Cardiovascular Risk Factors Cause Cortical Thinning in Cognitively Impaired Patients

Relationships Among Cardiovascular Risk Factors, White Matter Hyperintensities, and Cortical Atrophy

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Abstract: Cardiovascular risk factors are associated with cognitive impairments. However, the effects of cardiovascular risk factors on the topography of cortical thinning have not yet been studied in patients with mild cognitive impairment (MCI) or dementia. Thus, we aimed to evaluate the topography of cortical thinning related to cardiovascular risk factors and the relationships among cardiovascular risk factors, white matter hyperintensities (WMH), and cortical atrophy. Participants included 226 patients with Alzheimer disease or subcortical vascular dementia and 135 patients with amnestic MCI or subcortical vascular MCI. We automatically measured the volume of WMH and cortical thickness. Hypertension was associated with cortical thinning in the frontal and perisylvian regions, and cortical thinning related to diabetes mellitus (DM) occurred in the frontal region. In path analyses, hypertension accounted for 0.04 of the frontal thinning with the mediation of WMH and 0.16 without the mediation of WMH. In case of DM, it accounted for 0.02 of the frontal thinning with the mediation of WMH and 0.13 without the mediation of WMH. Hypertension and DM predominantly affected frontal thinning both with and without the mediation of WMH, where the effects without the mediation of WMH were greater than those with the mediation of WMH.

Key Words: hypertension, diabetes mellitus, hyperlipidemia, white matter hyperintensities, cortical thickness

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Cardiovascular risk factors are closely associated with vascular dementia or vascular mild cognitive impairment (MCI).[1] More specifically, these risk factors play important roles in producing multiple territorial infarctions, resulting in multi-infarct dementia.[1] Alternatively, these risk factors often produce small vessel diseases, which manifest on magnetic resonance images (MRIs) as white matter hyperintensities (WMH), and lacunes, resulting in subcortical vascular dementia (SVaD) or its prodromal stage, namely, subcortical vascular MCI (svMCI).[1]

Recent studies have shown that cardiovascular risk factors are also implicated in Alzheimer disease (AD) and its prodromal stage, amnestic type of MCI (aMCI).[2] First, it was reported that the risk factors trigger Alzheimer changes per se.[3] In line with these results, recent pathologic studies have shown that individuals with risk factors had more AD pathologies compared with those without risk factors.[3,4] Second, these risk factors add small vessel pathology to the underlying degenerative processes, leading to the comorbidity of Alzheimer and vascular changes.[5] Therefore, patients with AD or aMCI with cardiovascular risk factors commonly have some degree of WMH, quite often to such a great extent that the distinction between AD and SVaD or that between aMCI and svMCI is impossible. Third, patients with AD or aMCI who have risk factors show more rapid progression compared with those without. Therefore, evaluations of cardiovascular risk factors are important in the spectrum of both aMCI/AD and svMCI/SVaD, especially as these risk factors can be modified.

Cortical atrophy is one of the most important factors representing the severity of svMCI/SVaD and aMCI/AD.[6,7] Cortical changes in AD[6] have correlated significantly with cognitive impairments and disease severity. Previous studies have also shown that a reduction in gray matter volume might occur in SVaD[8,9] and that a hierarchy exists between svMCI and SVaD in terms of the amount and topography of cortical thinning.[7]

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Despite the important role of cardiovascular risk factors in cognitive impairment in patients with MCI or dementia, effects of cardiovascular risk factors on the topography of cortical thinning have not yet been studied in these patients. Previous studies involved cognitively normal individuals and investigated the effect of hypertension[10] or diabetes mellitus (DM) on the topography of cortical atrophy[11,12] or regional glucose hypometabolism.[13] Furthermore, these studies did not look at the relationship among cardiovascular risk factors, WMH, and cortical atrophy.[14–16] It is well known that cardiovascular risk factors are associated with WMH.[1,14] Recent studies have also suggested that WMH correlated with cortical atrophy.[17,18] This raises the question whether cardiovascular risk factors cause cortical thinning with the mediation of WMH in patients on the spectrum of aMCI/AD or svMCI/SVaD. Alternatively, it is possible that these risk factors might cause cortical atrophy without the mediation of WMH through other possible mechanisms such as cortical ischemia or AD pathologies.[3,9]

