with WMHV progression became significant only as HbA_{1c} approached the glycemic level. In addition, APOE ε4 non-carriers showed a stronger association between HbA_{1c} and WMHV progression. Third, the associations between HbA_{1c} and WMHV change were evident

in deep WMH compared to periventricular WMH and were evident for the frontal and parietal WMHV change compared to the occipital and temporal WMHV change.

Our study emphasizes the importance of managing diabetic health to improve brain health outcomes. Several cross-sectional studies have observed an association between diabetes and WMHV (14-16); however, longitudinal studies investigating this association have yielded divergent findings (17-21). Our study agrees with the recent findings of a 6-year prospective study of an elderly cohort, which observed faster WMHV accumulation in prediabetes and diabetes (17). Furthermore, numerous studies have shown that a greater baseline WMHV was associated with greater WMHV progression, yet we observed that it was significant only as HbA_{1c} approached the diabetic level (6.51%). Our study utilized a continuous measure of HbA_{1c} as opposed to categorizing participants (healthy, prediabetic, and diabetic), yet our findings still align well with the traditional cutoff for clinical diabetes diagnosis (22). A greater WMHV is a surrogate for CSVD; thus, this interaction highlights how diabetes may exacerbate poor cerebrovascular health.

We also observed that the change in WMHV was more strongly associated with HbA_{1c} in participants who did not carry APOE ε4 allele. The relationship between diabetes and the APOE genotype in contributing to CSVD and dementia has yet been clarified. In one study, APOE ε4 carriers were associated with long-term memory decline, a cognitive deficit strongly correlated with conversion to AD, whereas diabetes correlated with impairment of working memory and a weak correlation with conversion to AD. Diabetes did not exacerbate the risk of AD in APOE ε4 carriers (10). Another study showed that diabetes was associated with earlier deterioration of cognitive function and increased vascular pathology scores in APOE ε3 carriers but not in APOE ε4 carriers (7). Aligning with this study, we found that HbA_{1c} had a more significant effect on

CSVD progression in APOE E4 non-carriers. Future studies examining this mechanistic pathway is warrant.

This study also has some limitations. Our modest sample size (N = 64) might have not enabled us to display the full effects of each variable tested, particularly HbA_{1c}'s effect since there were a limited number of participants diagnosed with diabetes. Our participants were recruited from a clinical cohort with cognitive impairments and thus might not be representative of the general population. Additionally, other potential risk factors for WMHV progression and CSVD could interact on a different timescale; thus, a two-year interval between MRI scans might have not been enough to display their effects. We did not have information on diabetes nor antihypertensive medication which might have also impacted the results. While the Johnson-Neyman technique helps visualize its complexity, the method could not capture the full extent of the nonlinear relationship that might occur between baseline WMHV and HbA_{1c} on WMHV progression. Finally, survival bias might have partially contributed to our findings.

Future studies should examine how hyperglycemia impacts other MRI biomarkers of CSVD and whether treatment of diabetic health can attenuate WMHV progression.

In conclusion, our findings demonstrate the potential effects of hyperglycemia on cerebrovascular health.

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acquisition of imaging data; S.W.S.: acquisition of data; J.Y.C.: study coordination; Y.H.C.: data verification; Y-S.A.: data acquisition and verification; S.Y.M.: data acquisition; S.J.H.: critical review.

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Table 1. Participant Characteristics

