## Title

Association between APOE ε2 and Aβ burden in patients with Alzheimer- and vascular-type cognitive impairment.



## Journal

Neurology, 95(17)

## ISSN

0028-3878

## Authors

Lee, Jin San
Lee, Hyejoo
Park, Seongbeom
et al.

## Publication Date

2020-10-27

## DOI

10.1212/wnl.0000000000010811

Peer reviewed

ARTICLE

# Association between *APOE* ε2 and Aβ burden in patients with Alzheimer- and vascular-type cognitive impairment

Jin San Lee, MD, PhD, Hyejoo Lee, PhD,* Seongbeom Park, MS, Yeongsim Choe, BA, Yu Hyun Park, BA, Bo Kyoung Cheon, MS, Alice Hahn, MA, Rik Ossenkoppele, PhD, Hee Jin Kim, MD, PhD, Seonwoo Kim, PhD, Heejin Yoo, MS, Hyemin Jang, MD, Soo Hyun Cho, MD, PhD, Seung Joo Kim, MD, Jun Pyo Kim, MD, Young Hee Jung, MD, Key-Chung Park, MD, PhD, Charles DeCarli, MD, PhD, Michael W. Weiner, MD, PhD, Duk L. Na, MD, PhD, and Sang Won Seo, MD, PhD*

**Correspondence**
Dr. Seo
sangwonseo@empal.com
or Dr. Lee
hyejoo271@gmail.com

*Neurology*® 2020;95:e2354-e2365. doi:10.1212/WNL.0000000000010811

## Abstract

### Objective

To investigate the association between *APOE* genotype and β-amyloid (Aβ) 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 Aβ 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 ε3 homozygotes, in the ADCI group, ε2 carriers showed a lower frequency of Aβ positivity (odds ratio [OR] 0.43, 95% confidence interval [CI] 0.23–0.79), while in the SVCI group, ε2 carriers showed a higher frequency of Aβ positivity (OR 2.26, 95% CI 1.02–5.01). In particular, we observed an interaction effect of ε2 carrier status and diagnostic group on Aβ positivity (OR 5.12, 95% CI 1.93–13.56), in that relative to ε3 homozygotes, there were more Aβ-positive ε2 carriers in the SVCI group than in the ADCI group. We also identified latent subgroups of Aβ-positive *APOE* ε2 carriers with SVCI and Aβ-positive *APOE* ε4 carriers with ADCI.

### Conclusions

Our findings suggest that *APOE* ε2 is distinctly associated with Aβ deposition in patients with SVCI and those with ADCI. Our findings further suggest that there is a distinctive subgroup of Aβ-positive *APOE* ε2 carriers with SVCI among patients with cognitive impairment.

*These authors contributed equally to this work.

From the Department of Neurology (J.S.L., H.L., S.P., Y.C., Y.H.P., B.K.C., A.H., H.J.K., H.J., J.P.K., D.L.N., S.W.S.), Samsung Alzheimer Research Center (H.J.K., H.J., J.P.K., D.L.N., S.W.S.), and Statistics and Data Center (S.K., H.Y.), Samsung Medical Center; Department of Intelligent Precision Healthcare Convergence (S.W.S.), Sungkyunkwan University School of Medicine; Department of Health Sciences and Technology (S.W.S.), SAIHST, Sungkyunkwan University; Department of Neurology (J.S.L., K.-C.P.), Kyung Hee University College of Medicine, Kyung Hee University Hospital, Seoul, Korea; Department of Neurology and Alzheimer Center (R.O.), Neuroscience Campus Amsterdam, VU University Medical Center, the Netherlands; Department of Neurology (S.H.C.), Chonnam National University Medical School, Gwangju; Department of Neurology (S.J.K.), Gyeongsang National University School of Medicine and Gyeongsang National University Changwon Hospital, Changwon; Department of Neurology (Y.H.J.), Myungji Hospital, Goyang, Korea; Department of Neurology and Center for Neuroscience (C.D.), University of California, Davis; Department of Medicine (M.W.W.), University of California; and Department of Veterans Affairs Medical Center (M.W.W.), Center for Imaging of Neurodegenerative Diseases, San Francisco, CA.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

## Glossary

**AAL** = automated anatomical labeling; **Aβ** = β-amyloid; **AD** = Alzheimer disease; **ADCI** = Alzheimer disease–related cognitive impairment; **aMCI** = amnestic 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; **SVCI** = subcortical vascular cognitive impairment; **svMCI** = subcortical vascular mild cognitive impairment; **VOI** = volume of interest; **WMH** = white matter hyperintensities.

