의학박사 학위논문

Association of extracranial carotid and intracranial stenosis with beta-amyloid deposition and neurodegeneration: a clinical stage-specific approach

두개외 경동맥 및 두개내 협착과 베타 아밀로이드 침착 및 신경 퇴화와의 연관성: 임상 단계별 접근법

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ABSTRACT

Background: Although accumulating evidence suggests that cerebrovascular disease may contribute to the development of Alzheimer's disease (AD), it remains unclear whether atherosclerosis of the carotid and intracranial arteries is related to the AD pathology *in vivo*. Thus, we investigated the associations of carotid and intracranial artery stenosis with *in vivo* cerebral beta-amyloid (Aβ) deposition and neurodegeneration in middle- and old-aged individuals. Given the differential progression of Aβ deposition and neurodegeneration across clinical stages of AD, we focused separately on cognitively normal (CN) and cognitively impaired (CI) groups.

Methods: A total of 281 CN and 199 CI (mild cognitive impairment and AD dementia) subjects underwent comprehensive clinical assessment, [^{11}C] Pittsburgh Compound B-positron emission tomography, and magnetic resonance (MR) imaging including MR angiography. We evaluated extracranial carotid and intracranial arteries for the overall presence, severity (i.e. number and degree of narrowing) and location of stenosis.

Results: There were no associations between carotid and intracranial artery stenosis and cerebral Aβ burden in either CN or CI group. In terms of neurodegeneration, exploratory univariable analyses showed some associations between the presence and severity of stenosis and regional neurodegeneration biomarkers (i.e. reduced hippocampal volume [HV] and cortical thickness in the AD-signature regions) in both CN and CI groups. In confirmatory multivariable analyses controlling for demographic covariates and diagnosis, the association between number of stenotic intracranial arteries ≥ 2 and reduced HV in the CI group remained significant.

Conclusions: Neither carotid nor intracranial artery stenosis appears to be associated with brain Aβ burden, while intracranial artery stenosis is related to amyloid-independent neurodegeneration, particularly hippocampal atrophy. These observations support the importance of proper management of intracranial artery stenosis for delaying the progression of AD neurodegeneration and related cognitive decline.

Keywords: Alzheimer's disease, amyloid beta, neurodegeneration, atherosclerosis, intracranial stenosis, carotid stenosis, cognitive impairment

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INTRODUCTION

There is accumulating evidence that vascular risks may play important roles in the development of Alzheimer's disease (AD)(1). Vascular lesions detected on brain magnetic resonance imaging (MRI), such as white matter hypertensities (WMH), lacunar infarctions, or microbleeds were also reported to be associated with AD (2).

Clinical or epidemiological studies indicate the association between atherosclerosis of the carotid and intracranial arteries and Alzheimer's disease (AD) dementia (3-6). However, the mechanisms linking carotid and intracranial atherosclerosis and AD or related cognitive impairment (CI) remain unclear. While some postmortem studies found the relationship between atherosclerosis and amyloid plaques (7-10), other studies were against such relationship (6, 11-13). A couple of in vivo brain imaging studies on patients with severe cerebral hypoperfusion have reported inconsistent findings on the association of very severe atherosclerosis with beta-amyloid (Aβ) deposition (14, 15). Recently, a study using high-resolution vessel wall magnetic resonance (MR) imaging reported that intracranial plaque or stenosis was not related with Aβ deposition in nondemented adults (16). However, whether the carotid and intracranial atherosclerosis are associated with other in vivo AD pathologies including regional neurodegeneration, as well as Aβ deposition, remains unclear.

We hypothesized that the relationships between carotid and intracranial artery atherosclerosis and in vivo brain pathologies may be different according to the cognitive status. In cognitively normal (CN) individuals, regional neurodegeneration is minimal while it is correlated with the degree of cognitive decline in those with cognitively impairment (17). In regards to Aβ deposition, it is

already saturated in many AD dementia patients (17). Given the differential progression of Aβ deposition and neurodegeneration across the clinical stages of AD, therefore, a clinical stage-specific approach, separately focusing on the CN stage and CI stage could be helpful.

The present study was performed to investigate the associations between carotid and intracranial artery stenosis and AD biomarkers including cerebral Aβ deposition and regional neurodegeneration in a large number of middle- and old-aged individuals, including both CN and CI groups.

MATERIALS AND METHODS

Participants

This study included a total of 480 middle- and old-aged adults consisting of 281 CN and 199 CI (mild cognitive impairment and AD dementia) subjects who participated in the Korean Brain Aging Study for the Early Diagnosis & Prediction of Alzheimer's disease (KBASE), an ongoing prospective, community-based cohort study since 2014 (18). The inclusion criteria for the CN group were as follows: (a) aged 55–90 years, (b) no diagnosis of MCI or dementia and (c) Clinical Dementia Rating (CDR) score of 0. For the MCI group, individuals 55-90 years old who fulfilled the core clinical criteria for diagnosis of MCI according to the recommendations of the National Institute on Aging- Alzheimer's Association (NIA-AA) guidelines (19) were included as follows: (a) memory complaints corroborated by the patient, an informant, or clinician, (b) objective memory impairment for age, education, and gender (*i.e.*, at least 1.0 SD below the respective age, education, and gender-specific mean for at least one of the four episodic memory tests included in the Korean version of Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) neuropsychological battery [Word List Memory, Word List Recall, Word List Recognition and Constructional Recall test]); (c) largely intact functional activities; and (d) no dementia. The global CDR score of all MCI individuals was 0.5. For the AD dementia group, participants 55-90 years old who fulfilled the following inclusion criteria were recruited: (a) criteria for dementia in accordance with the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV-TR), (b) the criteria for probable AD

dementia in accordance with the NIA-AA guidelines (20), and (c) a global CDR score of 0·5 or 1. For all groups, individuals with the following conditions were excluded from the study: 1) presence of major psychiatric illness; 2) significant neurological or medical condition or comorbidities that could affect mental function; 3) contraindications to MRI (*e.g.*, pacemaker, claustrophobia); 4) illiteracy; 5) presence of significant visual/hearing difficulty; severe communication or behavioral problems that would make clinical examination or brain scan difficult; and 6) taking an investigational drug. More detailed information on recruitment of the KBASE cohort was described in our previous report (18).

Clinical assessments

All participants underwent standardized clinical and neuropsychological assessments by trained psychiatrists and neuropsychologists based on the KBASE assessment protocol which incorporates the CERAD-K (18). Blood samples were collected to determine apolipoprotein E ε4 allele (APOE4) carrier status. Vascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, transient ischemic attack and stroke were evaluated by trained nurses during a systematic interview with the participants and their informants. The vascular risk score was calculated for the number of vascular risk factors present and is reported as a percentage (18).

Image data acquisition and analysis

All subjects underwent simultaneous three-dimensional (3D) [^{11}C] Pittsburgh

compound B (PiB)-positron emission tomography (PET), 3D T1-weighted MRI, fluid attenuated inversion (FLAIR) images and 3D time-of-flight (TOF)-MR angiography using the 3.0T Biograph mMR (PET-MR) scanner (Siemens, Washington DC, USA). 3D T1-weighted images and fluid attenuated inversion recovery (FLAIR) images were acquired in the sagittal plane. T1 weighted MRI was acquired as follows: repetition time (TR), 1,670ms; echo time (TE), 1 89ms; field of view (FOV), 250mm; matrix, 256 × 256; slice thickness, 1.0mm. The parameters for acquiring FLAIR images were as follows: TR, 5,000ms; TE, 173ms; echo spacing, 3.46ms; FOV, 250 mm; matrix size, 256 × 256; slice thickness, 1.0 mm. The parameters for acquiring intracranial TOF MRA were as follows: FOV, 220 × 178 mm^2 (frequency × phase); acquisition matrix, 512 × 208 (frequency × phase); pixel size, 0.43 × 0.86 mm^2 (frequency × phase); slice thickness, 0.6 mm. For the neck vessels, acquisition parameters were as follows: FOV, 220 × 176mm^2 (frequency × phase); acquisition matrix, 384 × 200 (frequency × phase); pixel size, 0.57 × 0.88 mm^2 (frequency × phase); slice thickness, 1. 6 mm.

