

Differences in Alzheimer's Disease–Related Pathology Profiles Across Apolipoprotein Groups

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Abstract

The apolipoprotein (APOE) $\epsilon 4$ allele is a risk factor for Alzheimer's disease (AD), whereas the $\epsilon 2$ allele is thought to be protective against AD. Few studies have examined the relationship between brain pathologies, atrophy, white matter hyperintensities (WMHs) and APOE status in those with the $\epsilon 2\epsilon 4$ genotype and results are inconsistent for those with an $\epsilon 2$ allele. Alzheimer's disease neuroimaging participants were divided into 1 of 4 APOE allele profiles ($E 4 = \epsilon 4\epsilon 4$ or $\epsilon 3\epsilon 4$; $E 2 = \epsilon 2\epsilon 2$ or $\epsilon 2\epsilon 3$; $E 3 = \epsilon 3\epsilon 3$; or $E 24 = \epsilon 2\epsilon 4$). Linear mixed models examined the relationship between APOE profiles and brain changes (i.e., regional WMHs, ventricle size, hippocampal and entorhinal cortex volume, amyloid level, and phosphorylated tau measures), while controlling for age, sex, education, and diagnostic status at baseline and over time. APOE $\epsilon 4$ was associated with increased pathology, whereas $\epsilon 2$ positivity is associated with reduced baseline and lower accumulation of pathologies and neurodegeneration. APOE $\epsilon 2\epsilon 4$ was similar to $\epsilon 4$ (increased neurodegeneration) but with a slower rate of change. The strong associations observed between APOE and pathology show the importance of how genetic factors influence structural brain changes. These findings suggest that $\epsilon 2\epsilon 4$ genotype is related to increased declines associated with the $\epsilon 4$ as opposed to the protective effects of the $\epsilon 2$. These findings have important implications for initiating treatments and interventions. Given that people with the $\epsilon 2\epsilon 4$ genotype can expect to have increased atrophy, they should be considered (alongside those with an $\epsilon 4$) in targeted interventions to reduce brain changes that occur with AD.

Keywords: Age-related pathology, APOE phenotype, Genetics, White matter hyperintensities

Background

The $\epsilon 4$ allele of the apolipoprotein E (APOE) gene is associated with a significant risk for the development of Alzheimer's disease (AD) (1). Although one $\epsilon 4$ allele has been shown to increase risk for AD by approximately 30%, two $\epsilon 4$ alleles increase risk by approximately 65%. Furthermore, the presence of the $\epsilon 4$ allele decreases the mean age of onset for AD diagnosis in a dose-dependent manner (2,3), and is associated with faster disease progression compared to non- $\epsilon 4$ carriers (2). On the other hand, $\epsilon 2$ carriers are observed to exhibit up to a 50% less risk of AD and a later mean age of onset compared to $\epsilon 3/\epsilon 3$ genotypes (4,5).

Given the relationship between APOE status and AD risk, several studies have examined the association between APOE genotype and AD pathology. Research has reported an association between $\epsilon 4$ and greater beta amyloid ($A\beta$) deposition (6). However, the relationship between $\epsilon 4$ and tau pathology may be more complex. Although researchers have observed

that the $\epsilon 4$ is associated with increased tau accumulation (7–9), some have reported that this relationship is observed only when $A\beta$ is also present (10). The $\epsilon 2$ allele has been found to be associated with low levels of tau (11–13) and $A\beta$ deposition (11,12). Of note, there are two studies, which observed the $\epsilon 2\epsilon 4$ genotype had similar baseline Thal phase amyloid (11), Braak staging (11,12), and neuritic plaques (11,12) compared to that of $\epsilon 4$, but with less severity. Nevertheless, in most studies, the $\epsilon 2$ and $\epsilon 4$ are compared to the neutral risk $\epsilon 3$ alleles.

Several reviews have reported that the $\epsilon 4$ is associated with extensive atrophy, especially in AD-specific brain regions such as the hippocampus (HC), amygdala, entorhinal cortex (EC), as well as with ventricular enlargement (14,15). Although some studies have reported lower atrophy rates in those with the $\epsilon 2$ allele compared to $\epsilon 3$ homozygotes (two $\epsilon 3$ alleles) (16,17) and those with an $\epsilon 4$ allele (17) these atrophy differences associated with the $\epsilon 2$ versus other APOE genotypes

are not always observed (18). Taken together, these findings indicate that more research is needed to fully understand the relationship between APOE status and AD-specific measures of neurodegeneration.

Another contributor to AD risk is cerebral small vessel disease (19), which is often quantified using white matter hyperintensities (WMHs) on T2 or FLAIR MRI (20). Increased WMH burden increases cognitive decline in normal aging (21) and progression to mild cognitive impairment (MCI) and dementia (20,22). Previous research has observed a significant association between the $\epsilon 4$ (23–25) and $\epsilon 2$ (23,26) and WMH burden. The relationship observed between the $\epsilon 4$ allele and WMH burden may explain why approximately 70% of diagnosed AD cases are of a mixed etiology (27).