Although β-amyloid (Aβ) deposition is a pathologic hallmark of Alzheimer disease (AD), Aβ deposition occurs in a number of heterogeneous conditions. In particular, Aβ deposition frequently coexists with subcortical vascular cognitive impairment (SVCI).[1,2] Previous studies have also shown that Aβ 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* ε4 allele is an important risk factor for Aβ deposition in SVCI as well as in AD. Whereas *APOE* ε2 is known to reduce the risk of Aβ deposition in AD,[6,7] the relationship between *APOE* ε2 and Aβ deposition in SVCI has not been fully determined. A prior study indicated that in *APOE* ε4 noncarriers with SVCI, CSVD severity was directly related to Aβ burden.[8] In addition, Aβ-positive patients with AD with *APOE* ε2 exhibited more severe CSVD than those with *APOE* ε4 in a recent study.[9] Because CSVD induces leakage of APOE, which is a plasma lipoprotein that functions in Aβ clearance[10] and eventually results in decreased Aβ clearance,[11] we hypothesized that *APOE* ε2 might increase Aβ positivity in patients with SVCI.

In this study, we investigated the associations between *APOE* genotype and Aβ burden in patients with SVCI and those with AD-related cognitive impairment (ADCI). Moreover, to resolve the complex relationships between *APOE* genotype, CSVD, and Aβ 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 SVCI (156 with subcortical vascular mild cognitive impairment [svMCI] and 156 with subcortical vascular dementia [SVaD]) who underwent $^{11}$C-Pittsburgh compound B (PiB), $^{18}$F-florbetaben, or $^{18}$F-flutemetamol PET scanning at the Samsung Medical Center (Seoul, Korea) from September 2008 to June 2018. All patients met the following criteria for SVCI 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 SVCI had lacunes and 66.2% of those had cerebral microbleeds. Patients with SVCI 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 SVCI, we recruited 1,015 patients with ADCI (549 with amnestic mild cognitive impairment [aMCI] and 466 with AD dementia) who underwent $^{11}$C-PiB, $^{18}$F-florbetaben, or $^{18}$F-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 $B_{12}$/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 ADCI and 2 patients with SVCI had the *APOE* ε2/ε4 genotype. These individuals were excluded from the main analysis due to the putative opposing effects of the ε4 and ε2 alleles.[21,22] Therefore, the final sample of the current study consisted of 1,309 individuals, 310 with SVCI (156 with svMCI and 154 with SVaD) and 999 with ADCI (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.

## $^{11}$C-PiB PET acquisition and analysis

We performed $^{11}$C-PiB PET scanning in 247 patients (133 with SVCI and 114 with ADCI) using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI) at Samsung Medical Center. We coregistered the $^{11}$C-PiB PET images to each individual's MRI data. Then the coregistered $^{11}$C-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 Aβ positivity at 1.5 or higher.[1] We followed the previously used methods for $^{11}$C-PiB PET scanning and acquisition of the global PiB retention ratio, and the detailed methods are particularized in previous studies.[1,8]

## $^{18}$F-labelled amyloid PET acquisition and analysis

A total of 1,062 patients (177 with SVCI and 885 with ADCI) were scanned with $^{18}$F-labeled amyloid PET (775 underwent $^{18}$F-florbetaben PET and 287 underwent $^{18}$F-flutemetamol PET) at Samsung Medical Center. Using the same type of scanner with $^{11}$C-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 $^{18}$F-florbetaben and $^{18}$F-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 $^{18}$F-florbetaben and 197.7 MBq $^{18}$F-flutemetamol. We also used the ordered-subset expectation maximization algorithm ($^{18}$F-florbetaben, iteration = 4 and subset = 20; $^{18}$F-flutemetamol, iteration = 4 and subset = 20) to reconstruct 3D PET images in a 128 × 128 × 48 matrix with a 2 × 2 × 3.27 $mm^3$ voxel size.

All PET images were visually assessed and dichotomized as Aβ-positive or Aβ-negative after being reviewed by nuclear medicine physicians who were blinded to patient information. $^{18}$F-florbetaben PET findings were considered positive for brain amyloid–plaque load (BAPL) score[24] 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. Aβ-negative status was given for those with a BAPL score of 1; Aβ-positive status was given for those with BAPL scores of 2 or 3. Our visual assessment highly corresponded with the binarized global $^{18}$F-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 $^{18}$F-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 Aβ-positive, any of the brain regions had to

**Table 1** Demographic and clinical characteristics of the study participants

| | | ADCI | | |
|---|---|---|---|---|
| | SVCI | 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 $\chi^2$ 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.