N	64
Age at first scan, M (SD)	72.13 (7.54)
Female, N (%)	46 (73.02)
Years of education, M (SD)	8.20 (4.54)
BMI, M (SD)	23.90 (3.71)
Cardiovascular Risk Factors	
SBP, mmHg, M (SD)	135.52 (22.05)
DBP, mmHg, M (SD)	76.13 (11.28)
LDL-C, mg/dL, M (SD)	89.63 (31.37)
HDL-C, mg/dL, M (SD)	55.50 (14.60)
Smoking Status, N (%)	12 (18.75)
HbA_{1c}, % mmol/mol, M (SD)	5.91 (0.73)
TSH, mIU/L, M (SD)	2.19 (1.53)
Global18F-flutemetamol SUVR, M (SD) §	0.69 (0.15)
APOE ε4 positive, N (%) ‡	19 (29.69)
WMHV at baseline, M (SD) †	-5.25 (0.96)
Change in WMHV, M (SD) †	1.97E-03 (7.80E-04)
Comorbidity, N (%)	
Hypertension	32 (50.00)
Diabetes mellitus	12 (18.75)
Hyperlipidemia	21 (32.81)
Clinical Diagnosis, N (%)	

Healthy	0 (0)
SCD	2 (3.13)
MCI	48 (75)
AD or other dementia	14 (21.88)

Unless otherwise indicated

§ ^{18}F-flutemetamol SUVR was available for 61 of 64 participants.

†WMHV expressed as log(cm^3/Intracranial volume)

‡ *APOE* ε4 positive: 2/4, ¾, 4/4

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; WMHV, white matter hyperintensity volume; TSH, thyroid-stimulating hormone; SCD, subjective cognitive decline; MCI, mild cognitive impairment; AD, Alzheimer's disease; SUVR, standard uptake value ratio; APOE, apolipoprotein E

Table 2. Multiple linear regression analysis of associations of change in normalized White Matter Hyperintensity volume (WMHV) with HbA_{1c}.

	Dependent Variable: Change in WMHV		
Independent variables	β	Std. error	*P*-value
Model 1 (diabetes main effects)			
HbA_{1c}	1.06E-03	3.57E-04	0.0042**
Model 2 (Model 1 + Cardiovascular Risks)			
HbA_{1c}	1.10E-03	3.46E-04	0.0023**
Model 3 (exploratory)			
HbA_{1c}	6.83E-03	2.14E-03	0.0024**
APOE ε4 positive	1.42E-02	4.90E-03	0.0053**
WMHV at first scan	-6.04E-03	2.4E-03	0.015*
HbA_{1c} * APOEε4 positive	-2.59E-03	8.66E-04	0.0042**
HbA_{1c} * WMHV at first scan	1.05E-03	4.08E-04	0.013**

*$p < 0.05$; **$p < 0.01$

Model 1: Adjusted for age at baseline, sex, BMI, and baseline WMHV; Model 2: Model 1 + HDL, SBP, and smoking status; Model 3: Model 1 + interaction effects between baseline WMHV, HbA_{1c} and APOEε4, HbA_{1c}