To date, most research examining the influence of APOE on brain pathology, compares $\epsilon 4$ homozygotes (two $\epsilon 4$ alleles) to $\epsilon 4$ heterozygotes (one $\epsilon 4$ and one $\epsilon 3$ allele) and $\epsilon 3$ homozygotes. This type of method is important to understand the dose-dependent effect of the $\epsilon 4$ on brain pathology, but it does not provide a clear understanding of how different APOE genotypes influence brain changes. The results remain unclear whether there are differences in brain pathology in those with an $\epsilon 2$ compared to other APOE profiles. Most studies exclude people who exhibit the $\epsilon 2\epsilon 4$ genotype because of the combined protective and detrimental nature of the 2 alleles and because this genotype is less common than other types. It remains unknown whether people with both an $\epsilon 4$ and $\epsilon 2$ allele have increased or decreased pathology change over time relative to other APOE profiles. It is thus possible that in response to some pathologies, the $\epsilon 2$ is protective and that the $\epsilon 4$ is detrimental for other pathologies. Furthermore, these studies have yet to examine whether rate of change in various pathologies differs based on APOE profile. The goal of this article was to examine AD-related pathologies in a longitudinal manner to improve our current understanding of how these pathological mechanisms are influenced by APOE.

Method

Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The study received ethical approval from the review boards of all participating institutions. Written informed consent was obtained from participants or their study partner. Participants were selected from all ADNI cohorts (ADNI-1, ADNI-GO, ADNI-2 and ADNI-3).

Participants

Full participant inclusion and exclusion criteria are available at www.adni-info.org. All participants were between the ages of 55 and 90 at baseline, with no evidence of depression. Cognitively healthy older adults exhibited no evidence of memory decline, as measured by the Wechsler Memory Scale and no evidence of impaired global cognition as measured by the Mini-Mental Status Examination (MMSE) or Clinical

Dementia Rating (CDR). MCI participants scored between 24 and 30 on the MMSE, 0.5 on the CDR, and abnormal scores on the Wechsler Memory Scale. Dementia was defined as participants who had abnormal memory function on the Wechsler Memory Scale, an MMSE score between 20 and 26 and a CDR of 0.5 or 1.0 and a probable AD clinical diagnosis according to the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria.

Participants were included if they had completed APOE genotyping and had at least one of the dependent variables of interest. That is, information from at least one of the following: MRIs from which WMHs could be extracted, or ventricle, hippocampal, and entorhinal cortex volumes, or pTau measures, or AV-45 measures. A total of 2079 participants with 9847 timepoints with MRIs from which WMHs could be extracted were included in the WMH analysis. A total of 2050 participants with 8707 timepoints had ventricle volumes, 2006 participants with 8026 timepoints had hippocampus (HC) volumes, and 1968 participants with 7630 had entorhinal cortex (EC) volumes. Only 1231 participants with 2412 timepoints had pTau measurements and 1212 participants with 2411 timepoints had AV-45 measurements. These participants were then divided into the 4 possible APOE profiles (see Figure 1). Participant demographic information for those included in the WMH analyses are presented in Table 1. Participants were used from the WMH subanalysis to examine demographics because it was the largest sample size available.

Structural MRI Acquisition and Processing

All longitudinal scans were downloaded from the ADNI website (see <http://adni.loni.usc.edu/methods/mri-tool/mri-analysis/> for the detailed MRI acquisition protocol). T1w scans for each participant were preprocessed through our standard pipeline including noise reduction (28), intensity inhomogeneity correction (29), and intensity normalization into

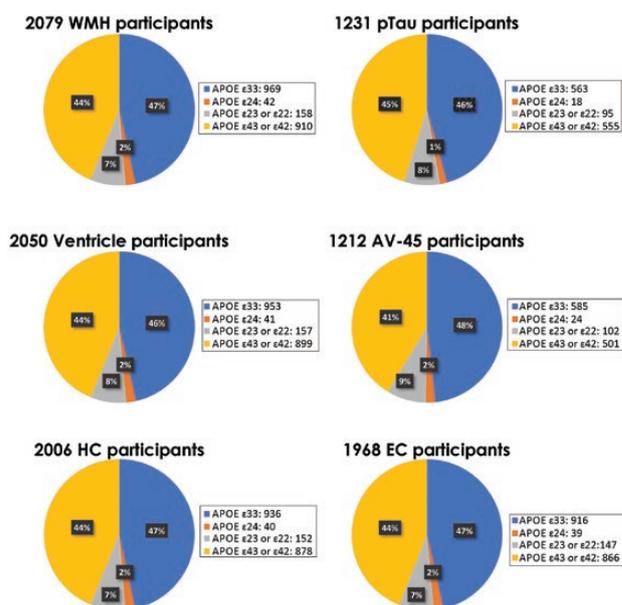


Figure 1. Proportion of participants in each analysis by APOE profile. Each plot presents the total number of participants with that pathology information. The percentage of the population with each APOE genotype is also provided.

range [0–100]. The preprocessed images were then linearly (9 parameters: 3 translation, 3 rotation, and 3 scaling) (22) registered to the MNI-ICBM152-2009c average (30).