Evaluation of stenosis on MR angiography

Diagnosis of extracranial carotid and intracranial arterial stenosis was reached by the consensus between two qualified neuroradiologists (KMK and CHS) blinded to the participants' clinical information. The overall presence, number and the degree of detectable stenotic lesions were recorded in the following 13 arterial segments: right and left proximal cervical internal carotid artery (ICA), right and left intracranial ICA, right and left anterior, middle, and posterior cerebral arteries, right and left intracranial vertebral artery, and basilar artery. For the extracranial carotid artery, the degree of stenosis was measured according to the North

American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (21) using maximum-intensity projections and source images of the bifurcation of the carotid artery. In cases of intracranial arterial stenosis, the degree of stenosis was calculated based on maximum-intensity projections and source images using the method published for the Warfarin-Aspirin Symptomatic Intracranial Disease Study (22): percent stenosis = $[(1 - (D_{stenosis}/D_{normal})] \times 100$. In the case of an artery with multiple stenotic lesions, the most severe degree was selected. Based on the above quantitative data, participants were categorized into stenosis-positive (stenosis+) vs stenosis-negative (stenosis-) groups according to the stenosis measurements for extracranial carotid and intracranial arteries as follows: i) overall presence of any detectable stenosis; ii) severity (*i.e.*, the degree of stenosis $\geq$ 50%, and number of stenotic arteries $\geq$ 2). In terms of the location of intracranial arterial stenosis, the presence of detectable stenosis in the anterior circulation and posterior circulations were also evaluated. Anterior circulation stenosis was defined as any detectable stenosis in ICA, anterior or middle cerebral arteries. Posterior circulation stenosis included any detectable stenosis in intracranial vertebral or basilar arteries. As there were only very limited numbers of cases with $\geq$ 50% stenotic lesions in the extracranial carotid arteries (1 of 281 subjects in the CN group and 1 of 196 subjects in the CI group), and those with bilateral extracranial carotid stenosis (6 of 281 subjects in the CN group and 6 of 196 subjects in the CI group) in our sample, these measurements could not be applied to the extracranial carotid arteries and only available for evaluation of intracranial arterial stenosis.

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Beta-amyloid (Aβ) biomarker

For measurement of Aβ biomarker of AD, a 30-minute emission scan was obtained 40 minutes after injection of intravenous administration of 555 MBq of [^{11}C]PiB (range, 450-610 MBq). The [^{11}C]PiB-PET data collected in list mode were processed for routine corrections such as uniformity, UTE-based attenuation, and decay corrections, and were reconstructed into a 344 × 344 image matrix using iterative methods (5 iterations with 21 subsets). The image pre-processing steps were performed using Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 2014a (MathWorks, Natick, MA, USA). Static [^{11}C]PiB-PET images were co-registered to individual T1 structural images and transformation parameters for spatial normalization of individual T1 images to a standard Montreal Neurological Institute (MNI) template were calculated. The inverse transformation of parameters to transform coordinates from the automatic anatomic labelling (AAL) 116 atlas (23) into an individual space for each subject (resampling voxel size = 1 × 0.98 × 0.98 mm) was performed using IBASPM (Individual Brain Atlases using Statistical Parametric Mapping) software in MATLAB. To extract gray matter (GM) and exclude the non-GM portions of the atlas (*i.e.*, white matter [WM] and cerebrospinal fluid space), a GM mask, which is a binary probabilistic GM map generated by preprocessing step using SPM8, was applied for each individual. The mean regional [^{11}C]PiB uptake values from cerebral regions were extracted using the individual AAL116 atlas from T1-coregistered [^{11}C]PiB-PET images. Cerebellar GM was used as the reference region for quantitative normalization of cerebral [^{11}C]PiB uptake values, due to its relatively low Aβ deposition (24), with a probabilistic cerebellar atlas (Institute of Cognitive Neuroscience, UCL; Cognitive Neuroscience Laboratory, Royal Holloway, University of London, UK) which was transformed into

individual space as described above. The AAL algorithm and a region combining method (25) were applied to determine regions of interest (ROIs) to characterize the [^{11}C]PiB retention levels in the frontal, lateral parietal, posterior cingulate-precuneus, and lateral temporal regions. A global Aβ retention value (standardized uptake value ratio, SUVR) was generated by dividing the voxel-weighted mean value of the four ROIs by the mean cerebellar uptake value (25-27). Aβ positivity was defined if [^{11}C]PiB SUVR value was > 1.4 in at least one of the abovementioned four ROIs (25-27).

Neurodegeneration biomarker of AD

All T1-weighted MR images were automatically segmented using FreeSurfer version 5.3 (http://surfer.nmr.mgh.harvard.edu/) with manual correction of minor segmentation errors. As AD-related neurodegeneration biomarkers, both AD-signature cortical thickness (AD-CT; *i.e.*, mean cortical thickness obtained from AD-signature regions) and hippocampal volume adjusted for intracranial volume (HVa) were measured as described previously (26). First, AD-CT was defined as the mean cortical thickness values of AD-signature regions including the entorhinal, inferior temporal, middle temporal, and fusiform gyrus, based on the Desikan–Killiany atlas (28). Second, to obtain HVa, left and right hippocampi volume from the FreeSurfer extracted output were first added together to yield the total hippocampal volume (HV). Then, the volume deviating from the expected total HV according to intracranial volume (ICV) based on the reference group (*i.e.*, young CN group of the study cohort [KBASE]), which was not included in the present study, was calculated to obtain HVa as described in the previous study (26, 29). Briefly, a linear regression line was derived based on the young control group (i.e.,

the reference group) using their ICV and total HV. HVa, then, is the residual from the linear regression of HV (y-axis) versus ICV (x-axis); therefore, the HVa is interpreted as the amount of deviation (mm^3) in a subject's hippocampal volume from what is expected given their ICV. For example, If HVa value of a subject is -2000mm^3, it means that the sum of right and left hippocampal volumes of the subject is reduced by 2000 mm^3 compared with the expected hippocampal volume given his ICV.

White matter hyperintensities

The volume of white matter hyperintensities (WMH) on FLAIR images was calculated using a validated automatic procedure (30) with two modifications, as follows: first, an optimal threshold of 70 instead of 65 in the original reference was applied because it was more suitable for our data; second, diffusion-weighted imaging was not used in the present automated procedure as there were no participants with acute cerebral infarcts in our study population. WMH candidate images were used to extract WMH volumes based on lobar ROIs in the native space for each subject (31). The WMH volume was normalized by dividing the corresponding ICV, expressed as WMH volume % of ICV.

Statistical Analysis

Demographic and clinical characteristics between CN and CI, and between MCI and AD dementia were compared using the Chi-square and Fisher exact tests for the prevalence of data, and independent t test for continuous variables. Interobserver agreement for stenosis was determined by calculating the Cohen's

kappa correlation coefficient from 125 randomly selected individuals.