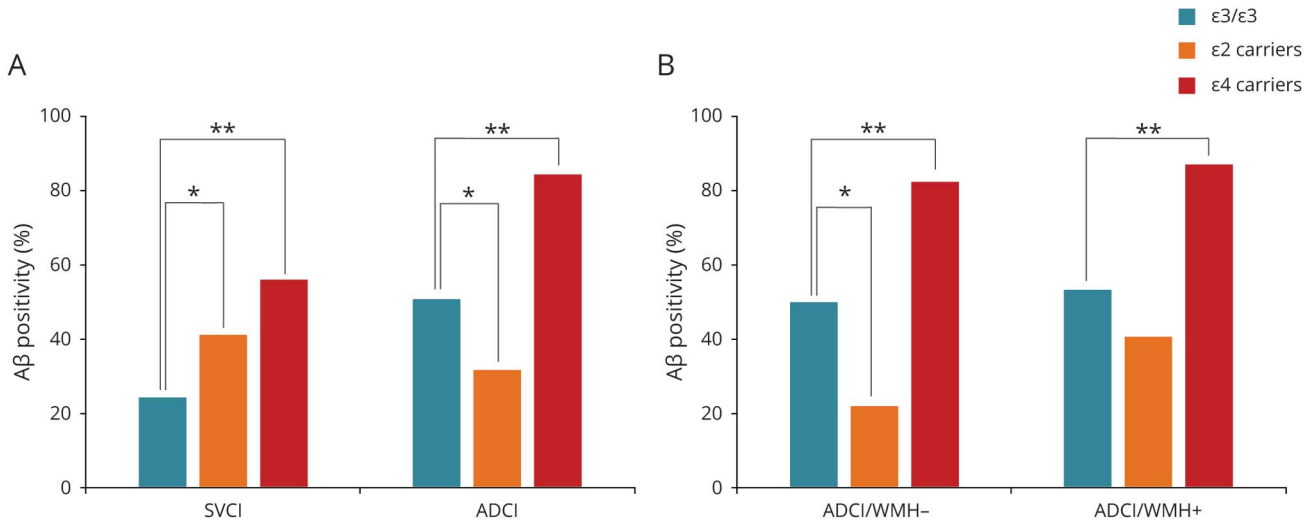
show positive findings in either hemisphere. Having 1 or more regions with high cortical gray matter signal (above 50%–60% peak intensity) or low (or absent) gray–white matter contrast (a less distinct white matter sulcal pattern) indicated positive scans. If the scan did not show any of these characteristics, 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 $^{18}$F-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 $\chi^2$ 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 ($^{11}$C-PiB, $^{18}$F-florbetaben, $^{18}$F-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 (Aβ) positivity




(A) Frequency of Aβ positivity according to *APOE* genotypes in the subcortical vascular cognitive impairment (SVCI) and Alzheimer disease–related cognitive impairment (ADCI) groups. (B) Frequency of Aβ positivity according to *APOE* genotypes in the ADCI/white matter hyperintensities (WMH)− and ADCI/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 (ε2 carriers, ε3 homozygotes, and ε4 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, Aβ positivity, sex, and diagnostic group (SVCI or ADCI). 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 (ε2 carriers, ε3 homozygotes, and ε4 carriers) were 11.0%, 61.9%, and 27.1% in the SVCI group and 5.4%, 50.3%, and 44.3% in the ADCI group, respectively. Comparisons between SVCI and ADCI showed that the SVCI group had a higher frequency of ε2 carriers ($p$ value = 0.001) and ε3 homozygotes ($p$ value < 0.001), whereas the ADCI group had a higher frequency of ε4 carriers ($p$ value < 0.001).

When we subdivided the ADCI group according to the presence of WMH into the ADCI/WMH+ and ADCI/WMH− groups, the ADCI/WMH+ group consisted of 348 individuals, thus representing 34.8% of the ADCI group. The proportions of *APOE* genotypes (ε2 carriers, ε3 homozygotes, and ε4 carriers) were 4.1%, 51.9%, and 43.9% in the ADCI/WMH− group and 7.8%, 47.1%, and 45.1% in the ADCI/WMH + group, respectively. The ADCI/WMH+ group had a higher frequency of ε2 carriers than the ADCI/WMH− group ($p$ value = 0.016).

## Frequency of Aβ positivity according to *APOE* genotype

The frequencies of Aβ positivity were 34.8% in the SVCI group (30.1% with svMCI and 39.6% with SVaD) and 64.7% in the ADCI group (47.9% with aMCI and 84.2% with AD dementia) (table 1). The frequencies of Aβ positivity according to *APOE* genotypes (ε2 carriers, ε3 homozygotes, and ε4 carriers) were 41.2%, 24.5%, and 56.0% in the SVCI