WMH Measurements

A previously validated WMH segmentation technique was employed to generate participant WMH measurements (20). This technique has been validated in ADNI in which a library of manual segmentations based on 50 ADNI participants (independent of those studied here) was created. The technique has also been validated in other multicenter studies such as the Parkinson's Markers Initiative (31) and the National Alzheimer's Coordinating Center (32). WMHs were automatically segmented using the T1w contrasts, along with a set of location and intensity features obtained from a library of manually segmented scans in combination with a random forest classifier to detect the WMHs in new images (33,34). White matter hyperintensity load was defined as the volume of all voxels as WMH in the standard stereotaxic space (in mm³) and is thus normalized for head size. The volumes of the WMHs for frontal, parietal, temporal, and occipital lobes as well as the entire brain were calculated based on regional masks from the Hammers atlas (33,35). The quality of the registrations and WMH segmentations was visually verified by an experienced rater (author, M.D.), anonymized to diagnostic group.

pTau and AV-45 Measurements

pTau and AV-45 measurements were obtained from ADNI. The pTau measurements were extracted from CSF samples obtained through lumbar punctures as described in the ADNI procedures manual. The pTau values were generated from the multiplex xMAP Luminex platform (Luminex Corp., Austin, TX) with the INNO-BIA AlzBio3 kit (Innogenetics) (36,37). AV-45 PET imaging was performed within 2 weeks (before or after) the baseline clinical assessments for all participants with follow-up imaging at 2 years. Full description of procedures and processing has been previously described (38).

HC, EC, and Ventricle Measurements

Hippocampal, EC, and ventricle volumes were extracted from ADNIMERGE (excel file provided on the ADNI website containing volumetric information). Volumetric segmentation was performed with the FreeSurfer image analysis suite, which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>).

Statistical Analysis

Analyses were performed using "R" software version 4.0.5. WMH and ventricle volumes were log-transformed to achieve a more normal distribution. Linear mixed-effects models were used to investigate the association between each pathology and the APOE groups. WMH load was examined for whole brain and frontal, temporal, parietal, and occipital regions. Regional WMH values (i.e., frontal, temporal, parietal, and occipital) were summed across the right and left hemispheres to obtain one score for each region. All continuous values (including log-transformed WMH volumes) were *z*-scored within the population prior to the analyses. All results were corrected for multiple comparisons using false discovery rate (FDR) of 0.05; *p* values are reported as raw values with significance then determined by FDR correction (39).

The first set of linear regressions were completed to determine if baseline pathology measures differed between the different APOE profiles. Age, education, sex, and baseline diagnosis were included as covariates. Models were run separately for each dependent variable: WMH burden at each region, pTau, AV-45, ventricle volume, HC volume, and EC volume.

$$\text{Dependent Variable} \sim \text{Age} + \text{Education} + \text{Sex} + \text{Diagnosis}_{-bl} + \text{APOE group} \quad (1)$$

The second set of analyses included linear mixed-effects models to determine if longitudinal change in pathology measures differed between the different APOE profiles. Age at baseline, education, sex, and baseline diagnosis were included as covariates. The interaction of interest was APOE group by

Table 1. Demographic Information for Each APOE Group and the Baseline Means for Each Dependent Variable

N = 2 079	ε2 (n = 158)	ε3 (n = 969)	ε4 (n = 910)	ε24 (n = 42)
Age	73.5 ± 7.0	74.0 ± 7.4	72.5 ± 6.9	74.6 ± 7.1
Sex (% female)	74 (47%)	453 (47%)	416 (46%)	24 (57%)
Education	16.1 ± 2.9	16.2 ± 2.7	15.8 ± 2.8	16.0 ± 2.4
Diagnosis				
CN	91 (58%)	432 (44.5%)	218 (24%)	12 (28%)
MCI	56 (35%)	425 (44%)	456 (50%)	23 (55%)
AD	11 (7%)	112 (11.5%)	236 (26%)	7 (17%)
Baseline dependent variables scores				
Baseline AV-45	1.07 ± 0.14	1.13 ± 0.21	1.32 ± 0.23	1.27 ± 0.18
Baseline Ptau (log)	3.04 ± 0.40	3.15 ± 0.43	3.43 ± 0.41	3.38 ± 0.44
Baseline total WMH (log)	8.74 ± 0.52	8.81 ± 0.59	8.81 ± 0.56	8.89 ± 0.60
Baseline ventricle volume (log)	10.4 ± 0.51	10.5 ± 0.55	10.5 ± 0.56	10.7 ± 0.50
Baseline HC volume	7192 ± 1 162	7046 ± 1181	6594 ± 1185	6862 ± 1113
Baseline EC volume	3847 ± 773	3684 ± 806	3395 ± 819	3517 ± 901
Baseline whole brain volume	1031 368 ± 110969	1032 206 ± 112738	1022 696 ± 112075	990656 ± 110490

Notes: Participants were used from the WMH subanalysis because it was the largest sample size available. AD = Alzheimer's disease; CN = cognitively normal; EC = entorhinal cortex; HC = hippocampus; MCI = mild cognitive impairment; WMH = white matter hyperintensities.

TimeFromBaseline to examine if rate of change in pathology accumulation differed by APOE group. Longitudinal models were run separately for each dependent variable including WMH burden at each region, pTau, AV-45, ventricle volume, HC volume, and EC volume. In this model, participant ID was included as a categorical random effect.

$$\begin{aligned} \text{Pathology} \sim & \text{Age}_{\text{bl}} + \text{Education} + \text{Sex} + \\ & \text{Diagnosis}_{\text{bl}} + \text{APOE group} + \\ & \text{Time From Baseline} + \text{APOE group} : \\ & \text{Time From Baseline} + (1 | \text{ID}) \end{aligned} \quad (2)$$

