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ABSTRACT

BACKGROUND AND PURPOSE: The presence of the *apolipoprotein E ε4* allele is the strongest sporadic Alzheimer disease genetic risk factor. We hypothesized that *apolipoprotein E ε4* carriers and noncarriers may already differ in imaging patterns in midlife. We therefore sought to identify the effect of *apolipoprotein E* genotype on brain atrophy across almost the entire adult age span by using advanced MR imaging–based pattern analysis.

MATERIALS AND METHODS: We analyzed MR imaging scans of 1472 participants from the Study of Health in Pomerania (22–90 years of age). We studied the association among age, *apolipoprotein E ε4* carrier status, and brain atrophy, which was quantified by using 2 MR imaging–based indices: Spatial Pattern of Atrophy for Recognition of Brain Aging (summarizing age-related brain atrophy) and Spatial Pattern of Abnormality for Recognition of Early Alzheimer Disease (summarizing Alzheimer disease-like brain atrophy patterns), as well as the gray matter volumes in several Alzheimer disease- and *apolipoprotein E*–related ROIs (lateral frontal, lateral temporal, medial frontal, and hippocampus).

RESULTS: No significant association was found between *apolipoprotein E ε4* carrier status and the studied ROIs or the MR imaging–based indices in linear regression models adjusted for age, sex, and education, including an interaction term between *apolipoprotein E* and age.

CONCLUSIONS: Our study indicates that measurable *apolipoprotein E*–related brain atrophy does not occur in early adulthood and midlife and suggests that such atrophy may only occur more proximal to the onset of clinical symptoms of dementia.

ABBREVIATIONS: AD = Alzheimer disease; *APOE* = *apolipoprotein E*; MCI = mild cognitive impairment; SHIP = Study of Health in Pomerania; SNP = single nucleotide polymorphism; SPARE-AD = Spatial Pattern of Abnormality for Recognition of Early Alzheimer Disease; SPARE-BA = Spatial Pattern of Atrophy for Recognition of Brain Aging

The presence of the *apolipoprotein E* gene (*APOE*) *ε4* allele is the strongest genetic sporadic Alzheimer disease (AD) risk factor.[1,2] The *APOE* gene has 2 additional codominant alleles (*APOE ε2* and *ε3*). These alleles code for the 3 corresponding apolipoprotein isoforms (ApoE ε2, ε3, and ε4). Compared with individuals with the *ε3* allele,[2] which is the most common in the general population, those with the *APOE ε4* allele have a higher risk of AD, whereas the *APOE ε2* allele is associated with a lower risk of AD. The *APOE* genotype modifies the age at which cognitively healthy subjects present biomarker changes that define AD preclinical stages.[3,4] There are several mechanisms that have been

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The corresponding authors (M.H. and J.B.T.) confirm that each author has contributed to all of the following: drafting the article or revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. In addition, each author's contribution was the following: M.H., J.B.T.: conception and design, acquisition of data, analysis and interpretation of data; S.M.R.: analysis and interpretation of data; J.D.: analysis and interpretation of data; S.V.d.A.: acquisition of data; G.E.: analysis and interpretation of data; D.J.: acquisition of data; K.H.: acquisition of data; G.H.: acquisition of data; H.V.: acquisition of data, analysis and interpretation of data; W.H.: acquisition of data, analysis and interpretation of data; and H.J.G. and C.D.: conception and design, acquisition of data, and analysis and interpretation of data.

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Indicates article with supplemental on-line appendix and tables.

Indicates article with supplemental on-line photos.

