Association between *APOE* $\epsilon 2$ and $A\beta$ burden in patients with Alzheimer- and vascular-type cognitive impairment

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Abstract

Objective

To investigate the association between *APOE* genotype and β -amyloid ($A\beta$) burden, as measured by PET in patients with subcortical vascular cognitive impairment (SVCI) and those with Alzheimer disease–related cognitive impairment (ADCI).

Methods

This was a cross-sectional study of 310 patients with SVCI and 999 with ADCI. To evaluate the effects of *APOE* genotype or diagnostic group on $A\beta$ positivity, we performed multivariate logistic regression analyses. Further distinctive underlying features of latent subgroups were examined by employing a latent class cluster analysis approach.

Results

In comparison with $\epsilon 3$ homozygotes, in the ADCI group, $\epsilon 2$ carriers showed a lower frequency of $A\beta$ positivity (odds ratio [OR] 0.43, 95% confidence interval [CI] 0.23–0.79), while in the SVCI group, $\epsilon 2$ carriers showed a higher frequency of $A\beta$ positivity (OR 2.26, 95% CI 1.02–5.01). In particular, we observed an interaction effect of $\epsilon 2$ carrier status and diagnostic group on $A\beta$ positivity (OR 5.12, 95% CI 1.93–13.56), in that relative to $\epsilon 3$ homozygotes, there were more $A\beta$ -positive $\epsilon 2$ carriers in the SVCI group than in the ADCI group. We also identified latent subgroups of $A\beta$ -positive *APOE* $\epsilon 2$ carriers with SVCI and $A\beta$ -positive *APOE* $\epsilon 4$ carriers with ADCI.

Conclusions

Our findings suggest that *APOE* $\epsilon 2$ is distinctly associated with $A\beta$ deposition in patients with SVCI and those with ADCI. Our findings further suggest that there is a distinctive subgroup of $A\beta$ -positive *APOE* $\epsilon 2$ carriers with SVCI among patients with cognitive impairment.

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Glossary

AAL = automated anatomical labeling; **A β** = β -amyloid; **AD** = Alzheimer disease; **ADCI** = Alzheimer disease–related cognitive impairment; **aMCI** = amnesic mild cognitive impairment; **BAPL** = brain amyloid–plaque load; **BIC** = Bayesian information criterion; **CAA** = cerebral amyloid angiopathy; **CI** = confidence interval; **CSVD** = cerebral small vessel disease; **LCA** = latent class cluster analysis; **MMSE** = Mini-Mental State Examination; **OR** = odds ratio; **PiB** = Pittsburgh compound B; **RCTU** = regional cortical tracer uptake; **SUV** = standardized uptake value; **SUVR** = standardized uptake value ratio; **SVaD** = subcortical vascular dementia; **SVC** = subcortical vascular cognitive impairment; **svMCI** = subcortical vascular mild cognitive impairment; **VOI** = volume of interest; **WMH** = white matter hyperintensities.

Although β -amyloid (A β) deposition is a pathologic hallmark of Alzheimer disease (AD), A β deposition occurs in a number of heterogeneous conditions. In particular, A β deposition frequently coexists with subcortical vascular cognitive impairment (SVC).^{1,2} Previous studies have also shown that A β is strongly associated with cerebral small vessel disease (CSVD).^{2–5} This suggests the possibility that amyloid clearance is decreased in CSVD, or, alternatively, that cerebral amyloid angiopathy (CAA) accelerates CSVD.

The *APOE* ϵ 4 allele is an important risk factor for A β deposition in SVC as well as in AD. Whereas *APOE* ϵ 2 is known to reduce the risk of A β deposition in AD,^{6,7} the relationship between *APOE* ϵ 2 and A β deposition in SVC has not been fully determined. A prior study indicated that in *APOE* ϵ 4 noncarriers with SVC, CSVD severity was directly related to A β burden.⁸ In addition, A β -positive patients with AD with *APOE* ϵ 2 exhibited more severe CSVD than those with *APOE* ϵ 4 in a recent study.⁹ Because CSVD induces leakage of *APOE*, which is a plasma lipoprotein that functions in A β clearance¹⁰ and eventually results in decreased A β clearance,¹¹ we hypothesized that *APOE* ϵ 2 might increase A β positivity in patients with SVC.

In this study, we investigated the associations between *APOE* genotype and A β burden in patients with SVC and those with AD-related cognitive impairment (ADCI). Moreover, to resolve the complex relationships between *APOE* genotype, CSVD, and A β positivity in cognitively impaired patients, we assessed the distinctiveness of latent subgroups identified using a latent class cluster analysis (LCA) approach.

Methods

Standard protocol approval, registration, and patient consent

Each patient provided written informed consent, and all procedures were carried out in accordance with approved guidelines. This study was approved by the institutional review board of the Samsung Medical Center.