Results

As can be observed in Figure 2A and Table 2, group differences were observed in the baseline results. The APOE $\epsilon 4$ and $\epsilon 2\epsilon 4$ were associated with increased AV-45 compared to $\epsilon 2$ and $\epsilon 3$ (t belongs to [13.49–3.30], $p < .001$). The APOE $\epsilon 4$ was also associated with increased pTau compared to $\epsilon 2$ ($t = 6.03$, $p < .001$) and $\epsilon 3$ ($t = 9.82$, $p < .001$). With respect to WMH burden, only the occipital region showed baseline differences, with $\epsilon 4$ having increased occipital WMH burden compared to $\epsilon 2$ ($t = 3.11$, $p = .002$) and $\epsilon 3$ ($t = 2.35$, $p = .019$). The $\epsilon 2\epsilon 4$ group had larger ventricles than $\epsilon 3$ ($t = 2.46$, $p = .014$) and $\epsilon 4$ ($t = 2.49$, $p = .013$). With respect to neurodegeneration, $\epsilon 4$ had smaller HC volumes than all other groups (t belongs to [2.46–6.06], $p < .01$), and smaller EC volumes compared to $\epsilon 2$ ($t = 2.95$, $p = .003$) and $\epsilon 3$ ($t = 4.02$, $p < .001$). No other APOE group differences were significant.

Longitudinal results can be observed in Figure 2B and Table 3. The APOE $\epsilon 4$ group had increased rate of AV-45 change compared to $\epsilon 2$ ($t = 4.91$, $p < .001$) and $\epsilon 3$ ($t = 3.83$, $p < .001$), and $\epsilon 3$ had increased rate of AV-45 change compared to $\epsilon 2$ ($t = 2.75$, $p = .006$). Interestingly, the $\epsilon 4$ group had a smaller rate of pTau accumulation than the $\epsilon 3$ group ($t = -4.76$, $p < .001$). Rate of total WMH accumulation differed between all groups (t belongs to [10.42–2.61], $p < .001$), except $\epsilon 2\epsilon 4$ versus $\epsilon 4$ and $\epsilon 2\epsilon 4$ versus $\epsilon 3$. Similar results were obtained for regional WMH burden rates (see Table 3). Rate of change for ventricle (t belongs to [20.92–2.57], $p < .01$) and HC volume (t belongs to [17.59–2.48], $p < .01$) significantly differed between all groups. The $\epsilon 4$ group had increased EC atrophy over time compared to $\epsilon 2$ ($t = 7.42$, $p < .001$) and $\epsilon 3$ ($t = 9.87$, $p < .001$), and the $\epsilon 2\epsilon 4$ had increased EC atrophy over time compared to $\epsilon 2$ ($t = 2.43$, $p = .015$).

Baseline and longitudinal WMH analyses were completed a second time removing age as a covariate. The results did not significantly differ from those presented but are shown in Supplementary Tables 1 and 2. Additional exploratory analyses were also completed on the 2058 participants with 8965 time points with whole brain volume measures; these results are also presented in Supplementary Table 3.

Discussion

Over the last several decades, an abundance of research has attempted to identify early risk factors for AD in order to mitigate cognitive decline and even prevent disease progression. One of the important risk factors for cognitive aging (40) and conversion to AD is presence of the APOE $\epsilon 4$ allele (41). The relationship between the $\epsilon 2$ allele and $\epsilon 2\epsilon 4$ genotype with cognitive functioning and AD progression remains more elusive than with $\epsilon 4$. The current study helps improve

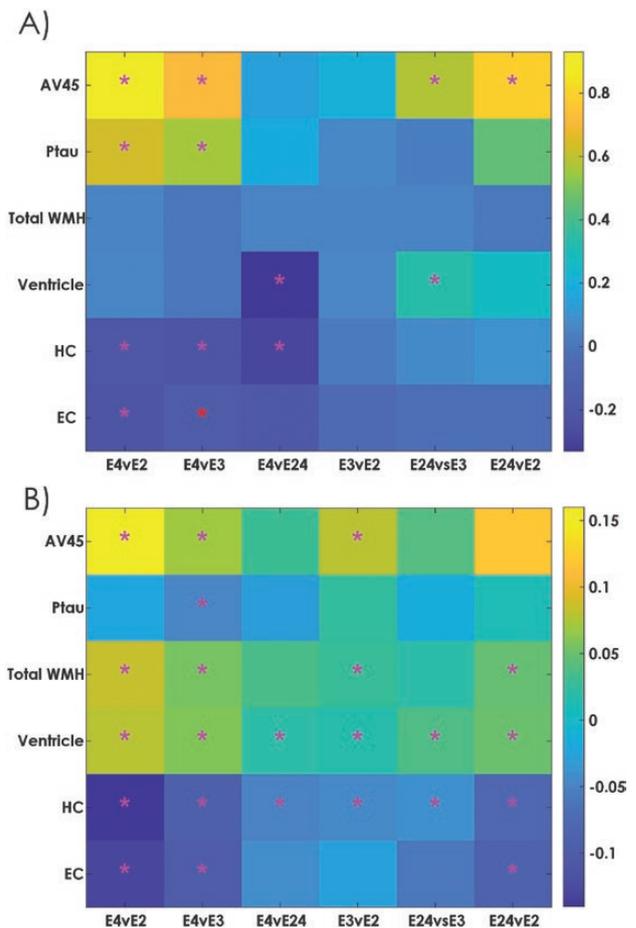


Figure 2. Colormap plots showing normalized beta estimates and an asterisk identifies statistically significant differences between the APOE profiles at baseline and over time. Color values represent beta estimates of the z-scored values with significant differences marked by an asterisk. Each column represents a comparison between the 2 groups presented. (A) Significant baseline differences between the APOE profiles. (B) Significant longitudinal differences showing the interaction of APOE profile and time from baseline to reflect rate of change group differences for each measure of pathology.