In this study, we aimed to evaluate the topography of cortical thinning related to cardiovascular risk factors, using a surface-based cortical thickness measurement (surface-based morphometry, SBM). The VBM can measure volume changes both in cortical gray matter and subcortical structures, but SBM measures only cortical changes. However, SBM may be more valid than voxel-based morphometry (VBM) as far as cortical thickness is concerned because it enables more precise measurements in gyri and deep sulci based on the actual thickness of the cortex in millimeters.[6] We also tested our hypothesis regarding the relationships among these risk factors, WMH, and cortical atrophy in a large patient sample with MCI or dementia with varying degrees of Alzheimer or small vessel vascular pathology.

METHODS

Participants

Participants consisted of 385 patients with MCI or dementia who underwent high-resolution T1-weighted volumetric MRI scans, all using the same scanner at Samsung Medical Center, Seoul, Korea, from April 2000 to February 2008. These 385 patients consisted of 109 aMCI, 34 svMCI, 214 AD, and 28 SVaD patients. Diagnostic criteria of these patients have been previously described in detail.[18] In brief, however, the MCI patients all met the Petersen criteria for MCI[19] with our previously described modifications.[15,20] The patients with AD fulfilled the probable AD criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association.[21] The patients with SVaD met the criteria for VaD described by the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition, and also fulfilled the imaging criteria for SVaD as proposed by Erkinjuntti et al.[22] However, as we recruited consecutive patients, some fell between the dichotomy of Alzheimer type and SVaD type—for instance, aMCI or AD patients with moderate ischemia but with focal signs, or svMCI or SVaD patients with severe ischemia but without any focal signs. In this study, we included all these patients rather than dichotomizing the patients into AD and SVaD. However, to include only patients with either Alzheimer pathology or small vessel vascular pathology, we excluded the patients who could represent degenerative dementias other than AD, such as patients who might have idiopathic Parkinson disease, diffuse Lewy body disease, corticobasal degeneration, or progressive supranuclear palsy, and those with territory infarction or hemorrhage.

All patients underwent a clinical interview and neurological examination, as described in previous studies.[20] Each participant's blood tests included a complete blood count, blood chemistry test, vitamin B_{12}/foliate measure, syphilis serology, and thyroid functioning test. Conventional brain MRI scans [T1-weighted, T2-weighted, and fluid attenuated inversion recovery (FLAIR) images] confirmed the absence of structural lesions, such as tumor, traumatic brain injury, or hydrocephalus.

We explored the following vascular risk factors: hypertension (defined as a previous diagnostic history of hypertension or the patient currently taking any antihypertensive medications), DM (defined as a previous diagnosis of DM or the patient currently taking any antidiabetics), and hyperlipidemia (defined as a previous diagnosis of hyperlipidemia or the patient currently taking any lipid-lowering agent). Table 1 presents our patients' clinical characteristics. The study was approved by the Institutional Review Board of the Samsung Medical Center.

Neuropsychological Tests

All patients underwent neuropsychological tests. We used a standardized neuropsychological battery called the Seoul Neuropsychological Screening Battery. The tests included in this battery and the results of these tests have been described in our earlier studies.[23] Age-specific, sex-specific, and education-specific norms for each test, based on 447 normal participants, are available.