To investigate whether a measure of extracranial carotid or intracranial stenosis was associated with AD biomarkers (*i.e.*, global Aβ deposition, ADT, and HVa) within the CN or CI group, two steps of analysis including exploratory and confirmative steps were conducted. Following statistical analyses were performed focusing on CN and CI separately. Exploratory univariable analyses were performed with independent t test to compare the quantitative values of AD biomarkers between stenosis+ and stenosis– groups. The Cohen's ***d*** was determined to imply the effect size of the discrepancy between sequences. The AD biomarkers with $p < 0.05$ in exploratory univariable analyses were selected for the next confirmatory multivariable analyses. Confirmative multivariable analyses using general linear model (GLM) were conducted for the selected biomarker adjusting for age, sex and APOE4 carrier status for the CN group, and for age, sex APOE4 carrier status and clinical diagnosis (MCI or AD dementia) for the CI group. As the CI group was composed of MCI and AD dementia, we performed the same including exploratory and confirmative analyses for each of MCI and AD dementia subgroup. Confirmative multivariable analyses using GLM were conducted for the selected biomarker adjusting for age, sex and APOE4 carrier status. The Bonferroni correction method was applied to multiple comparisons using $p < 0.05$/No. of confirmatory analyses within each cognitive group. The same analyses with WMH volume as an additional covariate were also conducted to evaluate the mediating effect of WM lesions. To evaluate the independence between global Aβ deposition and neurodegeneration, we performed GLM analyses for the association between the selected stenosis and neurodegeneration biomarkers (used in multivariable confirmatory analyses) in each of Aβ positive and negative

group. The Pearson correlation coefficient was used to evaluate the correlation between the continuous variables.

All statistical analyses except calculating cohen's d were performed using IBM SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ (two-sided) was taken to indicate statistical significance unless otherwise specified.

RESULTS

Characteristics of the participants

The demographic and clinical characteristics of the CN and CI groups are shown in Table 1. Their data regarding on the intracranial and extracranial carotid stenosis and AD biomarkers are also shown in Table 2. Three cases were excluded from the evaluation of extracranial carotid stenosis due to motion artefacts. For the MCI (n = 129) and AD dementia (n = 70) subgroups in the CI group, the demographic and clinical characteristics are shown in Tables 3 and 4.

Table 1. Demographic and clinical characteristics of participants

Variables	CN (N=281)	CI (N=199)	*P*-value
Age, y	69.1 ± 8.1	72.9 ± 7.4	< 0.001*
Females	146 (52.0%)	134 (67.3%)	0.001*
Education, y	11.9 ± 4.8	9.7 ± 4.9	< 0.001*
APOE4 carriers	52 (18.5%)	83 (41.7%)	< 0.001*
Global CDR (0/0.5/1)	281/0/0	0/153/46	< 0.001*
CDR-SOB	0.0 ± 0.1	2.7 ± 2.0	< 0.001*
Hypertension	133 (47.3%)	99 (49.7%)	0.602
Diabetes Mellitus	46 (16.4%)	34 (17.1%)	0.836
Coronary artery disease	16 (5.7%)	10 (5.0%)	0.470
Hyperlipidemia	96 (34.2%)	71 (35.7%)	0.731
Stroke	0 (0.0%)	0 (0.0%)	NA
Transient ischemic attack	2 (0.7%)	1 (0.5%)	0.774
Vascular risk factor score	17.4 ± 16.11	18.0 ± 16.8	0.679
Normalized WMH volume [a]	0.391 ± 0.368	0.448 ± 0.373	0.122

Note. Data are presented as mean ± SD or n (%).

[a]Data for 422 individuals were available (256 CN and 166 CI).
*p < 0.05

CN, cognitively normal; CI, cognitively impaired; CDR-SOB, Clinical Dementia Rating sum of box; WMH, white matter hyperintensities

Table 2. Vessel stenosis features and AD biomarkers of participants

Variables	CN (N=281)	CI (N=199)	*P*- value
Large vessel stenosis			
Presence of any detectable stenosis			
Any extracranial carotid stenosis	23 (8.2%)	22 (11.2%)[a]	0.264
Any intracranial stenosis	77 (27.4%)	71 (35.7%)	0.053
Both extracranial carotid and intracranial stenosis	12 (4.3%)	10 (5.0%)	0.697
Presence of stenosis based on severity threshold			
≥ 50 % intracranial stenosis	19 (6.8%)	21 (10.6%)	0.139
Number of stenotic intracranial arteries ≥ 2	44 (15.7%)	38 (19.1%)	0.324
Presence of stenosis according to location			
Anterior circulation stenosis	69 (24.6%)	61 (30.7%)	0.139
Posterior circulation stenosis	21 (7.5%)	21 (10.6%)	0.239
AD biomarkers			
Global Aβ deposition (SUVR)	1.184 ± 0.239	1.621 ± 0.156	< 0.001*
Aβ positivity	39 (13.9%)	112 (56.3%)	< 0.001*
Neurodegeneration biomarkers			
AD-CT (mm)	2.866 ± 0.174	2.584 ± 0.286	< 0.001*
HVa (mm^3)	-759 ± 838	-2132 ± 1219	< 0.001*

Note. Data are presented as mean ± SD or n (%).
[a]Among CI group, data for 196 individuals were available.
*p < 0.05
CN, cognitively normal; CI, cognitively impaired; AD-CT, Alzheimer's disease signature cortical thickness; HVa, Hippocampal volume adjusted for intracranial volume

Table 3. Demographic and clinical characteristics of MCI and AD dementia participants

Variables	MCI (N=129)	AD dementia (N = 70)	P value
Age, y	73.4 ± 7.0	72.0 ± 8.0	0.209
Females	85 (65.9%)	49 (70.0%)	0.555
Education, y	10.0 ± 4.5	9.2 ± 5.5	0.315
APOE4 carriers	42 (32.6%)	41 (58.6%)	< 0.001*
Global CDR (0.5/1)	129 (100%)/0 (0%)	24 (34.3%)/ 46 (65.7%)	< 0.001*
CDR-SOB	1.5 ± 0.6	5.0 ± 1.5	< 0.001*
Hypertension	70 (54.3%)	29 (41.4 %)	0.084
Diabetes Mellitus	22 (17.1%)	12 (17.1 %)	0.987
Coronary artery disease	5 (3.9 %)	5 (7.1%)	0.326
Hyperlipidemia	49 (38.0%)	22 (31.4 %)	0.357
Stroke	0 (0%)	0 (0%)	NA
Transient ischemic attack	1 (0.8%)	0 (0%)	1
Vascular risk factor score	19.0 ± 16.8	16.2 ± 16.8	0.262
Normalized WMH volume [a]	0.472 ± 0.399 (%)	0.402 ± 0.315 (%)	0.258

Note. Data are presented as mean ± SD or n (%).
[a]Data for 110 MCI and 56 AD dementia were available.
*p < 0.05
MCI, mild cognitive impairment; AD dementia, Alzheimer's dementia; CDR-SOB, Clinical Dementia Rating sum of box; WMH, white matter hyperintensity

Table 4. Vessel stenosis features and AD biomarkers of MCI and AD dementia participants

Variables	MCI (N= 129)	AD dementia (N =70)	*P*- value
Large vessel stenosis			
Presence of any detectable stenosis			
Any extracranial carotid stenosis	13 (10.1%)	9 (12.9%)	0.552
Any intracranial stenosis	46 (35.7)	25 (35.7%)	0.994
Both extracranial carotid and intracranial stenosis	5 (3.9%)	5 (7.1%)	0.314
Presence of stenosis based on severity threshold			
≥ 50 % intracranial stenosis	16 (12.4%)	5 (7.1%)	0.249
Number of stenotic intracranial arteries ≥ 2	24 (18.6%)	14 (20.0%)	0.811
Presence of stenosis according to location			
Anterior circulation stenosis	42 (32.6%)	19 (27.1%)	0.429
Posterior circulation stenosis	12 (9.3%)	9 (12.9%)	0.436
AD biomarkers			
Global Aβ deposition (SUVR)	1.492 ± 0.461	1.890 ± 0.529	< 0.001*
Aβ positivity	58 (45.0%)	54 (77.1%)	< 0.001*
Neurodegeneration biomarkers			
AD-CT (mm)	2.678 ± 0.253	2.409 ± 0.261	< 0.001*
HVa (mm^3)	-1773 ± 1181	-2792 ± 998	< 0.001*

Note. Data are presented as mean ± SD or n (%).

