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

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## Abstract

The apolipoprotein (APOE) ε4 allele is a risk factor for Alzheimer's disease (AD), whereas the ε2 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 ε2ε4 genotype and results are inconsistent for those with an ε2 allele. Alzheimer's disease neuroimaging participants were divided into 1 of 4 APOE allele profiles (E4 = ε4ε4 or ε3ε4; E2 = ε2ε2 or ε2ε3; E3 = ε3ε3; or E24 = ε2ε4). 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 ε4 was associated with increased pathology, whereas ε2 positivity is associated with reduced baseline and lower accumulation of pathologies and neurodegeneration. APOE ε2ε4 was similar to ε4 (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 ε2ε4 genotype is related to increased declines associated with the ε4 as opposed to the protective effects of the ε2. These findings have important implications for initiating treatments and interventions. Given that people with the ε2ε4 genotype can expect to have increased atrophy, they should be considered (alongside those with an ε4) in targeted interventions to reduce brain changes that occur with AD.

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

## Background

The ε4 allele of the apolipoprotein E (APOE) gene is associated with a significant risk for the development of Alzheimer's disease (AD) (1). Although one ε4 allele has been shown to increase risk for AD by approximately 30%, two ε4 alleles increase risk by approximately 65%. Furthermore, the presence of the ε4 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-ε4 carriers (2). On the other hand, ε2 carriers are observed to exhibit up to a 50% less risk of AD and a later mean age of onset compared to ε3/ε3 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 ε4 and greater beta amyloid (Aβ) deposition (6). However, the relationship between ε4 and tau pathology may be more complex. Although researchers have observed that the ε4 is associated with increased tau accumulation (7–9), some have reported that this relationship is observed only when Aβ is also present (10). The ε2 allele has been found to be associated with low levels of tau (11–13) and Aβ deposition (11,12). Of note, there are two studies, which observed the ε2ε4 genotype had similar baseline Thal phase amyloid (11), Braak staging (11,12), and neuritic plaques (11,12) compared to that of ε4, but with less severity. Nevertheless, in most studies, the ε2 and ε4 are compared to the neutral risk ε3 alleles.

Several reviews have reported that the ε4 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 ε2 allele compared to ε3 homozygotes (two ε3 alleles) (16,17) and those with an ε4 allele (17) these atrophy differences associated with the ε2 versus other APOE genotypes

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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 ε4 (23–25) and ε2 (23,26) and WMH burden. The relationship observed between the ε4 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 ε4 homozygotes (two ε4 alleles) to ε4 heterozygotes (one ε4 and one ε3 allele) and ε3 homozygotes. This type of method is important to understand the dose-dependent effect of the ε4 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 ε2 compared to other APOE profiles. Most studies exclude people who exhibit the ε2ε4 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 ε4 and ε2 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 ε2 is protective and that the ε4 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

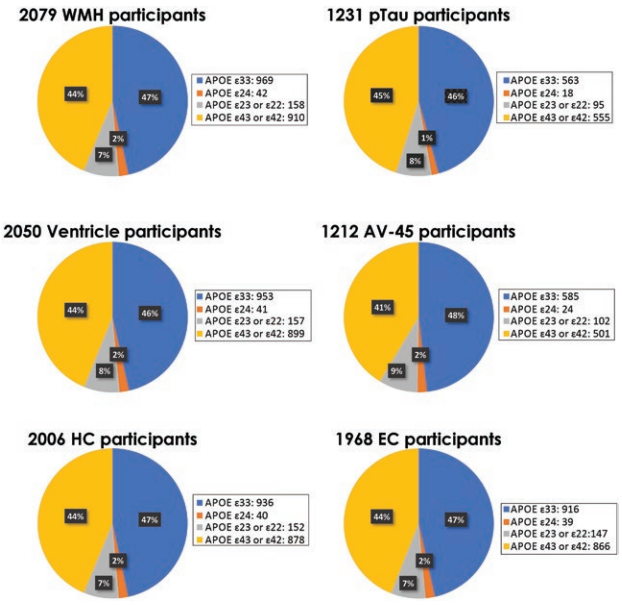


**Figure 1.** Proportion of participants in each analysis by APOE profile. Each plot presents the total number of participants with that pathology information. The percentage of the population with each APOE genotype is also provided.