Study participants

We recruited 312 patients with SVC (156 with subcortical vascular mild cognitive impairment [svMCI] and 156 with subcortical vascular dementia [SVaD]) who underwent ¹¹C-

Pittsburgh compound B (PiB), ¹⁸F-florbetaben, or ¹⁸F-flutemetamol PET scanning at the Samsung Medical Center (Seoul, Korea) from September 2008 to June 2018. All patients met the following criteria for SVC diagnosis: (1) a subjective cognitive complaint from either the patient or a caregiver; (2) an objective cognitive impairment below the 16th percentile in any domain, including attention, language, visuospatial, memory, and frontal/executive functions, on detailed neuropsychological tests^{12,13}; (3) significant ischemia on brain MRI, defined as periventricular white matter hyperintensities (WMH) ≥ 10 mm and deep WMH ≥ 25 mm, modified from the Fazekas ischemia criteria, as described in previous studies^{14,15}; and (4) focal neurologic symptoms or signs. Although we did not include other CSVD MRI markers in our inclusion criteria, 90.4% of patients with SVC had lacunes and 66.2% of those had cerebral microbleeds. Patients with SVC were classified as having svMCI or SVaD according to their impairment in general cognition, as measured by the Mini-Mental State Examination (MMSE) and instrumental activities of daily living scale.^{12,16}

For comparisons with SVC, we recruited 1,015 patients with ADCI (549 with amnesic mild cognitive impairment [aMCI] and 466 with AD dementia) who underwent ¹¹C-PiB, ¹⁸F-florbetaben, or ¹⁸F-flutemetamol PET scanning at the Samsung Medical Center from August 2015 to October 2018. Patients with aMCI were diagnosed using the Petersen criteria,¹⁷ with modifications that have been described in detail elsewhere.¹⁵ The patients with probable AD dementia fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria.¹⁸ Patients with ADCI presented with memory impairment rather than other cognitive impairments, and did not have focal neurologic symptoms or signs. To evaluate CSVD burden in patients with ADCI, we used a modified Fazekas scale for visual WMH rating.^{14,15} Nearly all patients with ADCI (94.6%) showed no to moderate degree of WMH. We classified patients with ADCI into the following 2 groups based on the presence of WMH: (1) minimal degree of WMH, referred to as ADCI/WMH–; and (2) moderate to severe degree of WMH, referred to as ADCI/WMH+.

All patients were evaluated through clinical interviews and neurologic and neuropsychological examinations, as

previously described.¹⁹ Patients also underwent laboratory tests, including a complete blood count, blood chemistry assessment, vitamin B₁₂/folate evaluation, syphilis serologic assessment, and thyroid function tests. Brain MRI confirmed the absence of structural lesions including territorial cerebral infarction, brain tumors, hippocampal sclerosis, and vascular malformation.

Genomic DNA was extracted from whole blood samples to perform *APOE* genotyping, as previously described.²⁰ A total of 16 patients with ADCl and 2 patients with SVCl had the *APOE* $\epsilon 2/\epsilon 4$ genotype. These individuals were excluded from the main analysis due to the putative opposing effects of the $\epsilon 4$ and $\epsilon 2$ alleles.^{21,22} Therefore, the final sample of the current study consisted of 1,309 individuals, 310 with SVCl (156 with svMCI and 154 with SVaD) and 999 with ADCl (537 with aMCI and 462 with AD dementia).

Brain MRI scans

We used a 3.0T MRI scanner (Philips, Best, the Netherlands) to acquire T1, fluid-attenuated inversion recovery, and T2*-weighted gradient recalled echo MRI from all participants at Samsung Medical Center. Achieva 3.0T MRI scanner (Philips) was used to obtain 3D T1 turbo field echo MRI data. The required imaging parameters for the acquisition were as follows: sagittal slice thickness, 1.0 mm with 50% overlap; no gap; repetition time 9.9 ms; echo time 4.6 ms; flip angle 8°; matrix size of 240 × 240 pixels reconstructed to 480 × 480 over a field view of 240 mm.

¹¹C-PiB PET acquisition and analysis

We performed ¹¹C-PiB PET scanning in 247 patients (133 with SVCl and 114 with ADCl) using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI) at Samsung Medical Center. We coregistered the ¹¹C-PiB PET images to each individual's MRI data. Then the coregistered ¹¹C-PiB PET images were normalized to a T1-weighted MRI template. Automated volume of interest (VOI) analysis by the automated anatomical labeling (AAL) atlas was conducted to obtain the quantitative regional values of PiB retention on the spatially normalized PiB images. SPM version 2 was used for data processing on MatLab 6.5 (Mathworks, Natick, MA).

In order to measure PiB retention, the cerebral cortical region-to-cerebellum uptake ratio that is identical to the standardized uptake value ratio (SUVR) was used. We used the cerebellum as the reference region because specific binding of PiB rarely occurs in postmortem samples of the cerebellar cortex, even among patients with AD at autopsy.²³ Using the AAL atlas, 28 cortical VOIs (additional methods available from Dryad, doi.org/10.5061/dryad.dr7sqv9vs.) were selected from both the left and right hemispheres. To calculate the regional cerebral cortical SUVRs, we divided the standardized uptake value (SUV) of each cortical VOI by the mean SUV of the cerebellar cortex (cerebellum crus1 and crus2). To calculate the global PiB uptake ratio, we used the volume-weighted average SUVR of the 28 bilateral cerebral

cortical VOIs. We set the global PiB SUVR cutoff value for A β positivity at 1.5 or higher.¹ We followed the previously used methods for ¹¹C-PiB PET scanning and acquisition of the global PiB retention ratio, and the detailed methods are particularized in previous studies.^{1,8}