TABLE 1. Demographics, Cardiovascular Risk Factors, and WMH

Age, yr (N = 361)	72.1 ± 7.9 (47-89)
Sex, female, n (%) (N = 361)	223 (61.8%)
Education, yr (N = 361)	9.0 ± 5.3 (0-22)
Intracranial volume (N = 361)	1311771.3 ± 127174.5 (999286.7-1785289.4)
Hypertension, n (%) (N = 361)	187 (51.8%)
Diabetes, n (%) (N = 361)	58 (16.1%)
Hyperlipidemia, n (%) (N = 361)	55 (15.2%)
MCI/dementia CDR 0.5/CDR 1/CDR 2+3, n (%) (N = 361)	135(37.4%)/75(20.8%)/110(30.5%)/41(11.4%)
WMH (N = 361)	10880.0 ± 18451.7 (0-118216)

CDR indicates clinical dementia rating; WMH, white matter hyperintensities.

Acquisition of 3-dimensional Volume MRI

We acquired 3-dimensional, T1-weighted, spoiled-gradient echo MRI using the same 1.5-Tesla MRI scanner (GE Signa, Milwaukee, WI). The method of acquisition of images have been described previously in detail.[20]

Measurement of WMH Volume

As the contrasting properties of FLAIR images allow automated segmentation and classification of WMH, we used FLAIR images to quantify WMH. The procedures for measuring the regional WMH volume have been described previously.[18]

The measurement of WMH volume using the FLAIR images was impossible in 24 participants because of motion effects (4 of 24), registration errors (1 of 24), or loss of raw data (19 of 24). Therefore, the final sample of this study consisted of 361 particpants (AD: 200, SVaD: 26, aMCI: 102, svMCI: 33), whose clinical characteristics are detailed in Table 1. These patients did not differ from the 21 patients who had been excluded because of the reasons already described in terms of age (included participants: 72.1 ± 7.9 vs. excluded participants: 74.5 ± 7.9), sex (female 61.8% vs. 70.8%), education (9.0 ± 5.3 vs. 9.5 ± 6.2), mini-mental state examination (21.3 ± 6.1 vs. 21.3 ± 6.3), and the Scheltens rating score of WMH (10.3 ± 7.6 vs. 8.1 ± 6.2).

Image Processing for Cortical Thickness Measurement

We processed images according to the standard Montreal Neurological Institute anatomic pipeline, which has been described previously in detail.[18]

The presence of extensive WMH on the MRI scans made it difficult to completely delineate the inner cortical surfaces with correct topology because of tissue classification errors. We used a semiautomated method to overcome this technical limitation, in which we manually outlined the WMH region and substituted it for normal tissue intensity, described earlier in detail.[7]

We defined cortical thickness as the Euclidean distance between linked vertices of the inner and outer surfaces[24] and calculated cortical thickness values in the native spaces of the brains instead of in the Talairach spaces because of the limitations of linear stereotaxic normalization. In the statistical analyses, we included intracranial volume (ICV) as a covariate to the control, for the brain size effect. As we extracted the cortical surface models from MRI volumes and transformed them into stereotaxic spaces, we measured cortical thicknesses in the native spaces by applying an inverse transformation matrix to the cortical surfaces and reconstructing them in the native spaces.[25]

Nonlinear Registration of Cortical Surface

To compare the thicknesses of the corresponding regions among the patients, we normalized the thickness values spatially using surface-based 2-dimensional registration with a sphere-to-sphere warping algorithm, in which the vertices of each subject nonlinearly registered to a surface group template. We used an improved surface registration algorithm and an unbiased iterative group template showing enhanced anatomic details.[26] Using this transformation, we transformed thickness information on the vertices into an unbiased iterative group template. Particularly for the global analysis, we used average values of the thickness of the whole vertex for each hemisphere and lobar region. Finally, diffusion smoothing with a full-width at half-maximum of 20 mm blurred each cortical thickness map, which increased the signal-to-noise ratio and the statistical power.[24,25]