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Table 1: Description of the SHIP sample included in this study ($n = 1472$)

Characteristic	SHIP-2	SHIP-TREND	SHIP-2 and SHIP-TREND (Analysis Sample)
Age (median) (SD) (yr)	56.3 (12.2)	51.1 (13.4)[a]	53.3 (13.0)
Education (No.) (%)			
<8 yr	137 (18.4)	77 (10.6)[a]	214 (14.5)
8–10 yr	430 (57.8)	415 (57.0)[a]	845 (57.4)
>10 yr	177 (23.8)	236 (32.4)[a]	413 (28.1)
APOE genotype: at least 1 ε4 allele (No.) (% positive)	145 (19.5)	177 (24.3)[a]	322 (21.9)
Female sex (No.) (%)	399 (53.6)	421 (57.8)	820 (55.7)
Verbal Learning and Memory Test (mean) (SD)	8.6 (3.0)		
Nuremberg Age Inventory (mean) (SD)		11.2 (2.5)	

[a] Significant difference at $P < .05$.

associated with the influence of *APOE ε4* on AD risk: decreased clearance of amyloid from the brain, impaired synaptic plasticity, altered blood-brain barrier permeability, and immune response and impaired membrane repair following neuronal injury.[5-7] In line with these results, neuropathologic studies have shown that plaques and tangles mediate *APOE*-related clinical changes.[8] ApoE is present in plasma and CSF, but there is a weak correlation between ApoE concentrations within these 2 compartments.[9,10] In *APOE* genotype–adjusted models, CSF, but not plasma, ApoE levels are associated with cognitive changes and brain atrophy.[9] Nevertheless, a large longitudinal study reported associations with plasma ApoE levels that dropped to borderline significance when adjusted for the *APOE* genotype.[11]

Most *APOE*-related findings regarding brain structure have been reported in elderly subjects. However, due to the long AD preclinical stage, it could be expected that subtle neuroimaging changes may appear at younger ages and become more pronounced with advancing age. In line with this hypothesis, there is limited information regarding associations related to brain structural changes and *APOE* genotypes in younger subjects. Previous studies have reported lower hippocampal, orbitofrontal, and entorhinal volumes in subjects with *APOE ε4* in the first decades of life.[12,13] Other studies have shown brain hypometabolism in AD-related areas[14] and increased activation of the default mode network[15] in young *APOE ε4* carriers but no differences in gray matter volume. The aforementioned changes reported in these studies would be taking place during the 3 decades before the ages that show at least 1% AD prevalence. These findings suggest that AD could have a neurodevelopmental component. However, the relation between regional brain atrophy and the *APOE* genotype needs to be evaluated across the adult life span.

We hypothesized that *APOE ε4* carriers and noncarriers could present different imaging patterns that start differing in midlife, much earlier than clinical diagnosis. To investigate this hypothesis, we sought to model structural MR imaging brain changes associated with the *APOE* genotype in a large population-based study spanning the third-to-ninth decades of life by using sensitive pattern-based aging and AD summary indices.

MATERIALS AND METHODS

Participants from the Study of Health in Pomerania

The Study of Health in Pomerania (SHIP) is a prospective cohort whose subjects are recruited from the general population of the German State of Mecklenburg–Western Pomerania. It is led by the Institute for Community Medicine at the Medical Faculty of the University of Greifswald.[16] SHIP started at baseline with SHIP-0 between 1997 and 2001. After about 5 years, all participants were reinvited for a follow-up visit (ie, SHIP-1). From 2008 to 2012, the second follow-up examination, SHIP-2, was performed. Concurrent with SHIP-2, a new population sample from the same area was drawn, and similar examinations were undertaken between 2008 and 2012 (SHIP-TREND). SHIP-2 and SHIP-TREND included whole-body MR imaging scans,[17] which were not present in SHIP-0 and SHIP-1. Trained certified radiologists, each with >5 years of MR imaging interpretation experience, visually inspected head MR imaging scans for artifacts and clinical findings. In our study, we included 1472 subjects of the total 3256 subjects with T1-weighted brain scans available in SHIP-2 and SHIP-TREND, 22–90 years of age at enrollment. We excluded 1784 subjects from this analysis on the basis of the following: 1) the presence of stroke, multiple sclerosis, epilepsy, cerebral tumor, intracranial cyst, or hydrocephalus ($n = 150$); 2) a high level of motion artifacts ($n = 98$); 3) failed quality control of the automatically skull-stripped data ($n = 121$); 4) lack of genomewide association study data ($n = 1008$); 5) an unidentifiable *APOE* genotyping ($n = 35$); and 6) lack of clinical data (cognitive scores, $n = 190$, or covariates, $n = 182$).