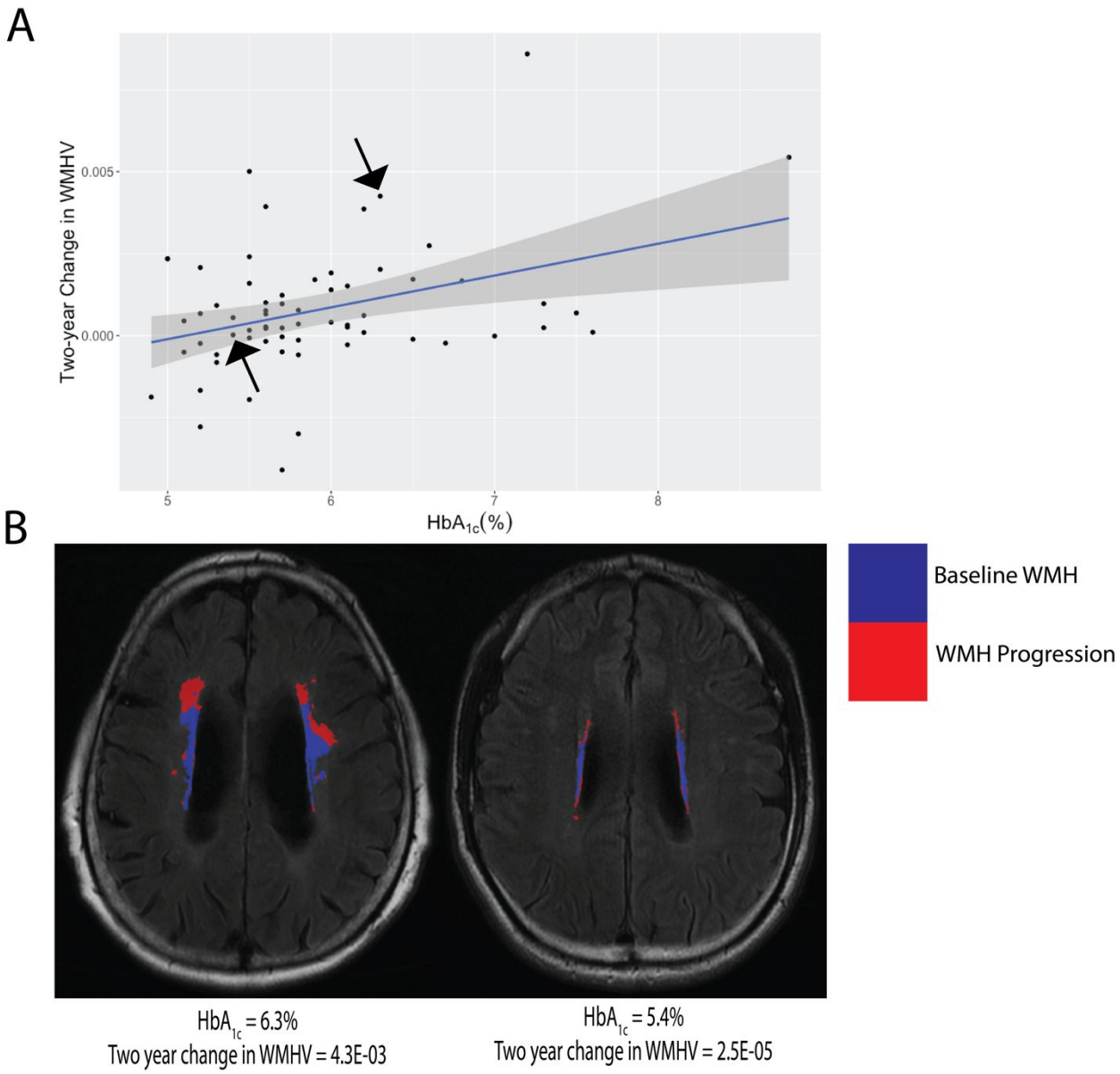
Adjusted R^2 values: Model 1, $R^2 = 0.082$; Model 2, $R^2 = 0.17$; Model 3, $R^2 = 0.19$

BMI, body mass index; HDL, high-density lipoprotein; SBP, systolic blood pressure; WMHV= white matter hyperintensity volume

Figure Legends

Figure 1. A) HbA_{1c} is significantly associated with two-year WMHV progression. The two black arrows represent the two participants shown in panel B. B) MRI scans of two individual participants. White matter hyperintensity from the first scan was registered and overlayed with the second scan and its WMH to display the WMH progression over two-years. One participant had high HbA_{1c}, WMHV, and WMHV change, and the other had low HbA_{1c}, WMHV, and WMHV change. Shaded area represents 95% confidence interval.
WMHV= white matter hyperintensity volume

Figure 2. Baseline WMHV is significantly associated with WMHV progression but only as HbA_{1c} approaches diabetic levels. The association between WMHV change and baseline WMHV becomes stronger as HbA_{1c} level increases, becoming significant ($p < 0.05$) at an HbA_{1c} of 6.51%. Shaded area represents 95% confidence interval.
APOE=apolipoprotein E, WMHV= white matter hyperintensity volume