¹⁸F-labelled amyloid PET acquisition and analysis

A total of 1,062 patients (177 with SVCl and 885 with ADCl) were scanned with ¹⁸F-labeled amyloid PET (775 underwent ¹⁸F-florbetaben PET and 287 underwent ¹⁸F-flutemetamol PET) at Samsung Medical Center. Using the same type of scanner with ¹¹C-PiB PET scanning, we ran a 3D scanning mode to examine 47 slices of 3.3-mm thickness spanning the entire brain. To correct attenuation, CT images were obtained using 16-slice helical CT (140 KeV, 80 mA; 3.75 mm section width). Regarding ¹⁸F-florbetaben and ¹⁸F-flutemetamol PET, we performed an emission PET scan for 20 minutes in dynamic mode (consisting of 4 × 5-minute frames), and there was a 90-minute time span after the injection of 311.5 MBq ¹⁸F-florbetaben and 197.7 MBq ¹⁸F-flutemetamol. We also used the ordered-subset expectation maximization algorithm (¹⁸F-florbetaben, iteration = 4 and subset = 20; ¹⁸F-flutemetamol, iteration = 4 and subset = 20) to reconstruct 3D PET images in a 128 × 128 × 48 matrix with a 2 × 2 × 3.27 mm³ voxel size.

All PET images were visually assessed and dichotomized as A β -positive or A β -negative after being reviewed by nuclear medicine physicians who were blinded to patient information. ¹⁸F-florbetaben PET findings were considered positive for brain amyloid-plaque load (BAPL) score²⁴ of 2 or 3 from the visual assessment. Regarding regional cortical tracer uptake (RCTU), image evaluators used the RCTU scoring system (RCTU 1, no tracer uptake; RCTU 2, moderate tracer uptake; RCTU 3, pronounced tracer uptake) in the brain areas of the lateral temporal cortex, frontal cortex, posterior cingulate cortex/precuneus, and parietal cortex. In regards to RCTU and BAPL correspondence, an RCTU score of 1 in each brain region was considered to be identical to a BAPL score of 1. An RCTU score of 2 in at least 1 brain region and no score of 3 was considered as a BAPL score of 2. An RCTU score of 3 in any of the 4 brain regions was considered as a BAPL score of 3. A β -negative status was given for those with a BAPL score of 1; A β -positive status was given for those with BAPL scores of 2 or 3. Our visual assessment highly corresponded with the binarized global ¹⁸F-florbetaben PET binding evaluations (SUVR cutoff, 1.407), as the comparison of the 2 methods resulted in a high accuracy of 94.4% (sensitivity 91.5% [43 of 47] and specificity 96.7% [58 of 60]).¹⁶

The technique for visual interpretation of ¹⁸F-flutemetamol PET images was based on a systematic review of the following brain regions: frontal, parietal, posterior cingulate and precuneus, striatum, and lateral temporal lobes.²⁵ For the scan to be considered A β -positive, any of the brain regions had to

Table 1 Demographic and clinical characteristics of the study participants

	SVCI	ADCI		
		Total	ADCI/WMH–	ADCI/WMH+
Total	310 (100.0)	999 (100.0)	651 (65.2)	348 (34.8)
Age, y	75.7 ± 6.9 ^a	70.2 ± 9.0	68.2 ± 9.1 ^b	74.0 ± 7.4
Female	202 (65.2) ^a	555 (55.6)	360 (55.3)	195 (56.0)
Education, y	8.9 ± 5.5 ^a	11.7 ± 4.9	12.0 ± 4.7 ^b	11.0 ± 5.3
MMSE score	21.9 ± 5.9	22.3 ± 6.4	22.4 ± 6.4	21.9 ± 6.3
CDR-SOB	4.2 ± 3.8 ^a	3.4 ± 3.3	3.3 ± 3.2	3.6 ± 3.3
APOE genotype				
ε2 carriers	34 (11.0) ^a	54 (5.4)	27 (4.1) ^b	27 (7.8)
ε3/ε3	192 (61.9) ^a	502 (50.3)	338 (51.9)	164 (47.1)
ε4 carriers	84 (27.1) ^a	443 (44.3)	286 (43.9)	157 (45.1)
Aβ positivity	108 (34.8) ^a	646 (64.7)	411 (63.1)	235 (67.5)
Sex				
Male	39 (36.1) ^a	272 (61.3)	175 (60.1)	97 (63.4)
Female	69 (34.2) ^a	374 (67.4)	236 (65.6)	138 (70.8)
APOE genotype				
ε2 carriers	14 (41.2)	17 (31.5)	6 (22.2)	11 (40.7)
ε3/ε3	47 (24.5) ^a	256 (51.0)	169 (50.0)	87 (53.0)
ε4 carriers	47 (56.0) ^a	373 (84.2)	236 (82.5)	137 (87.3)
Types of PET tracers				
¹¹ C-PiB	133 (42.9) ^a	114 (11.4)	72 (11.1)	42 (12.1)
¹⁸ F-FBB	157 (50.6) ^a	618 (61.9)	391 (60.1)	227 (65.2)
¹⁸ F-FMM	20 (6.5) ^a	267 (26.7)	188 (28.9) ^b	79 (22.7)

Abbreviations: Aβ = β-amyloid; ADCI = Alzheimer disease–related cognitive impairment; CDR-SOB = Clinical Dementia Rating Sum of Boxes; FBB = florbetaben; FMM = flutemetamol; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; SVCI = subcortical vascular cognitive impairment; WMH = white matter hyperintensities; WMH– = minimal degree of white matter hyperintensities; WMH+ = moderate to severe degree of white matter hyperintensities.

Values are mean ± SD or n (%). Statistical analyses were performed using χ^2 test, Fisher exact test, or Student *t* test.