Clinical data, including sociodemographic factors and medical history, were collected in a standardized computer-assisted face-to-face interview. Years of education were recorded and grouped into 3 categories: <8 years, 8–10 years, and >10 years. In SHIP, two cognitive tests were obtained: the Verbal Learning and Memory Test (the German version of the California Verbal Learning and Memory Test[18]) for SHIP-2 and the Nuremberg Age Inventory for SHIP-TREND. The Nuremberg Age Inventory is a German test developed to measure the cognitive abilities during brain aging.[19] It consists of subtests including, but not limited to, speed (eg, numbers) and memory (eg, words, numbers, and images). A description of the final SHIP sample included in our analysis ($n = 1472$) is shown in Table 1. The Ethics Committee of the Medical Faculty of the University of Greifswald approved SHIP.

Image Acquisition

In SHIP-2 and SHIP-TREND, a comprehensive whole-body MR imaging protocol was used. A full description of the image-acquisition parameters for SHIP can be found in Hegenscheid et al.[17] The neurocranium unit of SHIP included, among others, T1-weighted and fluid-attenuated inversion recovery sequences. Briefly, all images were obtained by using a 1.5T MR imaging scanner (Magnetom Avanto; Siemens, Erlangen, Germany). In this study, we used only the T1-weighted axial MPRAGE images for measuring regional patterns of AD-related brain atrophy. The T1-weighted image was acquired with the following parameters:

1×1 mm in-plane spatial resolution, section thickness = 1.0 mm, flip angle = 15°, TE = 3.4 ms, TR = 1900 ms.

Image Processing

An automated multiatlas segmentation method was applied on the T1-weighted image of each subject to calculate a brain mask, by removing extracranial material on the T1-weighted image.[20] Total intracranial volume was estimated by calculating the volume of a subject's brain mask, which included the volumes of gray matter, white matter, ventricles, and the CSF that were contained within the outer brain boundary. Each brain mask was visually inspected for quality, by M.H., and all low-quality brain masks (including either under- or oversegmented brain) were excluded.

A multiatlas label fusion–based segmentation method[21] was applied for segmentation of the brain into a set of anatomic ROIs. The volumes of ROIs were calculated and were normalized by total intracranial volume. In this analysis, we selected a set of gray matter ROIs on the basis of areas that were associated with AD-related atrophy and previously reported *APOE*-related findings. Further details are given in the On-line Appendix (On-line Method 1).

MR Imaging Pattern Classification

A pattern-classification method was previously proposed to derive Spatial Pattern of Abnormality for Recognition of Early AD (SPARE-AD),[22] an index summarizing the high-dimensional imaging data with a single value that quantifies the atrophy patterns in AD-related regions. SPARE-AD has been shown to discriminate between normal cognition and mild cognitive impairment (MCI)[23] and conversion from MCI to AD.[24] We calculated, in this study, the SPARE-AD index for the SHIP population by using a model based on a linear support vector machine,[25] which was trained on the external training dataset described in Da et al[24] and had been validated earlier.[22] More positive SPARE-AD implies a more Alzheimer disease–like brain structure, while more negative values reflect more normal brain structure.

Similar to the calculation of the SPARE-AD index, a linear support vector machine–based model was designed to predict an individual's age from the MR image and was used for quantifying Brain Aging (BA), summarized by the SPARE-BA index. The classification model was trained for optimally discriminating young and old subject groups and has been recently described.[26,27] The SPARE-BA index for an individual implied fewer brain aging patterns for higher (positive) values and the presence of more aging-related atrophy patterns for lower (negative) values. While the SPARE-AD index captured more localized atrophy patterns in AD-related regions, such as in the hippocampus and temporal lobe, the SPARE-BA index captured more global aging patterns, distributed in the cortex, but particularly in the frontal lobe. Further details are given in the On-line Appendix (On-line Method 2).

APOE Determination in SHIP

The *APOE* genotypes were determined on the basis of rs429358(C;C) and rs7412(T;T) from the resulting imputation of the SHIP genotyping. More details can be found in the On-line Appendix (On-line Method 3).