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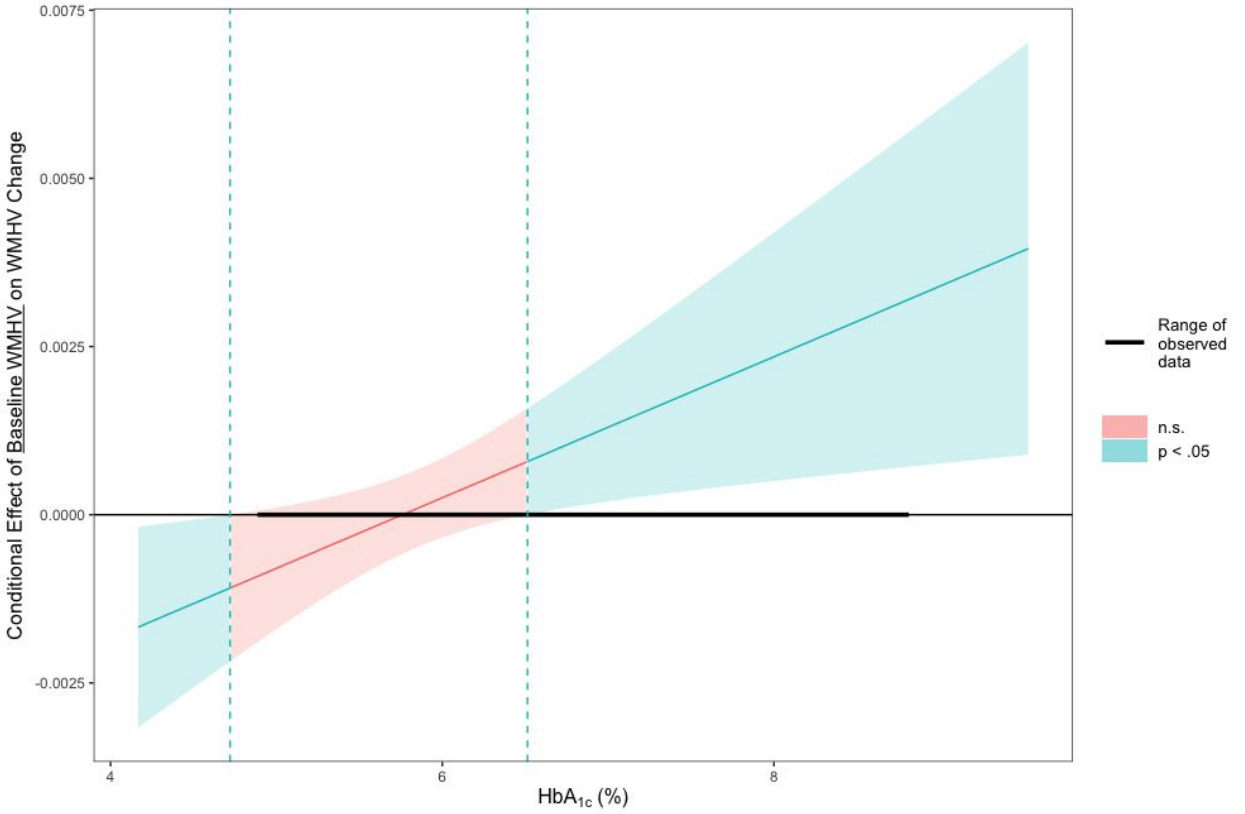

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APOE=apolipoprotein E, WMHV= white matter hyperintensity volume

Online-Only Supplemental Material

Expanded Methods

Biobank Innovations for Chronic Cerebrovascular Disease With ALZheimer's Disease Study (BICWALZS)

Biobank Innovations for Chronic Cerebrovascular Disease With ALZheimer's Disease Study (BICWALZS) and the Centre for Convergence Research of Neurological Disorders.

BICWALZS study is registered in the Korean National Clinical Trial Registry (Clinical Research Information Service; identifier, KCT0003391). The BICWALZS study was planned and initiated in October 2016 by the Korea Disease Control and Prevention Agency for the Korea Biobank Project. The study was approved by the Institutional Review Board of Ajou University Hospital (AJOUIRB-SUR-2021-038). Written informed consent was obtained from all the participants and caregivers.