**Table 2** Association of clinical information and *APOE* genotype with β-amyloid (Aβ) 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 Aβ positivity (95% CI) | *p* Value | Adjusted OR for Aβ positivity (95% CI) | *p* Value | Adjusted OR for Aβ positivity (95% CI) | *p* Value | Adjusted OR for Aβ positivity (95% CI) | *p* Value | Adjusted OR for Aβ positivity (95% CI) | *p* Value | Adjusted OR for Aβ positivity (95% CI) | *p* 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 |
| ***APOE* genotype** | | | | | | | | | | | | |
| **ε3/ε3** | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | |
| **ε2 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 |
| **ε4 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 Aβ 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, ε2 carriers showed a lower frequency of Aβ positivity than ε3 homozygotes (odds ratio [OR] 0.43, 95% CI 0.23–0.79), while ε4 carriers showed a higher frequency of Aβ positivity (OR 4.92, 95% CI 3.60–6.73). However, in the SVCI group, both ε2 carriers (OR 2.26, 95% CI 1.02–5.01) and ε4 carriers (OR 4.23, 95% CI 2.39–7.48) showed a higher frequency of Aβ positivity than ε3 homozygotes.

The frequencies of Aβ 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 Aβ positivity according to *APOE* genotypes (ε2 carriers, ε3 homozygotes, and ε4 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, ε2 carriers showed a lower frequency of Aβ positivity than ε3 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 ε2 carrier status and diagnostic group on Aβ positivity (OR 5.12, 95% CI 1.93–13.56) (figure 2), in that relative to ε3 homozygotes, there were more Aβ-positive ε2 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 ε2 carrier status and diagnostic group on Aβ 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 ε4 carrier status and diagnostic group (ADCI vs SVCI and ADCI/WMH− vs ADCI/WMH+) on Aβ 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 Aβ positivity according to age and *APOE* genotype

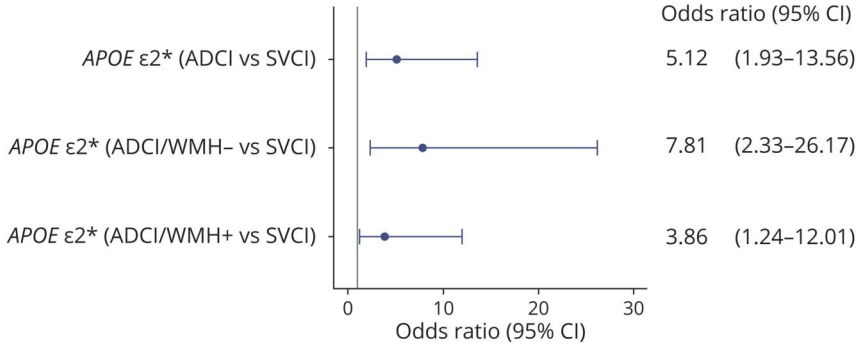
In the ADCI group, age tended to be inversely associated with Aβ positivity (OR 0.99, 95% CI 0.97–1.00), while in the SVCI group, age was positively associated with Aβ positivity (OR 1.10, 95% CI 1.05–1.15) (table 2). Figure 3 shows the prevalence estimates of Aβ positivity according to age and *APOE* genotype in the SVCI and ADCI groups. In the SVCI group, the difference in prevalence estimates of Aβ positivity between ε2 carriers and ε3 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 Aβ positivity. Class 1 showed a high percentage of patients with ADCI with ε3 homozygote or ε4 carrier status, while class 4 consisted of only patients with SVCI with ε2 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 ε3 homozygotes and a higher proportion of Aβ negativity overall than the other classes.

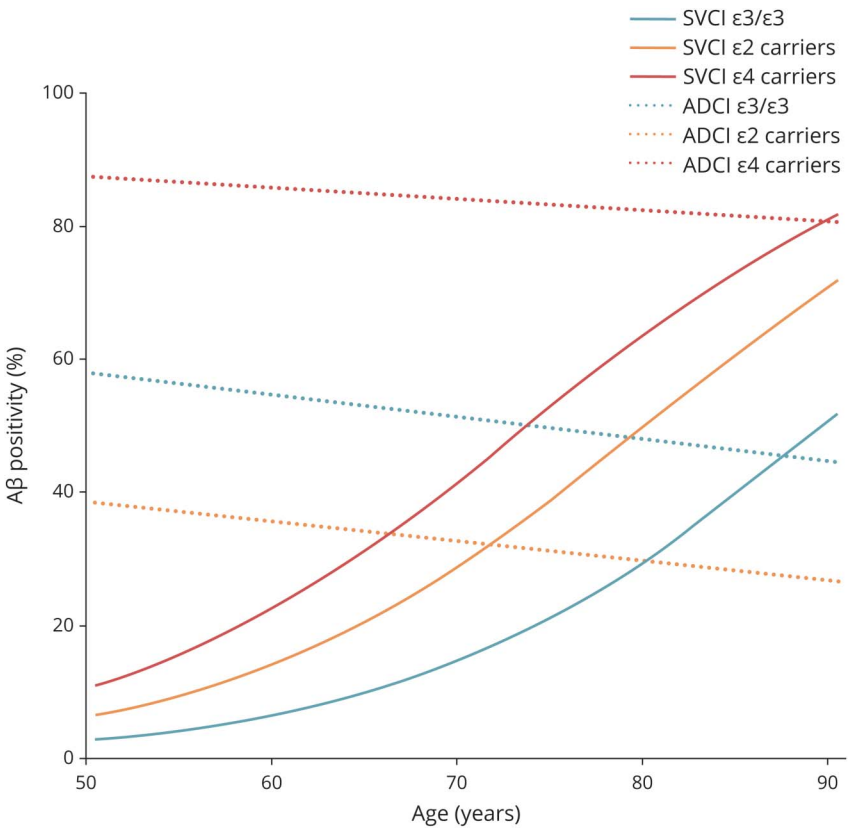
Table 3 shows the within-class means and percentages of demographic and clinical features produced by the LCA. The mean age was lower in class 1 (70.1 ± 0.4 years) than in the other classes (adjusted $p$ values < 0.05 for comparisons with class 2 and class 4), and these patients had a lower MMSE score (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* ε2 carriers in reference to ε3 homozygotes for β-amyloid (Aβ) positivity between the 2 diagnostic groups