^a Difference between SVCI and ADCI (total), *p* value < 0.05.

^b Difference between ADCI/WMH– and ADCI/WMH+, *p* value < 0.05.

show positive findings in either hemisphere. Having 1 or more regions with high cortical gray matter signal (above 50%–60% peak intensity) or low (or absent) gray–white matter contrast (a less distinct white matter sulcal pattern) indicated positive scans. If the scan did not show any of these characteristics, the scan was considered Aβ-negative. Only readers with successful completion of the electronic training program that was provided by the manufacturer were qualified to interpret ¹⁸F-flutemetamol PET images.

Statistical analyses

Continuous variables were compared using Student *t* tests and are presented as mean ± SD. Categorical variables were compared using the χ^2 test or Fisher exact test.

To investigate the effects of *APOE* genotype or diagnostic group (SVCI, ADCI, ADCI/WMH–, and ADCI/WMH+) on Aβ positivity, logistic regression analyses were conducted using age (continuous), *APOE* genotype (3 categories: ε2 carriers [ε2/ε2 and ε2/ε3], ε3 homozygotes [ε3/ε3], and ε4 carriers [ε3/ε4 and ε4/ε4]), type of PET tracer (¹¹C-PiB, ¹⁸F-florbetaben, ¹⁸F-flutemetamol), and diagnostic group as independent variables and Aβ positivity as the dependent variable (model 1). To evaluate the distinct effects of *APOE* genotype on Aβ positivity according to the diagnostic group, an interaction term (*APOE* genotype * diagnostic group) was added to the independent variables of model 1 (model 2). To estimate the frequency of Aβ positivity according to age and *APOE* genotype in the ADCI and SVCI groups,

Figure 1 Frequency of β -amyloid ($A\beta$) positivity

(A) Frequency of $A\beta$ positivity according to $APOE$ genotypes in the subcortical vascular cognitive impairment (SVCI) and Alzheimer disease-related cognitive impairment (ADICI) groups. (B) Frequency of $A\beta$ positivity according to $APOE$ genotypes in the ADICI/white matter hyperintensities (WMH)- and ADICI/WMH+ groups. * p value < 0.05. ** p value < 0.001. WMH- = minimal degree of WMH; WMH+ = moderate to severe degree of WMH.

estimated probabilities and 95% confidence intervals (CIs) were generated from logistic regression analyses after adjusting for age (continuous) and $APOE$ genotype ($\epsilon 2$ carriers, $\epsilon 3$ homozygotes, and $\epsilon 4$ carriers). Statistical significance was set at a p value < 0.05 in 2-tailed tests. Statistical analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, IL).

Further distinctive underlying features of latent subgroups were examined by employing an LCA, an unsupervised learning method that aims to find intrinsic structures and particular input patterns in data,^{26,27} thereby enabling the identification and summarization of complex risk factors in patients with multifactorial diseases. Since the LCA is generated by using categorical variables as observed variables, we included the following variables in the model: $APOE$ genotype, $A\beta$ positivity, sex, and diagnostic group (SVCI or ADICI). Unlike K-means clustering, a latent class model has a criterion for finding an optimal number of classes, such as the Bayesian information criterion (BIC).²⁸ The 4-class model had the lowest BIC value, and was therefore declared the best model in this study (table e-1, data available from Dryad, doi.org/10.5061/dryad.dr7sqv9vs).²⁹ Post hoc analyses using the Tukey honestly significant difference test or the Kruskal-Wallis test were conducted for multiple comparisons among the classes. All p values were Bonferroni-corrected. Statistical analyses were conducted in R version 3.5.2.³⁰

Data availability

Anonymized data will be shared upon request from any qualified investigator, only for the purpose of replicating procedures and results.

Results

Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of the study participants. The proportions (percentages) of $APOE$ genotypes ($\epsilon 2$ carriers, $\epsilon 3$ homozygotes, and $\epsilon 4$ carriers) were 11.0%, 61.9%, and 27.1% in the SVCI group and 5.4%, 50.3%, and 44.3% in the ADICI group, respectively. Comparisons between SVCI and ADICI showed that the SVCI group had a higher frequency of $\epsilon 2$ carriers (p value = 0.001) and $\epsilon 3$ homozygotes (p value < 0.001), whereas the ADICI group had a higher frequency of $\epsilon 4$ carriers (p value < 0.001).

When we subdivided the ADICI group according to the presence of WMH into the ADICI/WMH+ and ADICI/WMH- groups, the ADICI/WMH+ group consisted of 348 individuals, thus representing 34.8% of the ADICI group. The proportions of $APOE$ genotypes ($\epsilon 2$ carriers, $\epsilon 3$ homozygotes, and $\epsilon 4$ carriers) were 4.1%, 51.9%, and 43.9% in the ADICI/WMH- group and 7.8%, 47.1%, and 45.1% in the ADICI/WMH+ group, respectively. The ADICI/WMH+ group had a higher frequency of $\epsilon 2$ carriers than the ADICI/WMH- group (p value = 0.016).