our understanding of how different APOE profiles are associated with neurodegeneration and brain pathology. At baseline, $\epsilon 4$ exhibited increased pTau compared to $\epsilon 2$ and $\epsilon 3$ and smaller HC and EC volumes than all other APOE profiles. The $\epsilon 2\epsilon 4$ group exhibited smaller ventricles than $\epsilon 3$ and $\epsilon 4$. The $\epsilon 2$ group exhibited less amyloid than all other APOE profiles, whereas $\epsilon 4$ and $\epsilon 2\epsilon 4$ had more amyloid compared to $\epsilon 3$. Longitudinally, many more APOE profile differences were apparent. Ventricular enlargement and HC atrophy significantly differed between all profiles. Furthermore, $\epsilon 2$ was observed to have slower WMH accumulation compared to all other profiles, whereas $\epsilon 4$ exhibited faster accumulation compared to $\epsilon 3$. The $\epsilon 4$ group exhibited increased EC atrophy compared to $\epsilon 3$ and $\epsilon 2$, and $\epsilon 2\epsilon 4$ exhibited more atrophy than $\epsilon 2$. Amyloid increased faster in the $\epsilon 3$ group compared to $\epsilon 3$ and $\epsilon 2$, whereas $\epsilon 2$ amyloid progressed slower than $\epsilon 3$.

Consistent with previous findings indicating an association between $\epsilon 4$ and increased $A\beta$ (6), we observed that $\epsilon 4$ group exhibited elevated $A\beta$ levels compared to $\epsilon 2$ and $\epsilon 3$ at baseline and had greater change over time. At baseline, the $\epsilon 2\epsilon 4$ group also exhibited increased $A\beta$ levels compared to $\epsilon 2$ and $\epsilon 3$, but

Table 2. Estimates Provided From the Baseline Linear Regression

	e4ve2	e4ve3	e4ve24	e3ve2	e24ve3	e24ve2
AV-45	$\beta = 0.93, SE = 0.09, t = 9.90, p < .001$	$\beta = 0.72, SE = 0.06, t = 13.49, p < .001$	$\beta = 0.14, SE = 0.18, t = 0.78, p = .44$	$\beta = 0.21, SE = 0.09, t = 2.28, p = .023$	$\beta = 0.58, SE = 0.18, t = 3.30, p = .001$	$\beta = 0.79, SE = 0.19, t = 4.10, p < .001$
pTau	$\beta = 0.63, SE = 0.10, t = 6.03, p < .001$	$\beta = 0.56, SE = 0.06, t = 9.82, p < .001$	$\beta = 0.18, SE = 0.22, t = 0.82, p = .41$	$\beta = 0.06, SE = 0.10, t = 0.65, p = .51$	$\beta = 0.38, SE = 0.22, t = 1.73, p = .08$	$\beta = 0.45, SE = 0.24, t = 1.90, p = .06$
Total WMH	$\beta = -0.05, SE = 0.07, t = -0.75, p = .46$	$\beta = -0.01, SE = 0.04, t = -0.05, p = .96$	$\beta = 0.05, SE = 0.13, t = 0.39, p = .69$	$\beta = -0.05, SE = 0.07, t = -0.74, p = .46$	$\beta = 0.05, SE = 0.13, t = 0.41, p = .68$	$\beta = -0.10, SE = 0.14, t = -0.73, p = .68$
Ventricle	$\beta = 0.06, SE = 0.07, t = 0.78, p = .43$	$\beta = 0.01, SE = 0.04, t = 0.06, p = .95$	$\beta = 0.22, SE = 0.13, t = 2.46, p = .014$	$\beta = 0.06, SE = 0.07, t = 0.84, p = .40$	$\beta = 0.33, SE = 0.13, t = 2.49, p = .013$	$\beta = -0.28, SE = 0.15, t = -1.84, p = .07$
HC	$\beta = -0.20, SE = 0.07, t = -2.96, p = .003$	$\beta = -0.22, SE = 0.04, t = -6.06, p < .001$	$\beta = -0.29, SE = 0.11, t = -2.46, p = .01$	$\beta = -0.02, SE = 0.06, t = -0.34, p = .74$	$\beta = -0.08, SE = 0.12, t = -0.64, p = .53$	$\beta = -0.10, SE = 0.13, t = -0.74, p = .46$
EC	$\beta = -0.22, SE = 0.07, t = -2.95, p = .003$	$\beta = -0.16, SE = 0.04, t = -4.02, p < .001$	$\beta = -0.19, SE = 0.13, t = -1.39, p = .16$	$\beta = -0.06, SE = 0.07, t = -0.80, p = .43$	$\beta = -0.25, SE = 0.13, t = -0.18, p = .85$	$\beta = -0.33, SE = 0.15, t = -0.23, p = .82$
Regional WMHs						
Frontal WMH	$\beta = -0.06, SE = 0.07, t = -0.78, p = .43$	$\beta = 0.03, SE = 0.4, t = 0.68, p = .49$	$\beta = 0.03, SE = 0.13, t = 0.26, p = .79$	$\beta = -0.08, SE = 0.07, t = -1.18, p = .24$	$\beta = -0.01, SE = 0.13, t = -0.06, p = .95$	$\beta = -0.09, SE = 0.15, t = -0.64, p = .53$
Temporal WMH	$\beta = -0.01, SE = 0.08, t = -0.03, p = .98$	$\beta = -0.03, SE = 0.04, t = -0.76, p = .44$	$\beta = 0.08, SE = 0.14, t = 0.56, p = .58$	$\beta = 0.03, SE = 0.07, t = 0.39, p = .70$	$\beta = -0.11, SE = 0.14, t = -0.79, p = .43$	$\beta = -0.08, SE = 0.15, t = -0.05, p = .60$
Parietal WMH	$\beta = -0.01, SE = 0.08, t = -0.23, p = .84$	$\beta = -0.02, SE = 0.04, t = -0.61, p = .54$	$\beta = 0.03, SE = 0.13, t = 0.28, p = .78$	$\beta = 0.01, SE = 0.07, t = 0.13, p = .89$	$\beta = -0.06, SE = 0.13, t = -0.46, p = .65$	$\beta = -0.05, SE = 0.15, t = -0.35, p = .72$
Occipital WMH	$\beta = 0.25, SE = 0.08, t = 3.10, p = .002$	$\beta = 0.10, SE = 0.04, t = 2.35, p = .019$	$\beta = 0.05, SE = 0.15, t = 0.36, p = .72$	$\beta = 0.15, SE = 0.08, t = 1.87, p = .06$	$\beta = -0.05, SE = 0.15, t = -0.36, p = .72$	$\beta = -0.20, SE = 0.16, t = -1.23, p = .21$