The frequency of Aβ positivity for ε2 carriers compared to that for ε3 homozygotes was significantly higher in the subcortical vascular cognitive impairment (SVCI) group than in the respective reference group (Alzheimer disease–related cognitive impairment [ADCI] [total], ADCI/white matter hyperintensities [WMH]−, and ADCI/WMH+). CI = confidence interval; WMH− = minimal degree of WMH; WMH+ = moderate to severe degree of WMH.

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




The curves were plotted using the point estimates generated by logistic regression analyses. This model included age (continuous) and *APOE* genotype (ε2 carriers, ε3 homozygotes, and ε4 carriers) as predictors.

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).

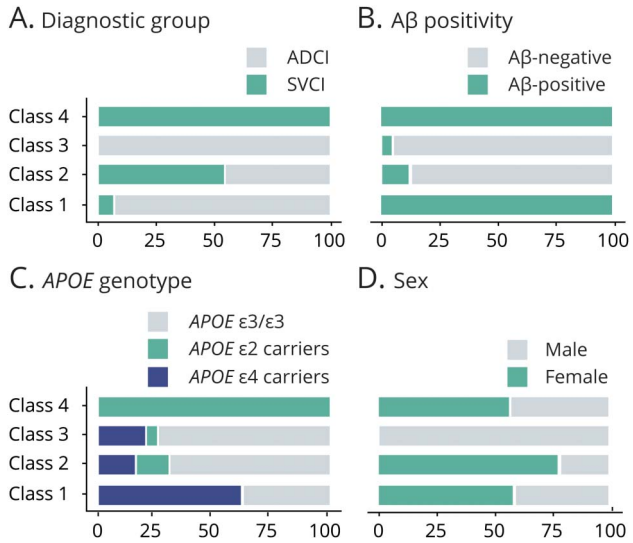
## Discussion

We report new evidence for a relationship between *APOE* genotype and Aβ in patients with SVCI. In the SVCI group of patients, *APOE* ε2 as well as *APOE* ε4 were associated with increased Aβ positivity. However, in the ADCI group, *APOE* ε4 was associated with increased Aβ positivity, while *APOE* ε2 was associated with decreased Aβ positivity. Furthermore, we noted an interaction of ε2 carrier status and diagnostic group on Aβ positivity, suggesting that in reference to ε3 homozygotes, the SVCI group had a significantly higher frequency of Aβ positivity in ε2 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 Aβ-positive *APOE* ε2 carriers with SVCI that showed particular characteristics. Taken together, our findings suggest that *APOE* ε2 shows distinct associations with Aβ deposition in patients with SVCI and those with ADCI. Distinguishing *APOE* ε2 carrier and SVCI status in patients with cognitive impairments might help clinicians predict Aβ positivity and provide personalized treatment strategies for the cognitive impairments, with the expectation that future treatment may target Aβ.

We found that the frequency of *APOE* ε2 carriers was significantly higher in the SVCI (11.0%) than in the ADCI (5.4%) group. A recent study showed that Aβ-positive *APOE* ε2 carriers had a greater CSVD burden than Aβ-positive *APOE* ε4 carriers.[9] Although the underlying mechanisms of the association between *APOE* ε2 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* ε2 had divergent association with Aβ positivity in the SVCI and ADCI groups. Specifically, *APOE* ε2 was associated with increased Aβ positivity in the SVCI group but with decreased Aβ positivity in the ADCI group. Moreover, we found an interaction effect of ε2 carrier status and diagnostic group on Aβ positivity, in that relative to ε3 homozygotes, there were more Aβ-positive ε2 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 (Aβ) 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, Aβ positivity in the (2) *APOE* ε2/ε4 carriers with SVCI was 100.0%, whereas in the (16) *APOE* ε2/ε4 carriers with ADCI, it was 68.8%. In the ADCI group, we also found that *APOE* ε2 had divergent association with Aβ positivity according to the presence of CSVD burden. Although the difference was not statistically significant, the frequency of Aβ positivity in *APOE* ε2 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* ε2 on Aβ positivity according to the presence of CSVD burden.