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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 $mm^3$) 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.

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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.

$$\begin{aligned}&\text{Pathology} \sim \text{Age\_bl} + \text{Education} + \text{Sex} + \\ &\text{Diagnosis\_bl} + \text{APOE group} + \\ &\text{Time From Baseline} + \text{APOE group} : \\ &\text{Time From Baseline} + (1 \mid \text{ID})\end{aligned} \tag{2}$$

## Results

As can be observed in Figure 2A and Table 2, group differences were observed in the baseline results. The APOE ε4 and ε2ε4 were associated with increased AV-45 compared to ε2 and ε3 ($t$ belongs to [13.49–3.30], $p < .001$). The APOE ε4 was also associated with increased pTau compared to ε2 ($t = 6.03$, $p < .001$) and ε3 ($t = 9.82$, $p < .001$). With respect to WMH burden, only the occipital region showed baseline differences, with ε4 having increased occipital WMH burden compared to ε2 ($t = 3.11$, $p = .002$) and ε3 ($t = 2.35$, $p = .019$). The ε2ε4 group had larger ventricles than ε3 ($t = 2.46$, $p = .014$) and ε4 ($t = 2.49$, $p = .013$). With respect to neurodegeneration, ε4 had smaller HC volumes than all other groups ($t$ belongs to [2.46–6.06], $p < .01$), and smaller EC volumes compared to ε2 ($t = 2.95$, $p = .003$) and ε3 ($t = 4.02$, $p < .001$). No other APOE group differences were significant.

Longitudinal results can be observed in Figure 2B and Table 3. The APOE ε4 group had increased rate of AV-45 change compared to ε2 ($t = 4.91$, $p < .001$) and ε3 ($t = 3.83$, $p < .001$), and ε3 had increased rate of AV-45 change compared to ε2 ($t = 2.75$, $p = .006$). Interestingly, the ε4 group had a smaller rate of pTau accumulation than the ε3 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 ε2ε4 versus ε4 and ε2ε4 versus ε3. 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 ε4 group had increased EC atrophy over time compared to ε2 ($t = 7.42$, $p < .001$) and ε3 ($t = 9.87$, $p < .001$), and the ε2ε4 had increased EC atrophy over time compared to ε2 ($t = 2.43$, $p = .015$).

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 ε4 allele (41). The relationship between the ε2 allele and ε2ε4 genotype with cognitive functioning and AD progression remains more elusive than with ε4. The current study helps improve our understanding of how different APOE profiles are associated with neurodegeneration and brain pathology. At baseline, ε4 exhibited increased pTau compared to ε2 and ε3 and smaller HC and EC volumes than all other APOE profiles. The ε2ε4 group exhibited smaller ventricles than ε3 and ε4. The ε2 group exhibited less amyloid than all other APOE profiles, whereas ε4 and ε2ε4 had more amyloid compared to ε3. Longitudinally, many more APOE profile differences were apparent. Ventricular enlargement and HC atrophy significantly differed between all profiles. Furthermore, ε2 was observed to have slower WMH accumulation compared to all other profiles, whereas E4 exhibited faster accumulation compared to ε3. The ε4 group exhibited increased EC atrophy compared to ε3 and ε2, and ε2ε4 exhibited more atrophy than ε2. Amyloid increased faster in the ε3 group compared to ε3 and ε2, whereas ε2 amyloid progressed slower than ε3.

Consistent with previous findings indicating an association between ε4 and increased Aβ (6), we observed that ε4 group exhibited elevated Aβ levels compared to ε2 and ε3 at baseline and had greater change over time. At baseline, the ε2ε4 group also exhibited increased Aβ levels compared to ε2 and ε3, but