Notes: EC = entorhinal cortex; HC = hippocampus; WMH = white matter hyperintensity. Bold values are those that remained significant after correction for multiple comparisons.

Table 3. Estimates Provided From the Longitudinal Linear Mixed-Effects Models Interaction Between APOE Profile and Time

	e4ve2	e4ve3	e4ve24	e3ve2	e24ve3	e24ve2
AV-45	$\beta = 0.16, SE = 0.03, t = 4.91, p < .001$	$\beta = 0.07, SE = 0.02, t = 3.83, p < .001$	$\beta = 0.03, SE = 0.06, t = 0.52, p = .60$	$\beta = 0.08, SE = 0.03, t = 2.75, p = .006$	$\beta = 0.04, SE = 0.06, t = 0.66, p = .51$	$\beta = 0.12, SE = 0.07, t = 1.85, p = .064$
pTau	$\beta = 0.02, SE = 0.02, t = 1.23, p = .22$	$\beta = -0.05, SE = 0.01, t = -4.76, p < .001$	$\beta = 0.03, SE = 0.02, t = 1.27, p = .21$	$\beta = 0.03, SE = 0.02, t = 1.62, p = .11$	$\beta = 0.38, SE = 0.22, t = 1.73, p = .08$	$\beta = 0.45, SE = 0.24, t = 1.90, p = .06$
Total WMH	$\beta = 0.08, SE = 0.01, t = 9.29, p < .001$	$\beta = 0.06, SE = 0.01, t = 10.42, p < .001$	$\beta = 0.03, SE = 0.01, t = 2.13, p = .03$	$\beta = 0.03, SE = 0.01, t = 3.24, p = .001$	$\beta = 0.02, SE = 0.02, t = 1.17, p = .24$	$\beta = 0.05, SE = 0.02, t = 2.61, p = .009$
Ventricle	$\beta = 0.08, SE = 0.01, t = 16.04, p < .001$	$\beta = 0.06, SE = 0.01, t = 20.92, p < .001$	$\beta = 0.02, SE = 0.01, t = 2.57, p = .010$	$\beta = 0.02, SE = 0.01, t = 3.53, p < .001$	$\beta = 0.04, SE = 0.01, t = 3.94, p < .001$	$\beta = 0.05, SE = 0.01, t = 5.25, p < .001$
HC	$\beta = -0.14, SE = 0.01, t = -15.37, p < .001$	$\beta = -0.09, SE = 0.01, t = -17.59, p < .001$	$\beta = -0.05, SE = 0.02, t = -3.19, p = .001$	$\beta = -0.04, SE = 0.01, t = -5.13, p < .001$	$\beta = -0.04, SE = 0.02, t = -2.48, p = .013$	$\beta = -0.08, SE = 0.02, t = -4.73, p < .001$
EC	$\beta = -0.14, SE = 0.02, t = -7.42, p < .001$	$\beta = -0.11, SE = 0.01, t = -9.87, p < .001$	$\beta = -0.05, SE = 0.03, t = -1.43, p = .15$	$\beta = 0.03, SE = 0.02, t = 1.53, p = .13$	$\beta = -0.06, SE = 0.03, t = -1.84, p = .065$	$\beta = -0.09, SE = 0.04, t = -2.43, p = .015$
Regional WMHs						
Frontal	$\beta = 0.07, SE = 0.01, t = 8.09, p < .001$	$\beta = 0.05, SE = 0.01, t = 9.11, p < .001$	$\beta = 0.01, SE = 0.02, t = 0.65, p = .52$	$\beta = 0.02, SE = 0.01, t = 2.80, p = .005$	$\beta = 0.04, SE = 0.02, t = 2.25, p = .024$	$\beta = 0.06, SE = 0.02, t = 3.39, p < .001$
Temporal	$\beta = 0.07, SE = 0.01, t = 6.41, p < .001$	$\beta = 0.03, SE = 0.01, t = 4.76, p < .001$	$\beta = 0.05, SE = 0.02, t = 2.68, p < .001$	$\beta = 0.04, SE = 0.01, t = 3.74, p < .001$	$\beta = 0.02, SE = 0.02, t = 1.20, p = .23$	$\beta = 0.01, SE = 0.02, t = 0.67, p = .50$
Parietal	$\beta = 0.08, SE = 0.01, t = 9.09, p < .001$	$\beta = 0.05, SE = 0.01, t = 10.23, p < .001$	$\beta = 0.05, SE = 0.02, t = 2.91, p = .003$	$\beta = 0.03, SE = 0.01, t = 3.14, p = .002$	$\beta = 0.01, SE = 0.02, t = 0.33, p = .75$	$\beta = 0.03, SE = 0.02, t = 1.78, p = .07$
Occipital	$\beta = 0.13, SE = 0.01, t = 9.67, p < .001$	$\beta = 0.08, SE = 0.01, t = 10.35, p < .001$	$\beta = 0.07, SE = 0.02, t = 2.62, p = .009$	$\beta = 0.05, SE = 0.01, t = 3.69, p < .001$	$\beta = 0.02, SE = 0.02, t = 0.65, p = .51$	$\beta = 0.06, SE = 0.03, t = 2.34, p = .019$