The exact pathobiology of the relationships between *APOE* ε2 and Aβ burden in SVCI has not been determined. In ADCI, several underlying mechanisms for the Aβ burden–lowering effects of *APOE* ε2 have been suggested, including increased Aβ clearance through the neurons, microglia, or delivery to the blood–brain barrier,[35,36] and a lower extent of Aβ deposition. However, it is possible that in contrast to patients with ADCI, in patients with SVCI, *APOE* ε2 may be associated with a reduction in Aβ clearance, as CSVD has been reported to decrease Aβ clearance through blood–brain barrier breakdown or deficits in perivascular drainage of Aβ from the brain interstitial fluid.[37,38] *APOE* ε2 might also be associated with a promotion of structural vasculopathic changes in patients with CSVD.[39] Thus, *APOE* ε2 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 Aβ, eventually resulting in increased Aβ burden in the brain parenchyma. Alternatively, the *APOE* ε2 allele might contribute to the development of CAA, which, in turn, leads to increased CSVD. A previous study revealed that the *APOE* ε2 allele contributes to an increased deposition of vascular Aβ 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* ε2 carriers were Aβ-positive on PET in this study. Thus, *APOE* ε2 as well as *APOE* ε4 may represent pathogenetic links between SVCI and Aβ burdens. However, how *APOE* ε2 contributes to Aβ 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, Aβ positivity increased with age. This finding is consistent with that of previous studies that have consistently shown the same positive correlation between age and Aβ 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* ε4 was associated with lower age at onset of estimated Aβ positivity in both SVCI and ADCI. However, in the SVCI group, *APOE* ε2 carriers had a lower mean age at onset of estimated Aβ positivity (about 10 years lower) than *APOE* ε3 homozygotes. Prevalence estimates of Aβ 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 Aβ-positive *APOE* ε2 carriers with SVCI (class 4) and a latent subgroup of Aβ-positive *APOE* ε4 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 Aβ and CSVD, which also are strongly associated with one another. Especially *APOE* ε2 and ε4 may have divergent effects on Aβ and CSVD burden. This approach thus provides information regarding distinctive latent subgroups according to *APOE* genotypes and the presence of Aβ 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* ε4 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* ε2 in SVCI in other cohorts.

Our findings show that *APOE* ε2 is associated with an increase in Aβ burden in patients with SVCI, which might be related to decreased Aβ 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.

## Study funding

This research was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI19C1132); by the Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2016M3C7A1913844); by a fund (2018-ER6203-02) by Research of Korea Centers for Disease Control and Prevention; by the Brain Research Program of the NRF funded by the Ministry of Science & ICT (NRF-2018M3C7A1056512); by the National Research Council of Science & Technology (NST) grant by the Korea government (MSIP) (No. CRC-15-04-KIST).

## Disclosures

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

## Publication history

Received by *Neurology* November 13, 2019. Accepted in final form June 3, 2020.

## Appendix Authors

| Name | Location | Contribution |
|---|---|---|
| **Jin San Lee, MD, PhD** | Kyung Hee University Hospital, Seoul, Korea | Conception and design of the study, acquisition of data, analysis and interpretation of the data, drafting and revising the manuscript |
| **Hyejoo Lee, PhD** | Samsung Medical Center, Seoul, Korea | Conception and design of the study, analysis and interpretation of the data, drafting and revising the manuscript, final approval of the manuscript |
| **Seongbeom Park, MS** | Samsung Medical Center, Seoul, Korea | Analysis and interpretation of the data |
| **Yeongsim Choe, BA** | Samsung Medical Center, Seoul, Korea | Analysis and interpretation of the data |
| **Yu Hyun Park, BA** | Samsung Medical Center, Seoul, Korea | Analysis and interpretation of the data |
| **Bo Kyoung Cheon, MS** | Samsung Medical Center, Seoul, Korea | Analysis and interpretation of the data |
| **Alice Hahn, MA** | Samsung Medical Center, Seoul, Korea | Analysis and interpretation of the data |
| **Rik Ossenkoppele, PhD** | VU University Medical Center, Amsterdam, the Netherlands | Analysis and interpretation of the data, drafting and revising the manuscript |
| **Hee Jin Kim, MD, PhD** | Samsung Medical Center, Seoul, Korea | Acquisition of data |
| **Seonwoo Kim, PhD** | Samsung Medical Center, Seoul, Korea | Analysis and interpretation of the data |
| **Heejin Yoo, MS** | Samsung Medical Center, Seoul, Korea | Analysis and interpretation of the data |
| **Hyemin Jang, MD** | Samsung Medical Center, Seoul, Korea | Acquisition of data |
| **Soo Hyun Cho, MD, PhD** | Chonnam National University Medical School, Gwangju, Korea | Acquisition of data |
| **Seung Joo Kim, MD** | Gyeongsang National University Changwon Hospital, Korea | Acquisition of data |
| **Jun Pyo Kim, MD** | Samsung Medical Center, Seoul, Korea | Acquisition of data |
| **Young Hee Jung, MD** | Myungji Hospital, Goyang, Korea | Acquisition of data |
| **Key-Chung Park, MD, PhD** | Kyung Hee University Hospital, Seoul, Korea | Analysis and interpretation of the data |
| **Charles DeCarli, MD, PhD** | University of California, Davis | Analysis and interpretation of the data |
| **Michael W. Weiner, MD, PhD** | University of California, San Francisco | Analysis and interpretation of the data |
| **Duk L. Na, MD, PhD** | Samsung Medical Center, Seoul, Korea | Acquisition of data, analysis and interpretation of the data |
| **Sang Won Seo, MD, PhD** | Samsung Medical Center, Seoul, Korea | Conception and design of the study, acquisition of data, analysis and interpretation of the data, drafting and revising the manuscript, final approval of the manuscript |