Frequency of $A\beta$ positivity according to $APOE$ genotype

The frequencies of $A\beta$ positivity were 34.8% in the SVCI group (30.1% with svMCI and 39.6% with SVaD) and 64.7% in the ADICI group (47.9% with aMCI and 84.2% with AD dementia) (table 1). The frequencies of $A\beta$ positivity according to $APOE$ genotypes ($\epsilon 2$ carriers, $\epsilon 3$ homozygotes, and $\epsilon 4$ carriers) were 41.2%, 24.5%, and 56.0% in the SVCI

Table 2 Association of clinical information and *APOE* genotype with β -amyloid ($A\beta$) positivity in the subcortical vascular cognitive impairment (SVCI) vs the Alzheimer disease-related cognitive impairment (ADCI) or the ADCI/white matter hyperintensities (WMH)– vs the ADCI/WMH+ group

	SVCI		ADCI		Total (SVCI + ADCI)		ADCI/WMH–		ADCI/WMH+		Total (ADCI)	
	Adjusted OR for $A\beta$ positivity (95% CI)	<i>p</i> Value	Adjusted OR for $A\beta$ positivity (95% CI)	<i>p</i> Value	Adjusted OR for $A\beta$ positivity (95% CI)	<i>p</i> Value	Adjusted OR for $A\beta$ positivity (95% CI)	<i>p</i> Value	Adjusted OR for $A\beta$ positivity (95% CI)	<i>p</i> Value	Adjusted OR for $A\beta$ positivity (95% CI)	<i>p</i> Value
Age	1.10 (1.05–1.15)	<0.001	0.99 (0.97–1.00)	0.094	1.00 (0.99–1.02)	0.869	0.98 (0.96–1.00)	0.014	1.00 (0.97–1.03)	0.968	0.98 (0.97–1.00)	0.027
Sex												
Male	Reference		Reference		Reference		Reference		Reference		Reference	
Female	0.79 (0.46–1.35)	0.391	1.20 (0.91–1.60)	0.203	1.14 (0.89–1.45)	0.312	1.21 (0.85–1.72)	0.300	1.21 (0.74–1.99)	0.447	1.20 (0.90–1.59)	0.215
PET tracers												
¹¹ C-PiB	Reference		Reference		Reference		Reference		Reference		Reference	
¹⁸ F-FBB	0.84 (0.49–1.46)	0.544	0.49 (0.30–0.82)	0.006	0.75 (0.53–1.06)	0.752	0.35 (0.18–0.69)	0.002	0.84 (0.38–1.83)	0.658	0.50 (0.30–0.82)	0.006
¹⁸ F-FMM	1.32 (0.47–3.71)	0.603	0.34 (0.20–0.58)	<0.001	0.53 (0.35–0.80)	0.528	0.24 (0.12–0.49)	<0.001	0.60 (0.25–1.42)	0.243	0.34 (0.20–0.59)	<0.001
<i>APOE</i> genotype												
$\epsilon 3/\epsilon 3$	Reference		Reference		Reference		Reference		Reference		Reference	
$\epsilon 2$ carriers	2.26 (1.02–5.01)	0.045	0.43 (0.23–0.79)	0.006	0.76 (0.47–1.23)	0.261	0.26 (0.10–0.68)	0.006	0.60 (0.26–1.37)	0.223	0.41 (0.22–0.75)	0.004
$\epsilon 4$ carriers	4.23 (2.39–7.48)	<0.001	4.92 (3.60–6.73)	<0.001	4.64 (3.55–6.06)	<0.001	4.58 (3.13–6.69)	<0.001	5.83 (3.31–10.28)	<0.001	4.90 (3.58–6.71)	<0.001
Diagnostic group												
ADCI					Reference							
SVCI					0.27 (0.20–0.38)	<0.001						
ADCI/WMH–											Reference	
ADCI/WMH+											1.39 (1.01–1.91)	0.044

Abbreviations: CI = confidence interval; FBB = florbetaben; FMM = flutemetamol; OR = odds ratio; PiB = Pittsburgh compound B; WMH– = minimal degree of WMH; WMH+ = moderate to severe degree of WMH. Statistical analyses were performed using logistic regression with age (continuous), sex, type of PET tracer, *APOE* genotype, and diagnostic group as independent variables and $A\beta$ positivity as a dependent variable.

group and 31.5%, 51.0%, and 84.2% in the ADCI group, respectively.

As shown in figure 1A and table 2, in the ADCI group, $\epsilon 2$ carriers showed a lower frequency of A β positivity than $\epsilon 3$ homozygotes (odds ratio [OR] 0.43, 95% CI 0.23–0.79), while $\epsilon 4$ carriers showed a higher frequency of A β positivity (OR 4.92, 95% CI 3.60–6.73). However, in the SVCI group, both $\epsilon 2$ carriers (OR 2.26, 95% CI 1.02–5.01) and $\epsilon 4$ carriers (OR 4.23, 95% CI 2.39–7.48) showed a higher frequency of A β positivity than $\epsilon 3$ homozygotes.

The frequencies of A β positivity were 63.1% in the ADCI/WMH– group (45.2% with aMCI and 87.1% with AD dementia) and 67.5% in the ADCI/WMH+ group (53.9% with aMCI and 79.8% with AD dementia) (table 1). The frequencies of A β positivity according to APOE genotypes ($\epsilon 2$ carriers, $\epsilon 3$ homozygotes, and $\epsilon 4$ carriers) were 22.2%, 50.0%, and 82.5% in the ADCI/WMH– group and 40.7%, 53.0%, and 87.3% in the ADCI/WMH+ group, respectively. In the ADCI/WMH– group, $\epsilon 2$ carriers showed a lower frequency of A β positivity than $\epsilon 3$ homozygotes (OR 0.26, 95% CI 0.10–0.68); however, no statistically significant difference was found in the ADCI/WMH+ group (OR 0.60, 95% CI 0.26–1.37) (figure 1B and table 2).