[a]Data for 127 MCI and 69 AD dementia individuals were available.

*$p < 0.05$

MCI, mild cognitive impairment; AD dementia, Alzheimer's dementia; AD-CT, AD signature cortical thickness; HVa, Hippocampal volume adjusted for intracranial volume

Reproducibility of a measure of extracranial carotid or intracranial stenosis

Detailed results of the interobserver agreement for a measure of stenosis are presented in Table 5. The kappa values were from 0.715 to 0.869 for a measure of extracranial carotid or intracranial stenosis except for 50% stenosis. The kappa value for ≥ 50% stenosis was 0.301 due to the very low prevalence of ≥ 50% stenosis despite the high degree of interobserver agreement.

Table 5. Interobserver agreement of a measure of extracranial carotid or intracranial stenosis

Any extracranial carotid stenosis	Observer 1			
	Stenosis-	Stenosis+	Total	Kappa
Observer 2				0.715
Stenosis-	113	3	116	
Stenosis+	2	7	9	
Total	115	10	125	

Any intracranial stenosis	Observer 1			
	Stenosis-	Stenosis+	Total	Kappa
Observer 2				0.869
Stenosis-	83	1	84	
Stenosis+	6	35	41	
Total	89	36	125	

≥ 50 % intracranial stenosis	Observer 1			
	Stenosis-	Stenosis+	Total	Kappa
Observer 2				0.301
Stenosis-	115	3	118	
Stenosis+	5	2	7	
Total	120	5	125	

Number of stenotic intracranial arteries ≥ 2	Observer 1			
	Stenosis-	Stenosis+	Total	Kappa
Observer 2				0.715
Stenosis-	102	7	109	
Stenosis+	2	14	16	
Total	104	21	125	

Anterior circulation	Observer 1			
	Stenosis-	Stenosis+	Total	Kappa
Observer 2				0.802
Stenosis-	85	3	88	
Stenosis+	7	30	37	
Total	92	33	125	

Posterior circulation	Observer 1			
	Stenosis-	Stenosis+	Total	Kappa
Observer 2				1
Stenosis-	117	0	117	
Stenosis+	0	8	8	
Total	117	8	125	

CN group

In the exploratory step of the analyses, global Aβ deposition was not significantly different between CN subjects with vs. those without any type of stenosis (Table 6). However, AD-CT was significantly decreased in CN subjects in the stenosis+ group compared with CN subjects in the stenosis- group for the presence of any extracranial carotid stenosis, presence of any intracranial stenosis, number of stenotic intracranial arteries $\geq$ 2, anterior circulation stenosis and posterior circulation stenosis (all $p < 0.05$; Table 6). In addition, the presence of any intracranial arterial stenosis was associated with reduced HVa in CN group. In the next confirmatory analyses, we tested the associations between AD-CT and each of the selected five measurements of stenosis that showed association in exploratory univariable analyses ($p < 0.05$), as well as the association between HVa and presence of any intracranial stenosis, after adjusting for age, sex and APOE4 carrier status (Table 7). As a result, these associations were not significant in the confirmatory analyses (Bonferroni corrected p-value [$p < 0.05/6 = 0.008$] was applied), although posterior circulation stenosis showed a trend for association with reduced AD-CT ($p = 0.030$).

Table 6. Exploratory univariable analyses for the association between extracranial carotid and intracranial arterial stenosis and AD biomarkers in the CN group.

AD biomarker	Variables	Presence of any detectable stenosis					
		Any extracranial carotid stenosis			Any intracranial stenosis		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.185 ± 0.245	1.173 ± 0.160	0.810	1.182 ± 0.243	1.190 ± 0.230	0.782
Neurodegeneration biomarker	AD-CT	2.877 ± 0.170	2.743 ± 0.173	< 0.001*	2.890 ± 0.171	2.804 ± 0.165	< 0.001*
	HVa	-732 ± 810	-1067 ± 1076	0.066	-686 ± 832	-953 ±0 827	0.017*
		Severity of stenosis					
		≥ 50 % intracranial stenosis [b]			Number of stenotic intracranial arteries ≥ 2[c]		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.179 ± 0.234	1.258 ± 0.293	0.165	1.189 ± 0.242	1.157 ± 0.221	0.409
Neurodegeneration biomarker	AD-CT	2.871 ± 0.175	2.801 ± 0.136	0.091	2.882 ± 0.169	2.780 ± 0.178	< 0.001*
	HVa	-746 ± 838	-937 ± 837	0.338	-726 ± 840	-938 ± 810	0.123
		Location of stenosis					
		Anterior circulation			Posterior circulation		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.187 ± 0.245	1.175 ± 0.220	0.711	1.185 ± 0.241	1.175 ± 0.212	0.854
Neurodegeneration biomarker	AD-CT	2.884 ± 0.172	2.811 ± 0.167	0.002*	2.876 ± 0.170	2.744 ± 0.181	0.001*
	HVa	-710 ± 837	-911 ± 828	0.082	-760 ± 836	-746 ± 875	0.943

Note. Data for continuous variables presented as means ± SD (SUVR for Global Aβ, mm for AD-CT and mm^3 for HVa).
[a] *d* indicates cohen's delta.
[b] "Stenosis-" group of "≥50% intracranial stenosis" means individuals with no stenosis or < 50% intracranial stenosis.
[c] "Stenosis-" group of "number of stenotic intracranial arteries ≥2" means patients with no stenosis or only one stenotic intracranial artery.
*p < 0.05

CN, cognitively normal; SUVR, standardized uptake value ratio; AD-CT, Alzheimer's disease signature cortical thickness; HVa, Hippocampal volume adjusted for intracranial volume

Table 7. Confirmatory multivariable analyses for the association between extracranial carotid and intracranial arterial stenosis and neurodegeneration biomarkers in the CN group.

AD biomarker	Variables	Type of stenosis	B	SE	*P*
Neurodegeneration biomarker	AD-CT	Any extracranial carotid stenosis	-0.051	0.033	0.121
		Any intracranial stenosis	-0.033	0.020	0.104
		Number of stenotic intracranial arteries ≥ 2	-0.040	0.025	0.113
		Anterior circulation	-0.024	0.021	0.254
		Posterior circulation	-0.074	0.034	0.030*
	HVa	Any intracranial stenosis	-30.760	95.491	0.748

Note. Covariates for confirmatory multivariable analyses include age, sex and APOE4 carrier status. Units for AD biomarker variables are as follows: SUVR for Global Aβ, mm for AD-CT and mm^3 for HVa. When Bonferroni corrected p-value ($p < 0.05/6 = 0.008$) was applied for confirmatory multivariable analyses regarding neurodegeneration biomarkers, these associations were not significant, although posterior circulation stenosis showed a trend for association with reduced AD-CT.