## References

1. Lee JH, Kim SH, Kim GH, et al. Identification of pure subcortical vascular dementia using 11C-Pittsburgh compound B. Neurology 2011;77:18–25.
2. Lee MJ, Seo SW, Na DL, et al. Synergistic effects of ischemia and beta-amyloid burden on cognitive decline in patients with subcortical vascular mild cognitive impairment. JAMA Psychiatry 2014;71:412–422.
3. Nielsen RB, Egefjord L, Angleys H, et al. Capillary dysfunction is associated with symptom severity and neurodegeneration in Alzheimer's disease. Alzheimers Dement 2017;13:1143–1153.
4. Kester MI, Goos JD, Teunissen CE, et al. Associations between cerebral small-vessel disease and Alzheimer disease pathology as measured by cerebrospinal fluid biomarkers. JAMA Neurol 2014;71:855–862.

5. Attems J, Jellinger KA. The overlap between vascular disease and Alzheimer's disease: lessons from pathology. BMC Med 2014;12:206.
6. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261: 921–923.
7. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 1994;7:180–184.
8. Noh Y, Seo SW, Jeon S, et al. White matter hyperintensities are associated with amyloid burden in APOE4 non-carriers. J Alzheimers Dis 2014;40:877–886.
9. Groot C, Sudre CH, Barkhof F, et al. Clinical phenotype, atrophy, and small vessel disease in APOEepsilon2 carriers with Alzheimer disease. Neurology 2018;91: e1851–e1859.
10. Bu G. Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. Nat Rev Neurosci 2009;10:333–344.
11. Utter S, Tamboli IY, Walter J, et al. Cerebral small vessel disease-induced apolipoprotein E leakage is associated with Alzheimer disease and the accumulation of amyloid beta-protein in perivascular astrocytes. J Neuropathol Exp Neurol 2008;67: 842–856.
12. Ahn HJ, Chin J, Park A, et al. Seoul Neuropsychological Screening Battery–dementia version (SNSB-D): a useful tool for assessing and monitoring cognitive impairments in dementia patients. J Korean Med Sci 2010;25:1071–1076.
13. Kang SH, Park YH, Lee D, et al. The cortical neuroanatomy related to specific neuropsychological deficits in Alzheimer's continuum. Dement Neurocogn Disord 2019;18:77.
14. Fazekas F, Kleinert R, Offenbacher H, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 1993;43:1683–1689.
15. Seo SW, Cho SS, Park A, Chin J, Na DL. Subcortical vascular versus amnestic mild cognitive impairment: comparison of cerebral glucose metabolism. J Neuroimaging 2009;19:213–219.
16. Kim HJ, Park S, Cho H, et al. Assessment of extent and role of tau in subcortical vascular cognitive impairment using 18F-AV1451 positron emission tomography imaging. JAMA Neurol 2018;75:999–1007.
17. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004; 256:183–194.
18. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services task force on Alzheimer's disease. Neurology 1984;34:939–944.
19. Seo SW, Im K, Lee JM, et al. Cortical thickness in single- versus multiple-domain amnestic mild cognitive impairment. Neuroimage 2007;36:289–297.
20. Kim YJ, Cho SK, Kim HJ, et al. Data-driven prognostic features of cognitive trajectories in patients with amnestic mild cognitive impairments. Alzheimers Res Ther 2019;11:10.
21. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis: APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 1997;278: 1349–1356.
22. Lovati C, Galimberti D, Albani D, et al. APOE epsilon2 and epsilon4 influence the susceptibility for Alzheimer's disease but not other dementias. Int J Mol Epidemiol Genet 2010;1:193–200.
23. Mathis CA, Wang Y, Holt DP, Huang GF, Debnath ML, Klunk WE. Synthesis and evaluation of 11C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. J Med Chem 2003;46:2740–2754.
24. Barthel H, Gertz HJ, Dresel S, et al. Cerebral amyloid-beta PET with florbetaben (18F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study. Lancet Neurol 2011;10:424–435.