Clinical Diagnosis Criteria

The clinical diagnosis criteria used for this study were as follows: SCD criteria included self- and/or informant reports of cognitive decline but no objective impairment in cognitive tasks (no less than -1.5 SD in each of the neurocognitive test domains and Clinical Dementia Rating [CDR]=0) (Molinuevo JL et al. Alzheimers Dement 2017;13:296-311); patients with MCI were evaluated based on a CDR (Morris JC. Neurology 1993;43:2412-2414) score of 0.5, the expanded Mayo Clinic criteria (Winblad B et el al. Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240-246); patients with AD dementia were evaluated using the National Institute on Aging-Alzheimer’s Association Core Clinical Probable AD Dementia Criteria (McKhann GM et al. Alzheimers Dement 2011;7:263-269); and subcortical vascular

dementia (SVaD) was evaluated based on above-moderate WMH and vascular dementia criteria in accordance with the Diagnostic Statistical Manual of Mental Disorders, fifth edition (Association AP. American Psychiatric Association Publishing, 2013).

Blood sampling and laboratory assessments

Blood samples were collected by venipuncture after an overnight fast in the morning. Blood laboratory tests included HbA_{1c}, serum lipid, and thyroid function tests.

APOE genotyping

Informed consent was obtained from all participants regarding the collection and genotyping of blood genomic DNA. Genomic DNA was isolated from the blood samples, and single-nucleotide polymorphism (SNP) genotyping was performed by DNA Link, Inc. (Seoul, Korea) using the Affymetrix Axiom KORV1.0-96 Array (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's protocol. The APOE genotypes were derived from rs429358 and rs7412, which were included in the array.

MR data processing for white matter hyperintensities

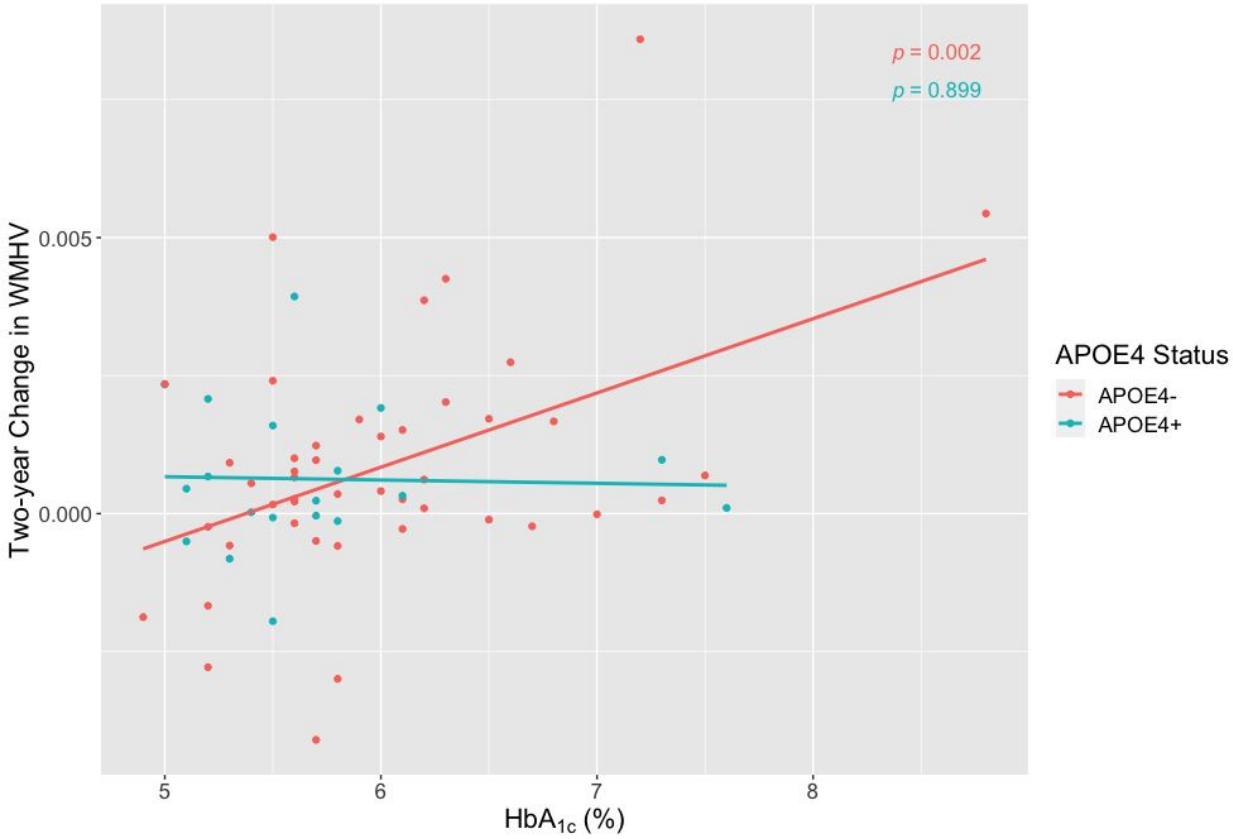
An automated method to segment WMH on T2w FLAIR images was used based on our previous study. Cerebral and cerebellar WM were segmented on the T1w image and mapped to the T2w FLAIR image space using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) and FreeSurfer (version 7.1.1, https://surfer.nmr.mgh.harvard.edu/). The mean and SD of the cerebellar WM were used to