[a] No significant findings in the exploratory univariable analyses step regarding Aβ biomarker.
*p <0.05 (before Bonferroni correction)

AD, Alzheimer's disease; CN, cognitively normal; SE, standard error; AD-CT, Alzheimer's disease signature cortical thickness; HVa, Hippocampal volume adjusted for intracranial volume

CI group

In the exploratory univariable analyses, there was an association between anterior circulation stenosis and lower global Aβ deposition ($p = 0.049$, Table 8). However, the confirmatory analysis showed that it was not significant after controlling for age, gender, APOE4 carrier status and clinical diagnosis (MCI vs. AD dementia) ($B = -0.096$, $SE = 0.072$, and $p = 0.183$). In regards to exploratory univariable analyses of neurodegeneration biomarkers, we found no differences in AD-CT between stenosis+ and stenosis- groups for all types of stenosis (Table 8). However, HVa was reduced in the stenosis+ CI group compared to the stenosis- CI group for the presence of any intracranial arterial stenosis and number of stenotic intracranial arteries ≥ 2 ($p = 0.047$ and $p = 0.008$, respectively; Table 8). The next confirmatory multivariable analyses were performed for these two selected associations after controlling for age, gender, APOE4 carrier status and clinical diagnosis (Table 9). When Bonferroni corrected p-value ($p < 0.05/2 = 0.025$) was applied, CI subjects with number of stenotic intracranial arteries ≥ 2 had significantly reduced HVa than those without when controlling for age, gender, APOE4 carrier status and clinical diagnosis ($p = 0.021$; Figures 1, 2). Additional adjustment for normalized WMH volume did not change the result ($B = -508.96$, $SE = 206.06$, and $p = 0.015$). There was a significant correlation between the CDR-SOB and HVa ($r = -0.413$ {95% confidence interval, -0.513 to -0.290}, $p < 0.0001$)

Finally, to evaluate the independence between global Aβ deposition and neurodegeneration, GLM analyses were performed for number of stenotic intracranial arteries ≥ 2 and HVa in each of Aβ positive and negative group. As shown in Table 10, there was no significant association between number of stenotic intracranial arteries ≥ 2 and HVa in both groups ($ps > 0.05$).

Table 8. Exploratory univariable analyses for the association between extracranial carotid and intracranial arterial stenosis and AD biomarkers in the CI group.

AD biomarker	Variables	Presence of any detectable stenosis					
		Any extracranial carotid stenosis			Any intracranial stenosis		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.627 ± 0.530	1.609 ± 0.412	0.857	1.648 ± 0.539	1.573 ± 0.472	0.304
Neurodegeneration biomarker	AD-CT	2.600 ± 0.284	2.518 ± 0.260	0.205	2.596 ± 0.311	2.561 ± 0.234	0.376
	HVa	-2064 ± 1225	-2396 ± 947	0.146	-2004 ± 1262	-2362 ± 1109	0.047*
		Severity of stenosis					
		≥ 50 % intracranial stenosis [b]			Number of stenotic intracranial arteries ≥ 2[c]		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.646 ± 0.522	1.415 ± 0.411	0.052	1.640 ± 0.536	1.544 ± 0.414	0.234
Neurodegeneration biomarker	AD-CT	2.584 ± 0.290	2.579 ± 0.254	0.940	2.598 ± 0.292	2.521 ± 0.252	0.136
	HVa	-2087 ± 1202	-2515 ± 1327	0.128	-2021 ± 1227	-2602 ± 1080	0.008*
		Location of stenosis					
		Anterior circulation			Posterior circulation		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.667 ± 0.535	1.519 ± 0.456	0.049*	1.623 ± 0.519	1.605 ± 0.498	0.878
Neurodegeneration biomarker	AD-CT	2.585 ± 0.309	2.580 ± 0.224	0.902	2.589 ± 0.289	2.540 ± 0.257	0.459
	HVa	-2047 ± 1244	-2323 ± 1147	0.142	-2100 ± 1217	-2400 ± 1236	0.287

Note. Data for continuous variables presented as means ± SD (SUVR for Global Aβ, mm for AD-CT and mm^3 for HVa).

[a] *d* indicates cohen's delta.

[b] "Stenosis-" group of "≥50% intracranial stenosis" means individuals with no stenosis or < 50% intracranial stenosis.

[c] "Stenosis-" group of "number of stenotic intracranial arteries ≥2" means patients with no stenosis or only one stenotic intracranial artery.

*p < 0.05

CI, cognitively impaired; SUVR, standardized uptake value ratio; AD-CT, Alzheimer's disease signature cortical thickness; HVa, Hippocampal volume adjusted for intracranial volume

Table 9. Confirmatory multivariable analyses for the association between extracranial carotid and intracranial arterial stenosis and HVa in the CI group.

AD biomarker	Variables	Type of stenosis	B	SE	P
Neurodegeneration biomarker	HVa	Any intracranial stenosis	-84.12	158.68	0.597
		Number of stenotic intracranial arteries ≥ 2	-428.82	184.92	0.021*†

Note. Covariates for confirmatory multivariable analyses include age, sex, APOE4 carrier status and clinical diagnosis (mild cognitive impairment or AD dementia). Units for AD biomarker variables are as follows: SUVR for Global Aβ, mm for AD-CT and mm^3 for HVa. When Bonferroni corrected p-value was applied for confirmatory multivariable analyses regarding neurodegeneration biomarkers, the association between presence of number of stenotic intracranial arteries ≥ 2 and lower HVa in the CI group remained significant.

[a] No significant findings in the exploratory univariable analyses step regarding AD-CT.
*$p < 0.05$ (before Bonferroni correction)
†$p < 0.025$ (Bonferroni corrected $p < 0.05/2 = 0.025$ was used as a statistical threshold)

AD, Alzheimer's disease; CI, cognitively impaired; SE, standard error; SUVR, standardized uptake value ratio; HVa, Hippocampal volume adjusted for intracranial volume

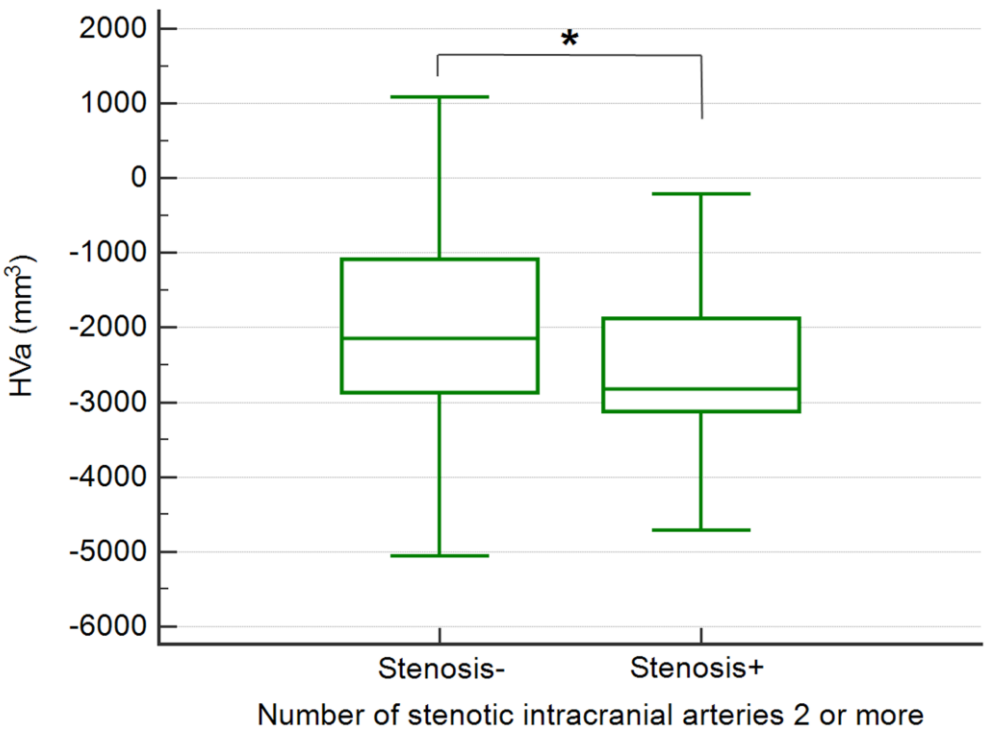

Figure 1. Comparison of HVa between stenosis- and stenosis+ groups for number of stenotic intracranial arteries ≥ 2 in CI subjects.