25. Curtis C, Gamez JE, Singh U, et al. Phase 3 trial of flutemetamol labeled with radioactive fluorine 18 imaging and neuritic plaque density. JAMA Neurol 2015;72:287–294.
26. Lazarsfeld PF, Henry NW. Latent Structure Analysis. Boston: Houghton Mifflin; 1968.
27. Collins LM, Lanza ST. Latent Class and Latent Transition Analysis: With Applications in the Social, Behavioral, and Health Sciences. Hoboken: John Wiley & Sons; 2010.
28. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: a Monte Carlo simulation study. J Struct Equation Model A Multidisciplinary J 2007;14:535–569.
29. Kass RE, Raftery AE. Bayes factors. J Am Stat Assoc 1995;90:773–795.
30. R Development Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2011.
31. Greenberg SM, Vonsattel JP, Segal AZ, et al. Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. Neurology 1998;50:961–965.
32. McCarron MO, Nicoll JA, Stewart J, et al. The apolipoprotein E epsilon2 allele and the pathological features in cerebral amyloid angiopathy-related hemorrhage. J Neuropathol Exp Neurol 1999;58:711–718.
33. Gesierich B, Opherk C, Rosand J, et al. APOE varepsilon2 is associated with white matter hyperintensity volume in CADASIL. J Cereb Blood Flow Metab 2016;36: 199–203.
34. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: the 3C-Dijon Study. Neurology 2012; 78:720–727.
35. Castellano JM, Kim J, Stewart FR, et al. Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. Sci Transl Med 2011;3:89ra57.
36. Conejero-Goldberg C, Gomar JJ, Bobes-Bascaran T, et al. APOE2 enhances neuroprotection against Alzheimer's disease through multiple molecular mechanisms. Mol Psychiatry 2014;19:1243–1250.
37. Charidimou A, Boulouis G, Gurol ME, et al. Emerging concepts in sporadic cerebral amyloid angiopathy. Brain 2017;140:1829–1850.
38. Grimmer T, Faust M, Auer F, et al. White matter hyperintensities predict amyloid increase in Alzheimer's disease. Neurobiol Aging 2012;33:2766–2773.
39. Charidimou A, Martinez-Ramirez S, Shoamanesh A, et al. Cerebral amyloid angiopathy with and without hemorrhage: evidence for different disease phenotypes. Neurology 2015;84:1206–1212.
40. Nelson PT, Pious NM, Jicha GA, et al. APOE-epsilon2 and APOE-epsilon4 correlate with increased amyloid accumulation in cerebral vasculature. J Neuropathol Exp Neurol 2013;72:708–715.
41. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015;313:1924–1938.
42. Ossenkoppele R, Jansen WJ, Rabinovici GD, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. JAMA 2015;313:1939–1949.
43. Lewis H, Beher D, Cookson N, et al. Quantification of Alzheimer pathology in ageing and dementia: age-related accumulation of amyloid-beta(42) peptide in vascular dementia. Neuropathol Appl Neurobiol 2006;32:103–118.
44. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol 2013;9:106–118.
45. Kaplan D. The Sage Handbook of Quantitative Methodology for the Social Sciences. Thousand Oaks: SAGE; 2004.
46. Lee H, Malaspina D, Ahn H, et al. Paternal age related schizophrenia (PARS): latent subgroups detected by k-means clustering analysis. Schizophr Res 2011;128: 143–149.
47. Yang CC. Evaluating latent class analysis models in qualitative phenotype identification. Comput Stat Data Anal 2006;50:1090–1104.
48. Pickles A, Bolton P, Macdonald H, et al. Latent-class analysis of recurrence risks for complex phenotypes with selection and measurement error: a twin and family history study of autism. Am J Hum Genet 1995;57:717.
49. Landau SM, Thomas BA, Thurfjell L, et al. Amyloid PET imaging in Alzheimer's disease: a comparison of three radiotracers. Eur J Nucl Med Mol Imaging 2014;41: 1398–1407.
50. Villemagne VL, Mulligan RS, Pejoska S, et al. Comparison of 11C-PiB and 18F-florbetaben for Abeta imaging in ageing and Alzheimer's disease. Eur J Nucl Med Mol Imaging 2012;39:983–989.