Notes: EC = entorhinal cortex; HC = hippocampus; WMH = white matter hyperintensity. Bold values are those that remained significant after correction for multiple comparisons.

they did not exhibit an increased rate of change longitudinally. The protective effect of the $\epsilon 2$ also resulted in reduced accumulation of A β compared to those with $\epsilon 3$. These findings are consistent with past reports that the $\epsilon 4$ is associated with increased A β , whereas the $\epsilon 2$ is associated with lower A β (11,12). Additionally, this study observed opposite $\epsilon 4$ and $\epsilon 2$ effects in rate of accumulation of A β , indicating the detrimental effect of $\epsilon 4$ and protective effect of $\epsilon 2$ on rate of amyloid accumulation. The finding of increased baseline $\epsilon 2\epsilon 4$ A β , but lack of longitudinal differences indicates that the change over time in this group is similar to that of all other groups. The heightened A β at baseline compared to $\epsilon 2$ and $\epsilon 3$ may reduce resiliency to other brain changes observed longitudinally.

Interestingly, although $\epsilon 4$ had increased pTau levels at baseline compared to $\epsilon 2$ and $\epsilon 3$, this group did not have increased rates of pTau levels longitudinally. No other pTau differences between the groups were observed at baseline or longitudinally. The minimal pTau differences between APOE profiles may be because of the inclusion of all diagnostic groups in our analyses. Previous research has observed that the relationship between APOE status and tau is found only in the presence of A β (10), therefore including some amyloid-negative normal controls may reduce the longitudinal associations. This finding may be a limitation of the current study as the sample size is not large enough to examine APOE profiles within each diagnostic group individually (i.e., cognitively healthy older adults, MCI, and AD).

WMH burden was measured as total brain WMH volume as well as regionally (at frontal, temporal, parietal, and occipital regions). At baseline, only occipital WMH burden showed differences based on APOE profile. More specifically, $\epsilon 4$ had increased occipital WMHs over both $\epsilon 2$ and $\epsilon 3$. The $\epsilon 4$ profile showed increased rates of WMH accumulation compared to $\epsilon 2$ and $\epsilon 3$ for total burden and for all regions, and more than $\epsilon 2\epsilon 4$ at the temporal, parietal, and occipital regions. Previous research has observed that parietal and occipital WMHs are the most prominent areas associated with WMH volume observed in AD (42,43). Therefore, people with the $\epsilon 4$ profile are exhibiting WMH burden that is associated with progression to dementia. The $\epsilon 2$ profile showed lower rates of WMH accumulation compared to $\epsilon 3$ for total burden and at all regions, and compared to $\epsilon 2\epsilon 4$ for total WMH accumulation and frontal and occipital regions. These findings are consistent with cross-sectional findings showing the protective effects of $\epsilon 2$ (23) and detrimental effects of $\epsilon 4$ (24,25). Extending on this research, the current study also observed that the $\epsilon 2$ offers protection against WMH accumulation over time. With respect to the $\epsilon 2\epsilon 4$, this group showed less WMH accumulation compared to $\epsilon 4$, no difference compared to $\epsilon 3$, but more than $\epsilon 2$ at total, frontal, and occipital regions. They showed a similar pattern of WMH change to that of $\epsilon 3$, indicating that the $\epsilon 2\epsilon 4$ profile provides a neutral effect on WMH burden.

Examination of overall neurodegeneration and overall atrophy was completed using ventricle volume. At baseline, the only ventricle differences observed were limited to $\epsilon 2\epsilon 4$ having larger ventricles compared to both $\epsilon 3$ and $\epsilon 4$. This slightly larger ventricle volume at baseline may be associated with the limited sample size of the $\epsilon 2\epsilon 4$. This baseline difference was followed by the $\epsilon 2\epsilon 4$ having increased ventricle volume over time compared to $\epsilon 2$ and $\epsilon 3$, but slightly lower rate of change compared to $\epsilon 4$. These findings suggest that the $\epsilon 2\epsilon 4$ genotype has a detrimental risk toward overall atrophy as measured