In the Box-and-whisker plot, the central box represents the values from the lower to upper quartile, the middle line represents the median, and the horizontal line extends from the minimum to the maximum value.

*Adjusted $p < 0.05$ (after controlling for the effects of age, gender, APOE4 and clinical diagnosis (MCI vs. AD dementia).

HVa, hippocampal volume adjusted for intracranial volume; MCI, mild cognitive impairment; AD, Alzheimer's disease

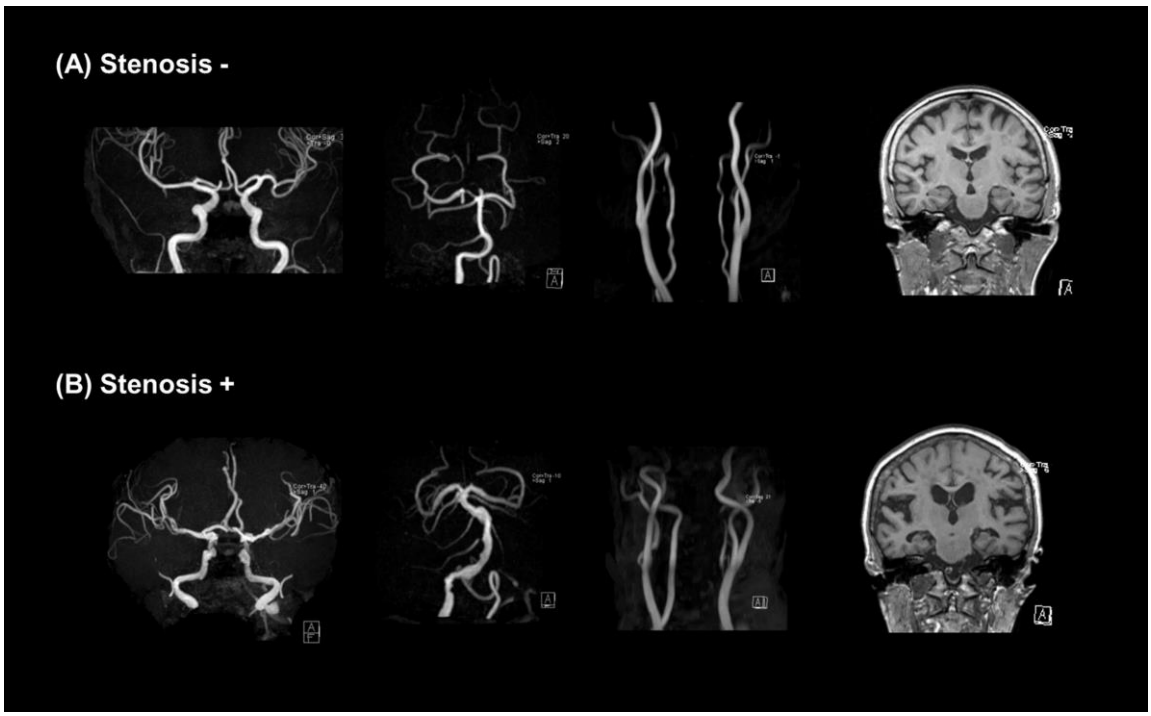

Figure 2. Representative MR angiographic images of intracranial and neck vessels, and coronal sections of T1-weighted images showing medial temporal structures including the bilateral hippocampi of CI individuals in the (A) stenosis- group and (B) stenosis+ group with regard to number of stenotic intracranial arteries ≥ 2.

(A) Stenosis-: MR angiography of 77-year-old woman with MCI with no steno-occlusive lesions in both intracranial and neck vessels. HVa was –1052mm^3, and no significant hippocampal atrophy was observed in coronal sections on T1-weighted MRI.

(B) Stenosis+: MR angiography of 81-year-old woman with MCI with multifocal intracranial arterial stenosis, while no steno-occlusive lesions were found in the extracranial carotid arteries. HVa was –3862mm^3, and coronal sections on T1-weighted MRI indicate bilateral hippocampal atrophy.

HVa, hippocampal volume adjusted for intracranial volume; MCI, mild cognitive impairment

Table 10. The association between number of stenotic intracranial arteries ≥ 2 and HVa in the Aβ positive and negative CI group

	Number of stenotic intracranial arteries ≥ 2	B	SE	*P*
HVa (mm^3)	Aβ positive group	-345.62	232.12	0.139
	Aβ negative group	-452.42	278.04	0.108

Note. Covariates for confirmatory multivariable analyses include age, sex, APOE4 carrier status and clinical diagnosis (mild cognitive impairment or AD dementia).

CI, cognitively impaired; SE, standard error; HVa, Hippocampal volume adjusted for intracranial volume

Subgroup analyses for CI: MCI and AD dementia

In the MCI group, there was an association of any extracranial carotid stenosis and ≥ 50% intracranial stenosis with HVa in the exploratory univariable analyses, ($p = 0.028$ and $p = 0.049$, Table 11). However, the confirmatory analysis showed that it was not significant after controlling for age, gender, and APOE4 carrier status ($B = -468.42$, $SE = 290.76$, $p = 0.110$ for any extracranial carotid stenosis and $B = -412.50$, $SE = 276.17$, and $p = 0.130$ for ≥ 50% intracranial stenosis). Additional adjustment for WMH volume did not change the result ($B = -555.85$, $SE = 327.48$, $p = 0.093$ for any extracranial carotid stenosis and $B = -485.68$, $SE = 298.93$, and $p = 0.107$ for ≥ 50% intracranial stenosis, Table 12). In the AD dementia group, the exploratory step of the analyses revealed an association between number of stenotic intracranial arteries ≥ 2 and HVa ($p = 0.031$, Table 13). The association was statistically significant in the confirmatory multivariable analyses after controlling for age, gender, and APOE4 carrier status ($B = -604.32$, $SE = 289.91$, and $p = 0.041$, Table 14). Additional adjustment for normalized WMH volume also revealed a statistically significant association between them ($B = -731.38$, $SE = 329.95$, and $p = 0.031$).

Table 11. Exploratory univariable analyses for the association between extracranial carotid and intracranial arterial stenosis and AD biomarkers in the MCI group.