Statistical Analysis

We transformed the volume of WMH and ICV using logarithm transformations (logWMH and logICV) because these variables were not normally distributed. To control for the degree of cognitive impairment, we classified the patients into 4 categories: MCI, dementia with CDR 0.5, CDR 1, or CDR 2, and we transformed them into dummy variables. To analyze the localized statistical map of cortical thickness on the surface model, we performed the multiple linear regression on a vertex-by-vertex basis. Dependent variables were cortical thicknesses, and independent variables were demographics (age, sex, and duration of education), the degree of cognitive impairment, logICV, and cardiovascular risk factors (histories of hypertension, DM, or hyperlipidemia). The resulting statistical maps were thresholded, using the false discovery rate (FDR) theory[27] at a q value of 0.05, after pooling the P values from regression analyses.

To evaluate the relationships among cardiovascular risk factors, volume of WMH, and cortical thickness, we performed path analyses. We set logWMH as the mediator and adjusted age, sex, education, the degree of cognitive impairment, and logICV. For the outcome, we used cortical thickness. The goodness-of-fit index in this model was 0.922 (Statistical software: AMOS 18.0 trial version).

RESULTS

Effects of Cardiovascular Risk Factors on Cortical Atrophy

After controlling for demographics, the degree of cognitive impairment, and logICV, hypertentive patients showed lower cortical thickness compared with normotensive patients (t, −3.319, $P = 0.001$). Likewise, patients with DM also had lower cortical thickness compared with those without DM (t, −2.153, $P = 0.032$). There were no differences between patients with and without hyperlipidemia ($t = 0.190$, $P = 0.850$) (Fig. 1).

Hypertensive patients had cortical thinning in both the superior frontal, medial frontal, orbitofrontal, lingual, insula, posterior cingulate gyrus, and left middle frontal, lateral temporal, and right inferior frontal gyrus. Diabetic patients showed cortical thinning in both the middle frontal, inferior, medial frontal and right posterior cingulate gyrus (Fig. 2). There were no brain regions for which cortical atrophy correlated with hyperlipdemia.

Relationships Among Cardiovascular Risk Factors, WMH, and Cortical Thinning

As cortical thinning related to hypertension and DM occurred primarily in the frontal region, we used mean frontal thickness instead of overall mean cortical thickness as the outcome in the path analysis. Hypertension and DM correlated with logWMH, whereas hyperlipidemia did not correlate with logWMH (Table 2). Hypertension and logWMH independently correlated with mean frontal thickness (Table 2). In addition, DM and logWMH independently correlated with mean frontal thickness (Table 2).

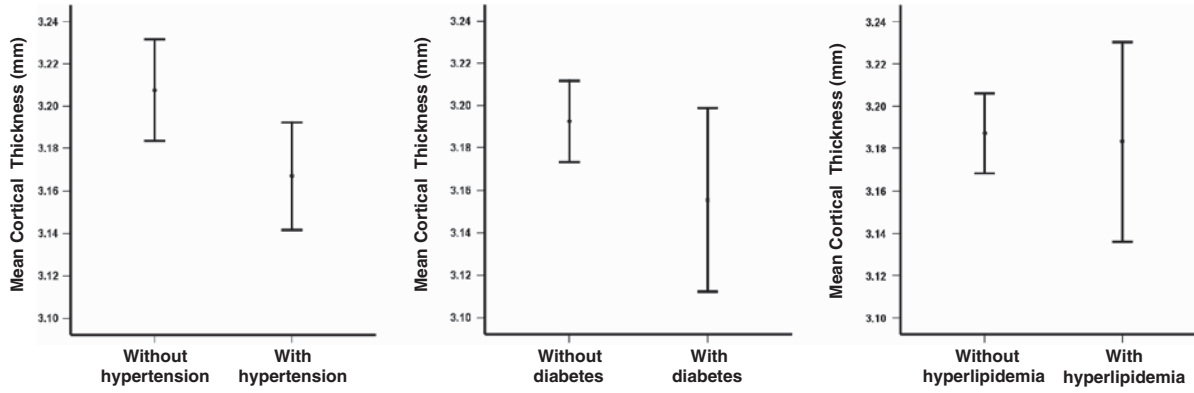

FIGURE 1. Comparisons of mean cortical thickness between patients with and without vascular risk factors.