When the ADCI and SVCI groups were combined, we observed an interaction effect of $\epsilon 2$ carrier status and diagnostic group on A β positivity (OR 5.12, 95% CI 1.93–13.56) (figure 2), in that relative to $\epsilon 3$ homozygotes, there were more A β -positive $\epsilon 2$ carriers in the SVCI group than in the ADCI group. When comparing the SVCI group with the ADCI/WMH– or the ADCI/WMH+ group, we also observed interactions of $\epsilon 2$ carrier status and diagnostic group on A β positivity (OR 7.81, 95% CI 2.33–26.17 in ADCI/WMH– [used as the reference] vs SVCI and OR 3.86, 95% CI 1.24–12.01 in ADCI/WMH+ [reference] vs SVCI) (figure 2). However, no effects of interactions between $\epsilon 4$ carrier status and diagnostic group (ADCI vs SVCI and ADCI/WMH– vs ADCI/WMH+) on A β positivity were observed

(OR 0.79, 95% CI 0.42–1.48 and OR 1.28, 95% CI 0.65–2.52).

Prevalence estimates of A β positivity according to age and APOE genotype

In the ADCI group, age tended to be inversely associated with A β positivity (OR 0.99, 95% CI 0.97–1.00), while in the SVCI group, age was positively associated with A β positivity (OR 1.10, 95% CI 1.05–1.15) (table 2). Figure 3 shows the prevalence estimates of A β positivity according to age and APOE genotype in the SVCI and ADCI groups. In the SVCI group, the difference in prevalence estimates of A β positivity between $\epsilon 2$ carriers and $\epsilon 3$ homozygotes was about 10 years (table e-2, data available from Dryad, doi.org/10.5061/dryad.dr7sqv9vs).

Identification of the clinical characteristics of latent subgroups according to diagnostic group

Figure 4 demonstrates the allocation of features to each group resulting from the LCA procedure. According to the LCA model, class 1 and class 4 were characterized by A β positivity. Class 1 showed a high percentage of patients with ADCI with $\epsilon 3$ homozygote or $\epsilon 4$ carrier status, while class 4 consisted of only patients with SVCI with $\epsilon 2$ carrier status. Class 2 had the highest proportion of females (353 out of 454 cases; 77.8%). Class 3 consisted of only men with ADCI and had more $\epsilon 3$ homozygotes and a higher proportion of A β negativity overall than the other classes.

Table 3 shows the within-class means and percentages of demographic and clinical features produced by the LCA. The mean age was lower in class 1 (70.1 ± 0.4 years) than in the other classes (adjusted p values < 0.05 for comparisons with class 2 and class 4), and these patients had a lower MMSE score (22.0 ± 0.2 , adjusted p values < 0.05 for comparisons with class 2 and class 3) and a higher Clinical Dementia Rating Sum of Boxes score (4.4 ± 0.1 , adjusted p values < 0.05 for comparisons with class 2 and class 3). Class 4 was characterized by the highest age (77.1 ± 2.3 years) and less educated individuals (8.3 ± 1.7 years of education). To further

Figure 2 Interactions of APOE $\epsilon 2$ carriers in reference to $\epsilon 3$ homozygotes for β -amyloid (A β) positivity between the 2 diagnostic groups

Figure 3 Estimated prevalence of β -amyloid ($A\beta$) positivity according to age and *APOE* genotype in subcortical vascular cognitive impairment (SVCI) and Alzheimer disease–related cognitive impairment (ADCI)

determine the characteristics of the latent classes, the presence of vascular risk factors in each class was evaluated. Class 1 contained the lowest proportion of patients with a history of ischemic heart disease (7.7%), while class 4 consisted of a higher proportion of individuals with a history of stroke (35.7%, all adjusted *p* values < 0.05).

Discussion

We report new evidence for a relationship between *APOE* genotype and $A\beta$ in patients with SVCI. In the SVCI group of patients, *APOE* $\epsilon 2$ as well as *APOE* $\epsilon 4$ were associated with increased $A\beta$ positivity. However, in the ADCI group, *APOE* $\epsilon 4$ was associated with increased $A\beta$ positivity, while *APOE* $\epsilon 2$ was associated with decreased $A\beta$ positivity. Furthermore, we noted an interaction of $\epsilon 2$ carrier status and diagnostic group on $A\beta$ positivity, suggesting that in reference to $\epsilon 3$ homozygotes, the SVCI group had a significantly higher frequency of $A\beta$ positivity in $\epsilon 2$ carriers than the ADCI group. Our LCA also demonstrated that some of the variability in patients with cognitive impairments could be explained by the latent subgroup of $A\beta$ -positive *APOE* $\epsilon 2$ carriers with SVCI that showed particular characteristics. Taken together, our findings suggest that *APOE* $\epsilon 2$ shows distinct associations with $A\beta$ deposition in patients with SVCI and those with ADCI. Distinguishing

APOE $\epsilon 2$ carrier and SVCI status in patients with cognitive impairments might help clinicians predict $A\beta$ positivity and provide personalized treatment strategies for the cognitive impairments, with the expectation that future treatment may target $A\beta$.