AD biomarker	Variables	Presence of any detectable stenosis					
		Any extracranial carotid stenosis			Any intracranial stenosis		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.499 ± 0.475	1.474 ± 0.355	0.847	1.515 ± 0.502	1.449 ± 0.379	0.444
Neurodegeneration biomarker	AD-CT	2.699 ± 0.244	2.572 ± 0.244	0.75	2.684 ± 0.285	2.668 ± 0.183	0.746
	HVa	-1662 ± 1158	-2395 ± 811	0.028*	-1624 ± 1211	-2042 ± 1087	0.054
		Severity of stenosis					
		≥ 50 % intracranial stenosis [b]			Number of stenotic intracranial arteries ≥ 2[c]		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.508 ± 0.466	1.378 ± 0.420	0.294	1.505 ± 0.476	1.434 ± 0.394	0.499
Neurodegeneration biomarker	AD-CT	2.681 ± 0.258	2.659 ± 0218	0.747	2.684 ± 0.265	2.652 ± 0.194	0.575
	HVa	-1697 ± 1136	-2315 ± 1378	0.049*	-1678 ± 1194	-2191 ± 1046	0.054
		Location of stenosis					
		Anterior circulation			Posterior circulation		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.527 ± 0.500	1.419 ± 0.363	0.217	1.497 ± 0.466	1.438 ± 0.422	0.673
Neurodegeneration biomarker	AD-CT	2.678 ± 0.286	2.679 ± 0.167	0.982	2.678 ± 0.258	2.682 ± 0.199	0.958
	HVa	-1659 ± 1207	-2010 ± 1100	0.113	-1752 ± 1160	-1984 ± 1236	0.519

Note. Data for continuous variables presented as means ± SD (SUVR for Global Aβ, mm for AD-CT and mm^3 for HVa).

[a] *d* indicates cohen's delta.

[b] "Stenosis-" group of "≥50% intracranial stenosis" means individuals with no stenosis or < 50% intracranial stenosis.

[c] "Stenosis-" group of "number of stenotic intracranial arteries ≥2" means patients with no stenosis or only one stenotic intracranial artery.

*p < 0.05

MCI, mild cognitive impairment; SUVR, standardized uptake value ratio; AD-CT, Alzheimer's disease signature cortical thickness; HVa, Hippocampal volume adjusted for intracranial volume

Table 12. Confirmatory multivariable analyses for the association between extracranial carotid and intracranial arterial stenosis and HVa in the MCI group.

AD biomarker	Variables	Type of stenosis	B	SE	P
Neurodegeneration biomarker	HVa (mm^3)	Any extracranial carotid stenosis	-468.42	290.76	0.110
		≥ 50% intracranial stenosis	-412.50	276.17	0.138

Note. Covariates for confirmatory multivariable analyses include age, sex, APOE4 carrier status.

[a] No significant findings in the exploratory univariable analyses step regarding AD-CT.
Bonferroni corrected $p < 0.05/2 = 0.025$ was used as a statistical threshold)

MCI, mild cognitive impairement; SE, standard error; HVa, Hippocampal volume adjusted for intracranial volume

Table 13. Exploratory univariable analyses for the association between extracranial carotid and intracranial arterial stenosis and AD biomarkers in the AD dementia group.

AD biomarker	Variables	Presence of any detectable stenosis					
		Any extracranial carotid stenosis			Any intracranial stenosis		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.867 ± 0.549	1.805 ± 0.429	0.745	1.895 ± 0.522	1.799 ± 0.546	0.470
Neurodegeneration biomarker	AD-CT	2.409 ± 0.259	2.442 ± 0.276	0.733	2.434 ± 0.293	2.364 ± 0.186	0.284
	HVa	-2829 ± 960	-2397 ± 1169	0.226	-2704 ± 1046	-2952 ± 903	0.322
		Severity of stenosis					
		≥ 50 % intracranial stenosis [b]			Number of stenotic intracranial arteries ≥ 2[c]		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.886 ± 0.531	1.533 ± 0.399	0.152	1.892 ± 0.556	1.733 ± 0.391	0.318
Neurodegeneration biomarker	AD-CT	2.416 ± 0.265	2.324 ± 0.192	0.450	2.437 ± 0.275	2.297 ± 0.158	0.073
	HVa	-2765 ± 1000	-3153 ± 1009	0.406	-2664 ± 1019	-3305 ± 735	0.031*
		Location of stenosis					
		Anterior circulation			Posterior circulation		
		Stenosis-	Stenosis+	*P*-value	Stenosis-	Stenosis+	*P*-value
Aβ biomarker	Global Aβ	1.905 ± 0.513	1.739 ± 0.565	0.247	1.865 ± 0.533	1.823 ± 0.527	0.845
Neurodegeneration biomarker	AD-CT	2.427 ± 0.285	2.362 ± 0.176	0.360	2.418 ± 0.269	2.350 ± 0.199	0.473
	HVa	-2710 ± 1013	-3014 ± 948	0.262	-2768 ± 1036	-2956 ± 707	0.602

Note. Data for continuous variables presented as means ± SD (SUVR for Global Aβ, mm for AD-CT and mm^3 for HVa).

[a] *d* indicates cohen's delta.

[b] "Stenosis-" group of "≥50% intracranial stenosis" means individuals with no stenosis or < 50% intracranial stenosis.

[c] "Stenosis-" group of "number of stenotic intracranial arteries ≥2" means patients with no stenosis or only one stenotic intracranial artery.

*p < 0.05

AD, Alzheimer's disease; SUVR, standardized uptake value ratio; AD-CT, Alzheimer's disease signature cortical thickness; HVa, Hippocampal volume adjusted for intracranial volume

Table 14. Confirmatory multivariable analyses for the association between extracranial carotid and intracranial arterial stenosis and HVa in the AD dementia group.

AD biomarker	Variables	Type of stenosis	B	SE	P
Neurodegeneration biomarker	HVa (mm^3)	Number of stenotic intracranial arteries ≥ 2	- 604.32	289.91	0.041*

Note. Covariates for confirmatory multivariable analyses include age, sex, APOE4 carrier status and clinical diagnosis (mild cognitive impairment or AD dementia).

[a] No significant findings in the exploratory univariable analyses step regarding AD-CT.
*$p < 0.05$
AD, Alzheimer's disease; SE, standard error; HVa, Hippocampal volume adjusted for intracranial volume

DISCUSSION

We investigated the associations of extracranial carotid and intracranial artery stenosis with global Aβ burden and neurodegeneration in a large number of older adults, in CN and CI groups separately. There was no significant association between global Aβ burden and any kinds of vessel stenosis in both groups. In terms of neurodegeneration, the CN group did not show any significant associations between carotid and intracranial artery stenosis and AD-CT or HVa. However, the CI group, number of stenotic intracranial arteries $\geq$ 2 was significantly related with reduced HVa even after adjusting for age, gender, APOE4 carrier status and diagnosis (i.e., MCI vs. AD dementia).

Previously, several *postmortem* brain studies investigated the association between cerebral atherosclerosis and Aβ burden, but the results were controversial. Although a number of previous autopsy studies found a significant relation between intracranial atherosclerosis and neuritic plaques in AD (3-6), several other studies did not report such associations (5-8). A recent in vivo, community based study in adults without dementia reported that intracranial atherosclerotic plaque or stenosis was not associated with Aβ deposition in the brain (16). Our results in both CN and CI groups are in agreement with the study (16). We could not find an association between carotid and intracranial stenosis and global Aβ burden via GLM analyses for the association between stenosis and HVa in each of amyloid positive and negative group analyses as well as multivariable analyses for the association between stenosis and global Aβ burden. Aforementioned positive association between cerebral atherosclerosis and Aβ deposition might be resulted from the possibility of coincidence of them in the elderly.