Statistical Analysis

We studied the association between age, the *APOE ε4* genotype, and AD-related gray matter volume (lateral frontal, lateral temporal, medial frontal, and hippocampus), as well as SPARE-AD and SPARE-BA, for the 1472 SHIP participants included in this study. In this study, subjects with at least 1 *ε4* allele were considered to have the *APOE ε4* genotype.

We applied linear regression models, which included total intracranial volume normalized ROI volumes as outcomes, and age square (if significant), age, *APOE ε4* carrier status, and sex as predictors adjusting for education level and study cohort. We also investigated the significance of interaction terms between the *APOE ε4* status and the variables: age^2, age, education, and sex, after adding those interaction terms one at a time to the regression models as predictors. Results were considered statistically significant if the 2-sided P value was $<.05$. No multiple comparison adjustment was applied because analyses were performed on a small number of predictors that were selected on the basis of previously published findings rather than determined on the basis of the data derived therein. To identify potentially cognitively impaired subjects on the basis of the residuals of linear regressions between age and the available cognitive scores, we labeled those subjects with a z-score of less than -1.5 SDs as possibly cognitively impaired ($n = 98$) (On-line Fig 1). Spearman rank correlation coefficients were used to assess correlations between variables. The Student t test was used to compare continuous variables, and the Pearson χ^2 test, to compare categoric variables. Analyses were performed by using the R statistical and computing software, Version 3.1 (http://www.r-project.org/).[28]

RESULTS

Subjects Included in the Study

A total of 1472 participants, from which 744 belonged to SHIP-2 and 728 belonged to SHIP-TREND, with ages ranging from 22 to 90 years (median, 53.3 years), were included in the analyses. Cohorts did not differ in sex, but significant differences were present with respect to education level ($P < .001$), age ($P < .0001$), and the number of *APOE ε4* carriers ($P = .03$). No differences were seen between subjects included in the study and those who were excluded based on the inclusion criteria described in the "Materials and Methods" section, except for sex (On-line Table 1).

Association between the MR Imaging–Based Indices and Age

The Spearman rank correlation coefficient was $r = 0.36$ between age and SPARE-AD, and $r = -0.77$ between age and SPARE-BA ($P < .001$). The Spearman rank correlation coefficient between SPARE-AD and SPARE-BA was $r = -0.44$ ($P < .001$).

Association between APOE and MR Imaging Findings

Figure 1 shows the relationship between the AD-related gray matter regions and age in *APOE ε4* carrier and noncarrier individuals. Similarly, Fig 2 shows the relationship between the MR imaging–based indices and age. In the age- and sex-adjusted models that included the interaction term between *APOE* and age, no significant association was found between *APOE ε4* carrier status and the studied MR imaging measurements in the regression models that in-