Hypertension accounted for 0.25 of logWMH, and logWMH accounted for 0.15 of mean frontal thickness. Therefore, hypertension accounted for 0.04 of mean frontal thickness with mediation by logWMH. Hypertension also directly accounted for 0.16 of mean frontal thickness. Thus, hypertension totally accounted for 0.20 of mean frontal thickness (Fig. 3). DM accounted for 0.10 of logWMH, and logWMH accounted for 0.15 of mean frontal thickness. Therefore, DM accounted for 0.02 of cortical thinning with mediation by logWMH. DM also directly accounted for 0.13 of mean frontal thickness. Thus, DM totally accounted for 0.15 of mean frontal thickness (Fig. 3).

DISCUSSION

We found that hypertension is associated with cortical thinning in the frontal and perisylvian regions, whereas DM is associated with cortical thinning in the frontal region. Both hypertension and DM affected cortical thinning with the mediation of WMH. These vascular risk factors also affected cortical thinning without mediation of WMH, the effect of which was greater than that with mediation of WMH.

With regard to cortical thinning related to hypertension, a previous VBM study showed that normal elderly individuals with higher systolic blood pressure have lower

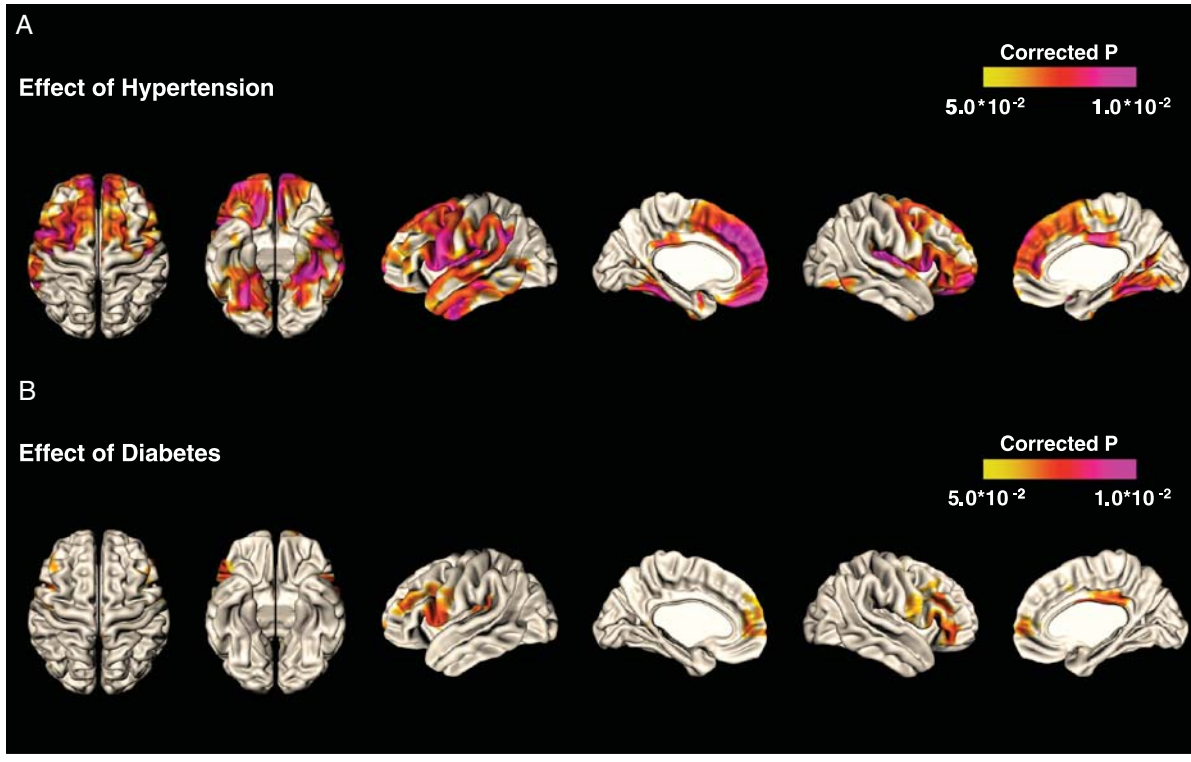

FIGURE 2. Statistical map of cortical thinning related to hypertension and diabetes mellitus.

TABLE 2. Relationships Among Cardiovascular Risk Factors, WMH, and Cortical Thickness

	logWMH			Mean Frontal Thickness		
	B (SE)	Beta	Significance Value	B (SE)	Beta	Significance Value
Hypertension	0.582 (0.116)	0.246	0.001 >	−0.061 (0.019)	−0.162	0.001
DM	0.316 (0.147)	0.100	0.032	−0.065 (0.024)	−0.128	0.008
Hyperlipidemia	−0.069 (0.153)	−0.021	0.654	0.008 (0.025)	0.015	0.759
logWMH				−0.024 (0.008)	−0.148	0.005

B indicates beta (unstandardized coefficients); Beta, beta (standardized coefficients); DM, diabetic mellitus; WMH, white matter hyperintensities.

gray matter volume in the supplementary motor area (BA 6), superior frontal gyrus (BA 8), anterior cingulate cortex (BA 24), and middle temporal gyrus (BA 21).