In contrast to global Aβ burden, intracranial artery stenosis in the CI group showed a significant association with a neurodegeneration biomarker. In particularly, number of stenotic intracranial arteries ≥ 2 was significantly associated with lower hippocampal volume in CI subjects in confirmatory multivariable analysis. There have been some previous studies which identified intracranial atherosclerosis as an independent risk factor for cerebral atrophy (7, 32). In these studies, however, intracranial atherosclerosis was assessed based only on cavernous ICA calcification on computed tomography (32) or pathological examination of the circle of Willis (33). In contrast, we evaluated stenosis of all cerebral arteries. With this approach and strict control for multiple testing errors, we could confirm the association between intracranial artery stenosis and HVa in the CI group. The association remained significant even after controlling for WMH volume, suggesting that intracranial artery stenosis affects hippocampal atrophy independently of changes in the WM. In addition, we checked the associations between stenosis and AD biomarkers in both MCI and AD separately. The results for each of MCI and AD subgroup were very similar to those for overall CI. In both MCI and AD, there was no significant relationship of stenosis with global Aβ burden deposition and AD-CT, while we found significant associations or trend level of associations between stenosis indices and HVa. There was a significant association between number of stenotic intracranial arteries ≥ 2 and reduced HVa in AD dementia. Because of relatively small number of stenosis in each MCI and AD dementia, the results in CI group provide more solid basis with sufficient statistical power. Hippocampal atrophy is a validated neurodegeneration biomarker of AD and is closely correlated with early cognitive decline in AD (34). Therefore, the association of intracranial stenosis with decreased HVa, together with no

association with Aβ burden, in the CI group indicates that intracranial stenosis contributes to the development of CI via Aβ-independent neurodegeneration of the hippocampus.

In the CN group, while exploratory univariable analyses found relations between various types of stenosis and AD-CT or HVa in CN, such relations were not significant in multivariable analyses using a strict statistical threshold. Nevertheless, an association between AD-CT and location of stenosis draw our attention. AD-CT tended to be lower in subjects with posterior circulation stenosis than those without ($p = 0.03$), although the difference was not statistically significant after Bonferroni correction. Actually, the AD-signature regions, where we measured cortical thickness, include the entorhinal, inferior temporal, and fusiform gyri that receive blood supply from the PCA. According to a previous *postmortem* study which investigated the association between intracranial artery atherosclerosis and AD dementia, the most severe atherosclerosis was found the posterior cerebral artery (PCA), one of the posterior circulation, among the circle of Willis arteries in AD dementia patients (9). Therefore, the potential association between posterior circulation stenosis and AD-CT deserves attention.

We found no significant associations between extracranial carotid stenosis and AD biomarkers in both CN and CI groups. Some previous *in vivo* studies with very small sample sizes investigated the associations between severe carotid stenosis or occlusion and Aβ deposition and provided in conflicting results. While one study using [^{18}F] AV-45 PET reported that Aβ deposition increased in dementia patients with unilateral carotid artery stenosis, and was lateralized to ipsilateral side of stenosis (14), a more recent study using [^{18}F] flutemetamol PET indicated that cerebral hypoperfusion caused by unilateral occlusion of the ICA was not related

with brain accumulation of Aβ (15). In terms of association between extracranial carotid stenosis and neurodegeneration, our results were in disagreement with several previous studies that showed increased carotid intima–media thickness and carotid stenosis were related with decreased total brain volume (10, 35). This discrepancy may have been due to difference in the severity of stenosis in the included subjects. In our study, there were only a very small number of subjects with ≥ 50% stenosis in the extracranial carotid artery (1 of 281 subjects in the CN group and 1 of 196 subjects in the CI group). However, many previous studies indicated associations of the degree of severity (5, 35) or severe carotid atherosclerosis (36, 37) with brain atrophy.

To our knowledge, this is the first study to investigate the association between MR angiography-based measured vessel stenosis in both extracranial carotid and intracranial arteries and several *in vivo* AD pathologies, including both Aβ deposition and neurodegeneration, in a large sample of older adults, focusing separately on CN and CI groups. However, there were several limitations. First, this was a cross-sectional design, so we cannot make conclusions regarding the cause and effect relationship between carotid and intracranial artery stenosis and *in vivo* AD pathologies. Second, in spite of a relatively large number of subjects, the frequencies of stenosis, particularly extracranial carotid stenosis, number of stenotic intracranial arteries ≥ 2, and posterior circulation stenosis were relatively low, which may have reduced statistical power and made it difficult to identify significant associations after multiple comparison correction. Carotid and intracranial artery stenosis has not been a common finding in community-dwelling subjects (38, 39), with reported prevalence rates of asymptomatic intracranial stenosis ranging from 5.9% to 24.5% (39). In addition, the prevalence of cervical

carotid artery stenosis varies significantly with ethnicity, and it was reported to be particularly uncommon in a Korean population-based screening cohort (38). Our study population seemed to reflect the prevalence of asymptomatic carotid and intracranial stenosis in the general Asian population. Third, given that about 55% of MCI individuals and 23% of clinically defined AD dementia patients among the subjects were Aβ negative, brain pathological conditions other than AD and vascular lesions, such as primary age-related taupathy and argyrophilic grain disease, might contribute to neurodegenerative changes. In addition, although CDR-SOB and HVa were significantly correlated, there are several clinical factors which can affect the cognition status other than HVa. Future studies including the examination of the conditions are needed.

In conclusion, our findings suggested that neither carotid nor intracranial artery stenosis are associated with brain Aβ burden, while intracranial artery stenosis is related to amyloid-independent neurodegeneration, particularly hippocampal atrophy. This supports the importance of proper management of intracranial artery stenosis for delaying the progression of AD neurodegeneration and related cognitive decline.

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초 록

서론: 뇌 혈관 질환이 알츠하이머 병 (AD)의 발병에 기여할 수 있음을 시사하는 증거들이 축적되고 있지만, 경동맥 및 두개내 동맥의 죽상 동맥 경화증이 생체 내 AD 병리와 관련이 있는지 여부는 명확하지 않다. 경동맥과 두개내 혈관의 협착이 알츠하이머병 병리와 관련이 있는지를 알아보기 위해, 대뇌 베타 아밀로이드 침착과 신경퇴행성 변화와 경동맥 및 두개내 혈관 협착과의 관계를 중년 및 노년 인구에서 조사하였다. 인지 기능 상태에 따라 AD 병리에 차이가 있음에 고려하여 인지기능 정상군과 인지기능 저하군에서 각각 연구를 시행하였다.

방법: 281명의 인지기능 정상군과 199명의 인지기능 저하군이 임상 평가를 받고, [11C] Pittsburgh compound B-양전자단층촬영, 자기공명혈관조영술을 포함한 자기공명영상을 시행하였다. 경동맥과 두개내 혈관의 협착 유무, 협착의 심각성(협착 수와 협착된 정도), 그리고 협착의 위치를 평가하였다.

결과: 두 군에서 모두 경동맥과 두개내 혈관의 협착과 대뇌 베타 아밀로이드 침착간의 관련성은 없었다. 신경퇴행성 변화에 대한 탐색적 단변수 분석에서 두 군 모두 협착의 유무 및 심각성과 지역적 신경퇴행성 바이오마커 (해마 부피 감소, 알츠하이머병 특정 부위의 피질 두께 감소)간에 관련성이 있었다. 인구학적 변수와 진단명을 통제한 확증적 다변수 분석에서는 인지기능 저하군에서, 협착이 있는 두개내 혈관의 수가 2군데 이상인 것과 해마 부피 감소가 관련성이 있었다.

결론: 경동맥과 두개내 혈관의 협착 모두 대뇌 베타 아밀로이드 침착과 관련이 없는 반면, 두개내 혈관의 협착은 인지기능 저하군에서 해마위축으로 나타나는 신경퇴행성 변화와 관련이 있었으며, 이는

아밀로이드 침착과는 독립적이었다. 본 연구는 AD의 치료에 뇌혈관질환의 조절이 신경퇴행성변화를 지연하는데 중요한 역할을 할 것임을 시사한다.

주요어: 알츠하이머병, 아밀로이드 베타, 신경퇴행, 동맥경화증, 두개내 혈관 협착, 경동맥 협착, 인지 저하

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