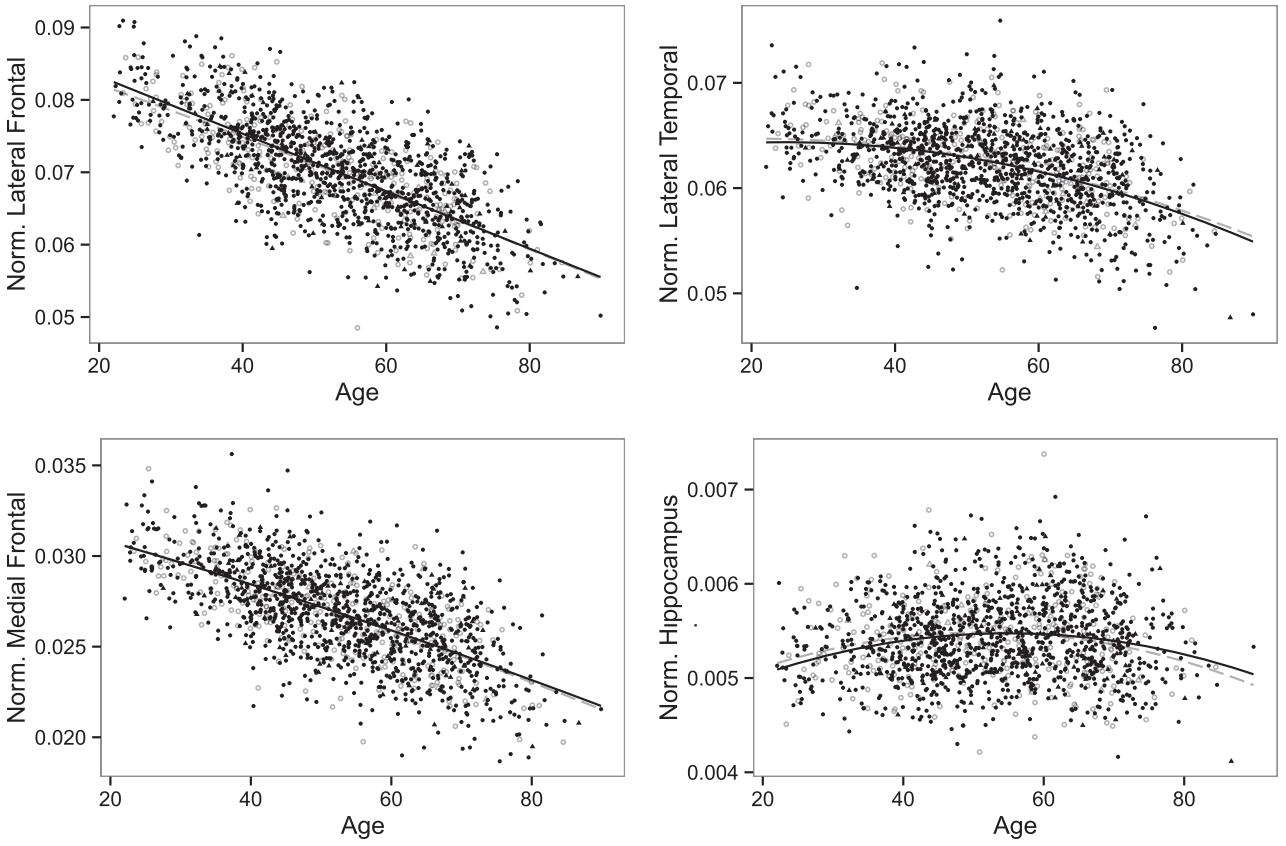

FIG 1. Relationship between AD-related gray matter regions (lateral frontal, lateral temporal, medial frontal, and hippocampus; all regions were normalized by total intracranial volume) and age within *APOE ε4* carrier (*open objects*, gray) and noncarrier (*filled objects*, black) SHIP individuals. *Circles* indicate cognitively healthy individuals, and *triangles* indicate cognitively impaired ones.