by ventricle volumes. The $\epsilon 4$ profile had increased ventricle volume rate of change compared to both $\epsilon 3$ and $\epsilon 2$, and $\epsilon 2$ had less ventricle volume increases than $\epsilon 3$. That is, $\epsilon 4$ has a negative influence on ventricle volume, whereas $\epsilon 2$ offers protection toward minimizing ventricle size. Despite inconsistent results in the literature on the relationship between ventricle size and APOE status (14), our findings suggest a strong relationship between APOE and ventricle volume. With respect to our exploratory analysis of whole brain volume, no group differences were observed at baseline. However, longitudinally, we observed that $\epsilon 4$ and $\epsilon 2\epsilon 4$ had reduced whole brain volume compared to both $\epsilon 2$ and $\epsilon 3$. Neither $\epsilon 2$ versus $\epsilon 3$ nor $\epsilon 4$ versus $\epsilon 2\epsilon 4$ differed in rate of whole brain volume change. Taken together, an increase in ventricular volume and reduction in whole brain volume suggest that the $\epsilon 2\epsilon 4$ genotype is associated with overall atrophy similar to that observed in those with $\epsilon 4$.

Both baseline and longitudinal rates of HC and EC volume were observed to be associated with APOE profile. Consistent with previous findings, at baseline the $\epsilon 4$ profile had increased HC atrophy compared to all other groups (16), and increased EC atrophy compared to $\epsilon 2$ and $\epsilon 3$ (14). Rate of change in HC volume was significantly different between all APOE profiles. The $\epsilon 2\epsilon 4$ exhibited increased HC atrophy over time compared to $\epsilon 2$ and $\epsilon 3$, but lower rate of change compared to $\epsilon 4$. These findings suggest that the $\epsilon 2\epsilon 4$ genotype has a detrimental risk toward HC atrophy, a known marker of AD disease staging (44). The $\epsilon 4$ profile had increased HC atrophy over time compared to both $\epsilon 3$ and $\epsilon 2$, and $\epsilon 2$ had less HC atrophy increases than $\epsilon 3$. That is, $\epsilon 4$ has a negative influence, whereas $\epsilon 2$ offers protection toward minimizing HC atrophy that occurs over time. Rate of atrophy change in the EC was increased in $\epsilon 4$ compared to $\epsilon 2$ and $\epsilon 3$, and $\epsilon 2\epsilon 4$ compared to $\epsilon 2$. As the $\epsilon 2\epsilon 4$ did not differ from $\epsilon 3$ or $\epsilon 4$ but was slightly increased compared to $\epsilon 2$, we can interpret this finding as the $\epsilon 2\epsilon 4$ profile exhibiting an intermediate rate of change between $\epsilon 3$ and $\epsilon 4$.

It should be noted that a weakness of the current study is the use of only ADNI data. This sample is highly educated and lacks diversity. Our participants had an average education of 16 years and were mainly White individuals (93% of the sample), which may reduce generalizability to more representative samples. Given that previous research has observed that the relationship between AD and APOE differs based on race (45), it is imperative that future research explore the longitudinal relationship between APOE status and pathology in other races. The longitudinal nature of this project is a major strength, as it improves our ability to draw causal relationships between APOE status and neuropathology. This study provides an in-depth analysis of both the protective and detrimental effects APOE can have on AD-related pathology.

Another possible limitation of this study is that we used T1w images to extract WMHs, which are normally obtained from FLAIR or T2w images. This imaging method was used to extract WMHs because only T1w images are consistently available through all ADNI cohorts. In our previous work, we have repeatedly shown that our T1w-based segmentation method exhibits very strong correlations with the multicontrast T1w and T2w or FLAIR-based WMHs segmentations ($r = 0.97$, $p < .0001$) and has similar relationships with clinical/cognitive scores as the multicontrast WMH segmentations (20,22). Additionally, we also compared a subcohort of ADNI participants who had T1w, T2w/PD (ADNI-1), and

FLAIR (ADNI-2) sequences and observed that the group differences using the T1w-based WHM segmentation sequences were similar to that of the T1 + T2w/PD and T1 + FLAIR segmentations (46). We thus believe that the T1w-based method employed has excellent reliability and validity to accurately measure WMHs.

The strong associations observed between APOE and pathology in this study show the importance of how genetic factors influence structural brain changes. These findings offer clarification on the protective effects that $\epsilon 2$ offers and the detrimental effects from the $\epsilon 4$ toward neurodegeneration and pathologies. Furthermore, the observation of the detrimental effect of $\epsilon 2\epsilon 4$ on both ventricle volume and hippocampal atrophy change over time is a novel result that may improve treatments and interventions. From a clinical standpoint, previous work has shown that APOE-specific targeted interventions (46) can help mitigate cognitive decline in people with $\epsilon 4$ status, and may offer greater chances of successful techniques to prevent AD. Given that people who have the $\epsilon 2\epsilon 4$ genotype can expect to have increased atrophy, they should be considered (alongside those with an $\epsilon 4$ profile) in targeted interventions to reduce brain changes that occur with AD.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None.

Data Availability

The data sets generated and/or analyzed during the current study are available in the Alzheimer's Disease Neuroimaging Initiative (ADNI) repository, adni.loni.usc.edu.

Author Contributions

C.M., M.D., F.K., and D.L.C. were involved with the conceptualization and design of the work. C.M. and M.D. completed analysis, and C.M., M.D., F.K., and D.L.C. were involved with data interpretation. C.M. wrote the manuscript and C.M., M.D, F.K., and D.L.C. revised and approved the submitted version.

Ethics Approval

The study received ethical approval from the review boards of all participating institutions.

Consent Statement

Written informed consent was obtained from participants or their study partner.

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