Z-transform the T2w FLAIR image (Z-T2w FLAIR) because there were very few lesions in the cerebellum in our sample. Using Z-T2w FLAIR images, voxels were identified as WMH if the z-score was ≥ 2 and within the cerebral WM mask.

We then investigated additional models of regional WMHs using lobular cortical and deep/periventricular masks by parcellating cortical white matter voxels according to their nearest cortex with the Deskian/Killiany atlas in FreeSurfer. The cortical white matter masks corresponding to each lobe did not overlap and were summed to create an overall cortical/deep white matter mask. The periventricular white matter mask was composed of white matter surrounding the ventricles that was not part of deep white matter mask.

Amyloid PET measurement of amyloid deposition

^{18}F-flutemetamol PET images were co-registered to individual MRI images, which were normalized to a T1-weighted MRI template using transformation parameters. To quantify ^{18}F-flutemetamol retention, the standard uptake value ratio (SUVR) was obtained using the pons as the reference region. Global cortical ^{18}F-flutemetamol retention was calculated using an automated anatomical labeling (AAL) atlas.



Supplemental Figure S1. Non-APOE ε4 carriers show a stronger association between HbA_{1c} and WMHV progression.

APOE=apolipoprotein E, WMHV=white matter hyperintensity volume (normalized)

Supplemental Table S1. MRI and PET parameters according to the study site

	Site	Vendor	Acquisition matrix	voxel size (mm)	Repetition time (sec)	Echo time (msec)	flip angle (^{0})	slice thickness (mm)	machine
3D-T1w	1	[GE]	256 x 256 512 x 512	0.39 x 0.39 0.78 x 0.78	7.1-9.9	2.8-4.8	12	1	GE Discovery MR750w
	2	[GE]	256 x 256	0·88 x 0·88	7·5-8·6	2·8-3·3	12	1	GE DISCOVERY MR750w
T2w-FLAIR	1	[GE]	512 x 512	0.39 x 0.39	9.7	125	160	5	GE Discovery MR750w
	2	[GE]	512 x 512	0·39 x 0·39	11	125	173	5	GE DISCOVERY MR750w
	Site	**Vendor**	**Acquisition matrix**	**voxel size (mm)**	**Tracer**				**machine**
PET	1	[GE]	128 x 128 x 47	1.9531-2, 1.9531-2	Flutemetamol				GE Discovery STE
	2	[GE]	128 x 128 x 47	1.9531-2, 1.9531-2	Flutemetamol				GE Discovery STE

MRI, magnetic resonance imaging; PET, positron emission tomography; 3D-T1w, three-dimensional whole-brain T1-weighted imaging; T2w-FLAIR, T2-weighted fluid-attenuated inversion recovery imaging.