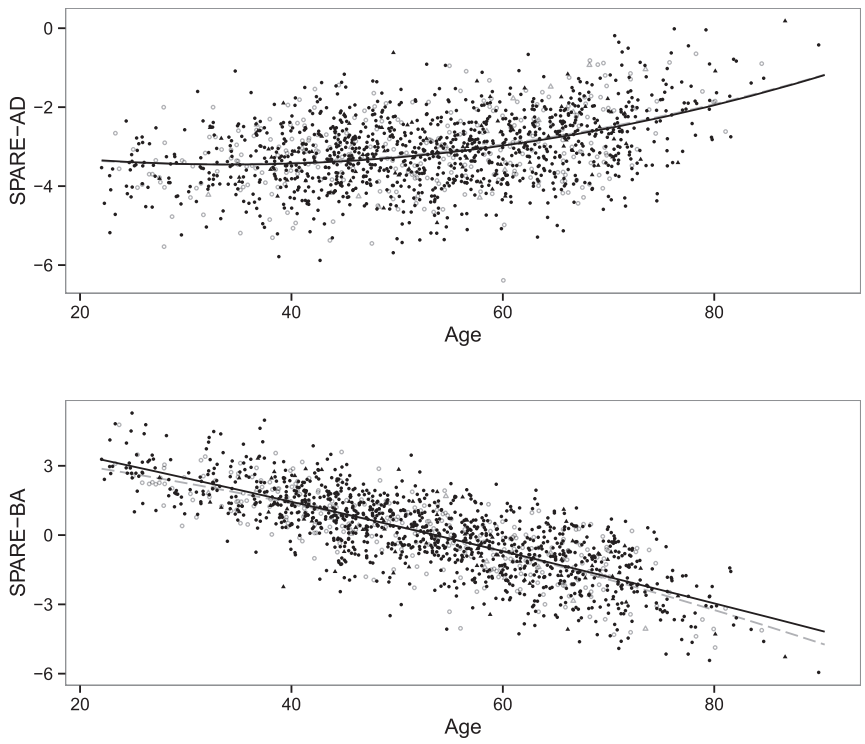

FIG 2. Relationship between age and SPARE-AD and between age and SPARE-BA in *APOE ε4* carrier (*open objects*, gray) and noncarrier (*filled objects*, black) individuals. *Circles* indicate cognitively healthy individuals, and *triangles* indicate cognitively impaired ones.

cluded the ROI volumes or the SPARE indices as outcomes (Table 2). Similarly, there was no significant interaction between *APOE ε4* carrier status and age ($P > .1$). In all models, older age was associated with greater brain atrophy, and a nonlinear square age term was significant for the models that included the lateral temporal regions, hippocampus, or SPARE-AD scores as outcomes (Table 2). Besides age, male participants showed smaller regional volumes, higher SPARE-AD, and lower SPARE-BA values over the studied life span. In additional analyses limiting the sample to younger (22–40 years) or older (60–90 years) participants, we did not find any *APOE* genotype–related differences (On-line Tables 2 and 3).

Association between APOE *and Cognitive Scores*

No significant association was detected among the Verbal Learning and Memory Test, Nuremberg Age Inventory, and *APOE ε4* carrier status in a linear regression model after adjusting for age, sex, and education (On-line Tables 4 and 5).

Table 2: Linear regression models between age and ROI volumes (normalized by total intracranial volume) and SPARE-AD and SPARE-BA[a]

Outcome	Age	Age^2	Female	*APOE ε4* Carriers
Lateral frontal volume	−0.0003900 (<.001)[b]	–	0.0021720 (<.001)[b]	−0.0002459 (.433)
Lateral temporal volume	0.0001020 (.040)[b]	−0.0000021 (<.001) [b]	0.0003695 (.040)[b]	0.0001112 (.605)
Medial frontal volume	−0.0001291 (<.001)[b]	–	0.0010690 (<.001)[b]	−0.0000055 (.964)
Hippocampal volume	0.0000415 (<.001)[b]	−0.0000005 (<.001)[b]	0.0001919 (<.001)[b]	0.0000118 (.649)
SPARE-AD	−0.0438960 (<.001)[b]	0.0006549 (<.001)[b]	−0.1775256 (<.001)[b]	0.0293579 (.582)
SPARE-BA	−0.1062550 (<.001)[b]	–	0.6416590 (<.001)[b]	−0.0514570 (.452)

[a] If age^2 was not significant in a model, the coefficients were recalculated after excluding. Data are coefficient (*P* value).
[b] Significant at $P < .05$. Models are adjusted for education and study cohort effects. Including interaction terms between *APOE* status and age^2, age, sex, and education one at a time to those regression models showed no significant interaction ($P > .1$).

DISCUSSION

Although the *APOE ε4* allele is the strongest genetic sporadic AD risk factor accounting for most of AD genetic-related risk and is associated with an earlier clinical onset of dementia and preclinical biomarker changes, we did not find brain volume differences between *APOE ε4* carriers and noncarriers.

Here we studied the association between the *APOE* genotype and brain structure in a large cohort of subjects with a wide age range recruited from the general population whose MR imaging scans were obtained by using a standardized sequence in all subjects. We quantified structural brain changes by using 2 approaches: 1) an ROI approach, guided by previous findings; and 2) a pattern-based analysis by using 2 machine-learning-based summary indices. The imaging indices, the SPARE-AD and the SPARE-BA, were developed to quantify AD- and age-related brain changes, respectively. SPARE-AD has been shown to predict early AD-related changes[23] and MCI stages.[24] The SPARE-AD index outperformed ROI-defined volumes in detecting the earliest changes associated with initial cognitive symptoms and showed that 1 single brain volume measure alone is unlikely to adequately reflect the complexity of neurodegeneration in AD, as previously demonstrated in Fan et al.[29] Therefore, it is unlikely that a lack of sensitivity of our approaches can explain the absence of associations between *APOE* and the structural MR imaging measures.