We found that the frequency of *APOE* $\epsilon 2$ carriers was significantly higher in the SVCI (11.0%) than in the ADCI (5.4%) group. A recent study showed that $A\beta$ -positive *APOE* $\epsilon 2$ carriers had a greater CSVD burden than $A\beta$ -positive *APOE* $\epsilon 4$ carriers.⁹ Although the underlying mechanisms of the association between *APOE* $\epsilon 2$ and greater CSVD burden are not clear, previous studies have suggested several potential explanations, including reduced integrity of amyloid-affected cerebral vasculature,^{31,32} microvascular damage in non-amyloidogenic angiopathy,³³ and vascular inflammation.³⁴

Our major finding is that *APOE* $\epsilon 2$ had divergent association with $A\beta$ positivity in the SVCI and ADCI groups. Specifically, *APOE* $\epsilon 2$ was associated with increased $A\beta$ positivity in the SVCI group but with decreased $A\beta$ positivity in the ADCI group. Moreover, we found an interaction effect of $\epsilon 2$ carrier status and diagnostic group on $A\beta$ positivity, in that relative to $\epsilon 3$ homozygotes, there were more $A\beta$ -positive $\epsilon 2$ carriers in the SVCI group than in the ADCI group. Interestingly,

Figure 4 Graphical representation of latent cluster class analysis results representing distinctive clinical features across classes

(A) Bar graphs show the proportion of the diagnostic group in each class. (B) Bar graphs illustrate the proportion of β -amyloid (A β) positivity in each class. (C) Bar graphs illustrate quantitative APOE genotypes across the classes. (D) Bar graphs show the proportion of female and male participants in each class. ADCI = Alzheimer disease-related cognitive impairment; SVCI = subcortical vascular cognitive impairment.

although the sample size was too small to draw clear conclusions, A β positivity in the (2) APOE $\epsilon 2/\epsilon 4$ carriers with SVCI was 100.0%, whereas in the (16) APOE $\epsilon 2/\epsilon 4$ carriers with ADCI, it was 68.8%. In the ADCI group, we also found that APOE $\epsilon 2$ had divergent association with A β positivity according to the presence of CSVD burden. Although the difference was not statistically significant, the frequency of A β positivity in APOE $\epsilon 2$ carriers was higher in the ADCI/WMH+ group (40.7%) than in the ADCI/WMH- group (22.2%). In particular, we found that the OR for comparison of the SVCI and ADCI/WMH+ groups was lower than that for comparison of the SVCI and ADCI/WMH- groups, which supports the notion of divergent association with APOE $\epsilon 2$ on A β positivity according to the presence of CSVD burden.

The exact pathobiology of the relationships between APOE $\epsilon 2$ and A β burden in SVCI has not been determined. In ADCI, several underlying mechanisms for the A β burden-lowering effects of APOE $\epsilon 2$ have been suggested, including increased A β clearance through the neurons, microglia, or delivery to the blood-brain barrier,^{35,36} and a lower extent of A β deposition. However, it is possible that in contrast to patients with ADCI, in patients with SVCI, APOE $\epsilon 2$ may be associated with a reduction in A β clearance, as CSVD has been reported to decrease A β clearance through blood-brain barrier breakdown or deficits in perivascular drainage of A β from the brain interstitial fluid.^{37,38} APOE $\epsilon 2$ might also be associated with a promotion of structural vasculopathic changes in patients with CSVD.³⁹ Thus, APOE $\epsilon 2$ might be related to the

acceleration of APOE leakage in the vessel wall or the perivascular space of patients with SVCI, which in turn leads to impaired vascular drainage of A β , eventually resulting in increased A β burden in the brain parenchyma. Alternatively, the APOE $\epsilon 2$ allele might contribute to the development of CAA, which, in turn, leads to increased CSVD. A previous study revealed that the APOE $\epsilon 2$ allele contributes to an increased deposition of vascular A β in patients with CAA.⁴⁰ However, among 310 patients with SVCI, 48 patients with SVCI who had multiple strictly lobar microbleeds, only 4 (8.3%, 4/48) APOE $\epsilon 2$ carriers were A β -positive on PET in this study. Thus, APOE $\epsilon 2$ as well as APOE $\epsilon 4$ may represent pathogenetic links between SVCI and A β burdens. However, how APOE $\epsilon 2$ contributes to A β burden in patients with SVCI remains undetermined and needs to be studied further.

In the present study, unlike in patients with ADCI, in the SVCI group, A β positivity increased with age. This finding is consistent with that of previous studies that have consistently shown the same positive correlation between age and A β positivity in cognitively normal individuals and patients with clinically diagnosed non-AD dementia, including vascular dementia.⁴¹⁻⁴³ In particular, in agreement with a previous study,⁴⁴ we found that APOE $\epsilon 4$ was associated with lower age at onset of estimated A β positivity in both SVCI and ADCI. However, in the SVCI group, APOE $\epsilon 2$ carriers had a lower mean age at onset of estimated A β positivity (about 10 years lower) than APOE $\epsilon 3$ homozygotes. Prevalence estimates of A β pathology in patients with SVCI, such as those provided in this study, are needed to better understand the development of AD pathology in SVCI.