[10] Our study involving patients with aMCI/AD or svMCI/SVaD replicated and extended these previous findings. That is, in addition to BA 6, 8, 24, and 21, our study also highlighted the inferior frontal gyrus (BA 44), superior temporal gyrus (BA 39), medial frontal gyrus (BA 9,10,11 and 32), and lingual gyrus (BA 34). Our observation that hypertension-related areas were more predominant in the frontal association areas than in the posterior cortical areas may be consistent with previous neuropsychological studies showing hypertension to be associated with frontal dysfunction.[28,29]

With regard to the topography of cortical thinning related to DM, previous studies involving a relatively small number of participants showed inconsistent results. A previous VBM study revealed that cognitively normal elderly individuals with diabetic retinopathy had reduced gray matter densities in the inferior frontal gyrus and/or occipital lobe.[12] The other study showed that diabetic patients had cortical thinning and volume reduction in the hippocampus and middle temporal gyrus.[11] In this study, however, we found that DM-related cortical areas were distributed only in the frontal areas such as the middle and inferior frontal gyri and anterior cingulated gyrus, but not in the posterior cingulate gyrus. Our findings may be in line with previous neuropsychological results showing that DM correlated with cognitive impairments in attention, executive functioning, and/or information processing.[29,30] The lack of association between hyperlipidemia and cortical thinning is notable, because hyperlipidemia is an important risk factor for dementia and ischemia. To date, studies have yielded inconsistent results regarding a relationship between hyperlipidemia and cognitive impairment.[31,32] Moreover, a previous study had shown no association between hyperlipidemia and cortical atrophy.[16]

Analyses of the relationships among cardiovascular risk factors, WMH, and cortical thinning may aid in understanding the underlying mechanisms by which hypertension and DM cause cortical thinning. Our findings suggested that both hypertension and DM affected cortical thinning with the mediation of WMH. The mechanisms underpinning how WMH secondary to hypertension and DM produces cortical thinning in patients with MCI or dementia are not entirely clear. However, it could be explained by the hypothesis of secondary degeneration.[9,18] That is, cerebral arteriosclerosis secondary to hypertention