The difference in SPARE-AD scores of *APOE ε4* carriers and noncarriers was statistically insignificant. Our results indicate that *APOE*-related MR imaging atrophy is not prominent at younger ages and suggest that atrophy may only be observable more proximal to the onset of clinical symptoms. Whereas older subjects with more severe degrees of cognitive impairment might be underrepresented in our population-based sample and thus lead to an underrepresentation of *APOE ε4* carriers in the elderly (21.9% *APOE ε4* carriers among the individuals older than 60 years of age), this underrepresentation would have not been the case for the younger subjects (27.0% *APOE ε4* carriers among the individuals younger than 40 years of age). Therefore, we would not expect any recruitment bias to explain the lack of observed associations in the younger individuals included in our study.

Our findings agree with studies following cognitively healthy subjects with autosomal dominant mutations with an expected age at onset of disease, which report structural MR imaging changes taking place within ≤1 decade from the diagnosis of dementia.[30,31] In addition, recent CSF and postmortem biomarker studies have shown that amyloid deposition starts in the fifth decade,[3,32] usually without the individual having scans positive for amyloid. On the basis of the current AD biomarker[33] model that predicts occurrence of amyloid β deposition before brain atrophy, a finding of brain atrophy in the third decade of life would be unlikely.

Previous studies have reported lower hippocampal, orbitofrontal, and entorhinal volumes in subjects with *APOE ε4* in the early decades of life.[12,13] The possible reasons for conflicting results could be differences in selection of the sample, the sample size, or processing pipelines of the MR imaging scans. Another potential explanation is that negative results are less likely to be reported than positive ones. Our study included a similar, or even larger, sample size than that in previous studies and applied sensitive methods to detect even subtle MR imaging changes associated with early AD-related changes and aging. However, it is possible that differences in functional changes associated with the *APOE* genotype at a younger age, as reported previously, precede structural changes[14,15] and potentially even widespread amyloid β deposition, though this hypothesis still requires larger samples to validate initial reports based on small-sized cohorts.

In recent work, AD pathology from preclinical-to-clinical stages was associated with a decrease in the metabolism of the posterior cingulate cortex, even before any sign of AD.[34] The appearance of hypometabolism before clinical change could vary depending on cognitive reserve. The results on cognitive reserve and *APOE* are controversial in the literature. However, *APOE* does not seem to modulate the effect of cognitive reserve on cognitive function.[35] Due to the lack of functional imaging measures in our cohort, we could not evaluate the presence of these changes in the framework of SHIP.

While we did not find associations between *APOE* and brain volume measures, several studies reported the effects of the *APOE* genotype on white matter microstructure, which we did not assess in the current study. *APOE* was associated with white matter microstructure in 2 of 14 tracts in elderly persons free of dementia and preclinical dementia.[36] Furthermore, *APOE ε4* was associated with a decline in fractional anisotropy, a marker of white matter integrity, compared with noncarriers.[37] On the other hand, *APOE ε2* carriers had more robust white matter integrity.[38] The mechanisms underlying the white matter microstructural changes are still not well-understood,[39] but it is possible that detection of more subtle associations between *APOE* and brain structure in preclinical dementia requires microstructural assessment.

Limitations of our study include the use of imputed genotype data from single nucleotide polymorphism (SNP) arrays and not a specific assay for *APOE*[40] to determine the *APOE* genotype, the

limited clinical testing data available for the subjects, and the lack of longitudinal MR imaging scans.

CONCLUSIONS

Our study indicates that measurable *APOE*-related brain atrophy does not occur during early adulthood and midlife and suggests that *APOE*-related MR imaging atrophy may only be present later in life, more proximal to clinical disease onset.

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