Despite using a different analysis method, our LCA results replicate the findings of the logistic regression model, specifically the identification of a latent subgroup of A β -positive APOE $\epsilon 2$ carriers with SVCI (class 4) and a latent subgroup of A β -positive APOE $\epsilon 4$ carriers with ADCI (class 1). The LCA clustered patients with cognitive impairments who had multifactorial diseases into several subtypes. The purpose of cluster analyses is to assign individual data that have not been labeled in advance into homogeneous groups. The resulting groups explain new relationships and variability that expand and support previous findings.^{27,45,46} In addition, LCA is becoming the preferred method for the classification of phenotypes and genotypic variables, since it can be used to partition a set of qualitative (noncontinuous) variables.^{47,48} Cognitive impairments result from multiple etiologies, including A β and CSVD, which also are strongly associated with one another. Especially APOE $\epsilon 2$ and $\epsilon 4$ may have divergent effects on A β and CSVD burden. This approach thus provides information regarding distinctive latent subgroups according to APOE genotypes and the presence of A β in patients with or without CSVD. Interestingly, compared to the other classes, patients in class 4 were older while those in class 1 were younger, in line with results from a previous study showing that the APOE $\epsilon 4$ allele is associated with the development of AD and shortens the age at onset in AD dementia.⁴⁴

Table 3 Results of within-class means and percentages of the demographic and clinical features determined by latent cluster class analysis

	N	Class 1	Class 2	Class 3	Class 4
Age, y	1,309	70.1 (0.4)	73.5 (0.4) ^a	71.5 (0.7) ^b	77.1 (2.3) ^{a,c}
Education, y	1,305	11.5 (0.2)	9.5 (0.3) ^a	13.5 (0.3) ^{a,b}	8.3 (1.7) ^{a,c}
MMSE score	1,297	22.0 (0.2)	23.1 (0.3) ^a	26.2 (0.3) ^{a,b}	22.0 (2.0) ^c
CDR-SOB	1,239	4.4 (0.1)	3.6 (0.2) ^a	2.0 (0.2) ^{a,b}	3.8 (1.0)
Sex	1,309				
Male		280 (41.4)	101 (22.2) ^a	165 (100.0) ^{a,b}	6 (42.9) ^{a,c}
Diagnostic group	1,309				
ADCI		629 (93.0)	205 (45.2) ^a	165 (100.0) ^{a,b}	0 ^{a,c}
SVCI		47 (7.0)	249 (54.8)	0	14 (100.0)
APOE genotype	1,309		a	a	a,b,c
ε2 carriers		0	66 (14.5)	8 (4.9)	14 (100.0)
ε3/ε3		256 (37.9)	315 (69.4)	123 (74.5)	0
ε4 carriers		420 (62.1)	73 (16.1)	34 (20.6)	0
Aβ positivity	1,309				
Aβ positive		676 (100.0)	56 (12.3) ^a	8 (4.8) ^{a,b}	14 (100.0) ^{b,c}
Hypertension	1,309				
Presence		277 (41.0)	285 (62.8) ^a	73 (44.2) ^b	8 (57.1)
Diabetes	1,309				
Presence		93 (13.8)	123 (27.1) ^a	51 (30.9) ^a	3 (21.4)
Hyperlipidemia	1,309				
Presence		200 (29.6)	148 (32.6)	52 (31.5)	2 (14.3)
History of IHD	1,309				
Presence		52 (7.7)	58 (12.8) ^a	29 (17.6) ^a	2 (14.3)
History of stroke	1,309				
Presence		20 (3.0)	54 (11.9) ^a	7 (4.2) ^b	5 (35.7) ^{a,b,c}

Abbreviations: Aβ = β-amyloid; ADCI = Alzheimer disease–related cognitive impairment; CDR-SOB = Clinical Dementia Rating Sum of Boxes; IHD = ischemic heart disease; MMSE = Mini-Mental State Examination; SVCI = subcortical vascular cognitive impairment.

Values are means (standard error) or n (%).

^a Significantly different from class 1.

^b Significantly different from class 2.

^c Significantly different from class 3.

Considering that the mean age was highest in class 4, which consisted only of patients with SVCI, Aβ-positive and ε2 carriers, our findings also provide new evidence that aging has a strong influence on Aβ-positive *APOE* ε2 carriers with SVCI. High incidences of hypertension and stroke were observed in class 2 and class 4, which may be partially explained by higher proportions of patients with SVCI in these classes.

The strengths of this study are the large sample size, including a unique cohort of individuals with SVCI in a single memory clinic, and the standardized phenotyping of cognitive

impairment. Several limitations should also be acknowledged. First, the study participants underwent amyloid PET with different types of tracers. Although we controlled for PET tracer type, as suggested in a recent meta-analysis,⁴² diversity in tracer types might affect proportions of Aβ positivity. However, this argument is mitigated to some degree by the very high correlations among amyloid PET tracers.^{49,50} Second, because the number of *APOE* ε2 carriers among patients with SVCI was relatively small (n = 34), the statistical power of our analyses was relatively low. However, considering the frequency of *APOE* ε2 in the general population

(5%–10%),^{21,44} the results of our study nevertheless have clinical significance. Third, we did not consider the effects of other mixed pathologies (e.g., α -synuclein and frontotemporal lobar degeneration), which are also associated with SVCI. Finally, our study participants were enrolled from a single memory clinic, which might limit the generalizability of this study. Further investigation is necessary to examine the association between age and APOE ϵ 2 in SVCI in other cohorts.

Our findings show that APOE ϵ 2 is associated with an increase in A β burden in patients with SVCI, which might be related to decreased A β clearance due to the presence of vascular amyloid. Our findings will help advance our understanding of the heterogeneity of cognitively impaired patients, provide better treatments to patients, and eventually lay the groundwork for the development of personalized medicine.

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Disclosures

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Appendix (continued)

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