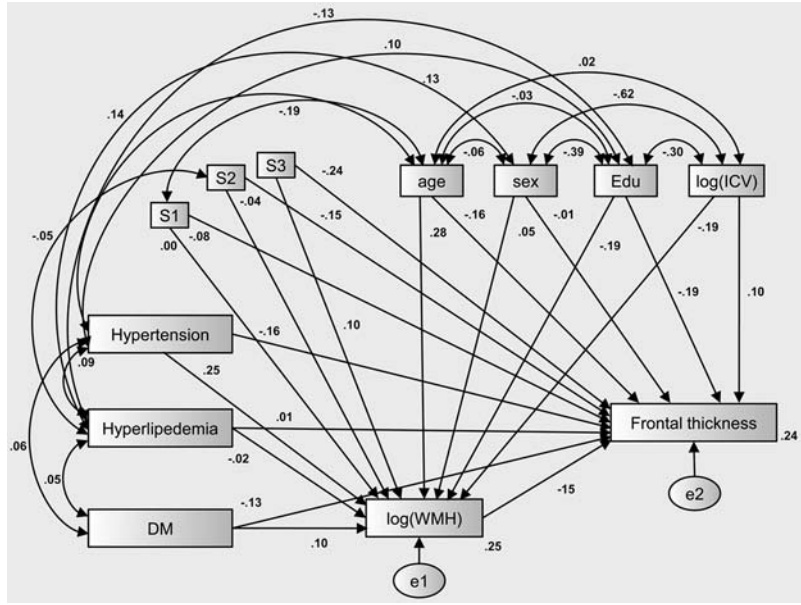

FIGURE 3. Path analysis diagram of the relationships among cardiovascular risk factors, white matter hyperintensities (WMH), and mean frontal thickness. We set logWMH as the mediator and adjusted age, sex, education, the degree of cognitive impairment, and logICV. DM indicates diabetic mellitus, ICV, included intracranial volume.

or DM leads to ischemia in the white matter causing axonal damage and interruption of the white matter tract, leading to secondary neuronal damage and cortical atrophy. It has been reported that when axons in the brain are injured, dying back and Wallerian degeneration occur in the proximal and distal portion of degeneration of the neuron, respectively.[33,34]

We also found that hypertension and DM affected cortical thinning even without the mediation of WMH, which, furthermore, accounted for the cortical thinning more than with the mediation of WMH. The mechanism for this remains unclear. However, there may be several explainable mechanisms. First, cerebral arteriosclerosis secondary to hypertention or DM causes ischemia and infarction both in the WM causing WMH and in the cortex leading to thinning simultaneously. Specifically, earlier studies have shown that hypertention or DM is associated with cortical microinfarcts.[35,36] A pathologic study also showed that multiple small cortical microinfarcts are associated with granular cortical atrophy.[37] Moreover, cortical microinfarcts reportedly contribute to the progression of cognitive deficits in brain aging.[38] Second, hypertension and DM may affect cortical thinning through changes at the microvascular level of the white matter. These risk factors may result in white matter microdamage, which, however, is too subtle to be detected by conventional MRI. Hypertensive patients reportedly have abnormalities in normal-appearing white matter when seen on diffusion tensor imaging— that is, increased mean diffusivity.[39] Finally, cardiovascular risk factors may cause cortical atrophy in association with Alzheimer changes. Recent studies looking at the effects of DM on AD demonstrated that DM might lead to medial temporal atrophy, possibly associated with Alzheimer changes.[40] Although the topography of the cortical thinning that we observed is unlikely to be cortical atrophy associated with AD, we cannot completely exclude this hypothesis.

This study has some limitations. As discussed previously, cardiovascular risk factors may contribute to cortical thinning through pathologies other than WMH. However, we could not directly measure other pathologies including cortical microinfarcts, microstructural changes in the white matter, and AD pathologies. Thus, further studies investigating other possible mechanisms are required.

In conclusion, hypertension and DM affected cortical thinning both with and without the mediation of WMH, where the effect without the mediation of WMH was greater than that with the mediation of WMH.

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