1. **Supplemental Table S2**. Multiple linear regression analysis for associations of regional White Matter Hyperintensity volume (WMHV) changes.

	Change in regional WMHV					
	Deep B(SE)	Periventricular B(SE)	Frontal B(SE)	Occipital B(SE)	Parietal B(SE)	Temporal B(SE)
Model 1: Diabetes' main effects						
HbA_{1c}	**6.38E-04 (2.03E-04)****	3.81E-04 (2.09E-04)	**4.01e-04 (1.20E-04)****	6.43E-05 (3.40E-05)	**1.45E-04 (5.58E-05)***	2.73E-05 (4.67E-05)
Model 3: Model 1 + Exploratory						
HbA_{1c}	**4.49E-03 (1.19E-03)*****	1.91E-03 (1.31E-03)	**3.04E-03 (6.92E-04)*****	**4.45E-04 (2.11E-04)***	**9.95E-04 (3.36E-04)****	1.64E-05 (2.97E-04)

APOE ε4 positive	**7.81E-03 (2.73E-03)****	**6.64E-03 (3.00E-03)***	**3.96E-03 (1.58E-03)***	**1.07E-03 (4.82E-04)***	**2.24E-03 (7.68E-04)****	5.34E-04 (6.80E-04)
WMHV at scan 1	**-4.07E-03 (1.34E-03)****	-1.45E-03 (1.47E-03)	**-2.91E-03 (7.77E-04)*****	-3.72E-04 (2.37E-04)	**-8.83E-04 (3.77E-04)***	9.37E-05 (3.33E-04)
HbA_{1c} *APOE ε4 positive	**-1.462E-03 (4.82E-04)****	**1.18E-03 (5.30E-04)***	**-7.46E-04 (2.80E-04)***	**-1.99E-04 (8.52E-05)***	**-4.07E-04 (1.36E-04)****	-1.11E-04 (1.20E-04)
HbA_{1c} *WMHV at scan 1	**7.17E-04 (2.28E-04)****	2.54E-04 (2.45E-04)	**5.00E-04 (1.32E-04)*****	6.86E-05 (4.01E-05)	**1.534-04 (6.39E-05)***	-5.06E-06 (5.66E-05)

*$p < 0.05$; **$p < 0.01$, ***$p < 0.001$

Model 1: Adjusted for age at baseline, sex, BMI, and baseline WMHV; Model 3: Model 1 + interaction effects between baseline WMHV, HbA_{1c} and APOEε4, HbA_{1c}

Adjusted R^2 values:

Model 1 Deep WMHV, $R^2 = 0.12$; Model 1 Periventricular WMHV, $R^2 = 0.0067$; Model 1 Frontal WMHV, $R^2 = 0.17$; Model 1 Occipital WMHV, $R^2 = -0.011$; Model 1 Parietal WMHV, $R^2 = 0.061$; Model 1 Temporal WMHV, $R^2 = -0.035$

Model 3 Deep WMHV, $R^2 = 0.26$; Model 3 Periventricular WMHV, $R^2 = 0.26$; Model 3 Frontal WMHV, $R^2 = 0.32$; Model 3 Occipital WMHV, $R^2 = 0.23$; Model 3 Parietal WMHV, $R^2 = 0.17$; Model 3 Temporal WMHV, $R^2 = -0.026$

APOE=apolipoprotein E, WMHV=normalized white matter hyperintensity volume, BMI = Body Mass Index