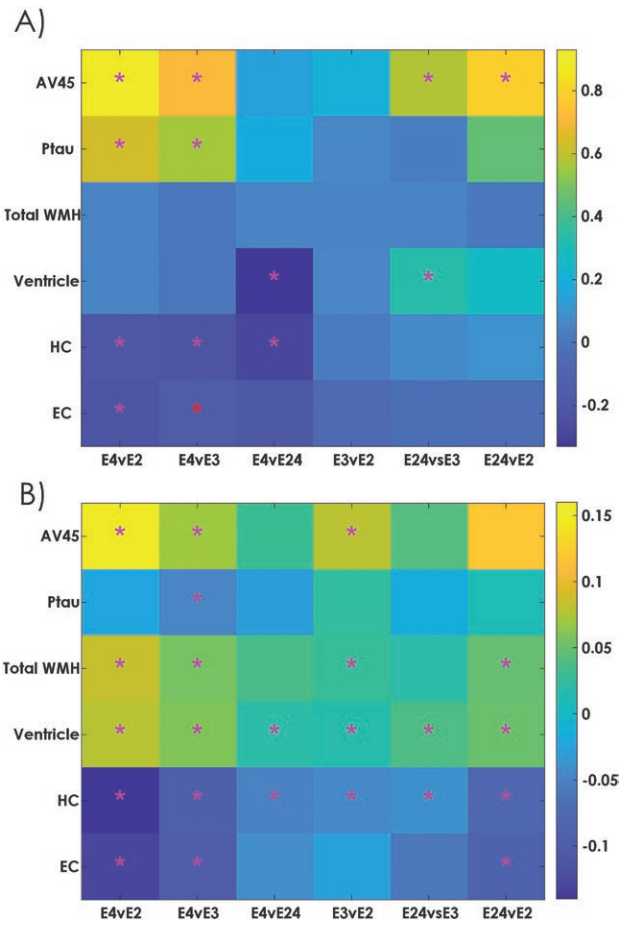


**Figure 2.** Colormap plots showing normalized beta estimates and an asterisk identifies statistically significant differences between the APOE profiles at baseline and over time. Color values represent beta estimates of the $z$-scored values with significant differences marked by an asterisk. Each 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.

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**Table 2.** Estimates Provided From the Baseline Linear Regression

| | ε4vε2 | ε4vε3 | ε4vε24 | ε3vε2 | ε24vε3 | ε24vε2 |
|---|---|---|---|---|---|---|
| AV-45 | **β = 0.93, *SE* = 0.09, *t* = 9.90, *p* < .001** | **β = 0.72, *SE* = 0.06, *t* = 13.49, *p* < .001** | β = 0.14, *SE* = 0.18, *t* = 0.78, *p* = .44 | β = 0.21, *SE* = 0.09, *t* = 2.28, *p* = .023 | **β = 0.58, *SE* = 0.18, *t* = 3.30, *p* = .001** | **β = 0.79, *SE* = 0.19, *t* = 4.10, *p* < .001** |
| pTau | **β = 0.63, *SE* = 0.10, *t* = 6.03, *p* < .001** | **β = 0.56, *SE* = 0.06, *t* = 9.82, *p* < .001** | β = 0.18, *SE* = 0.22, *t* = 0.82, *p* = .41 | β = 0.06, *SE* = 0.10, *t* = 0.65, *p* = .51 | β = 0.38, *SE* = 0.22, *t* = 1.73 *p* = .08 | β = 0.45, *SE* = 0.24, *t* = 1.90, *p* = .06 |
| Total WMH | β = −0.05, *SE* = 0.07, *t* = −0.75, *p* = .46 | β = −0.01, *SE* = 0.04, *t* = −0.05, *p* = .96 | β = 0.05, *SE* = 0.13, *t* = 0.39, *p* = .69 | β = −0.05, *SE* = 0.07, *t* = −0.74, *p* = .46 | β = 0.05, *SE* = 0.13, *t* = 0.41, *p* = .68 | β = −0.10, *SE* = 0.14, *t* = −0.73, *p* = .68 |
| Ventricle | β = 0.06, *SE* = 0.07, *t* = 0.78, *p* = .43 | β = 0.01, *SE* = 0.04, *t* = 0.06, *p* = .95 | **β = 0.22, *SE* = 0.13, *t* = 2.46, *p* = .014** | β = 0.06, *SE* = 0.07, *t* = 0.84, *p* = .40 | **β = 0.33, *SE* = 0.13, *t* = 2.49, *p* = .013** | β = −0.28, *SE* = 0.15, *t* = −1.84, *p* = .07 |
| HC | **β = −0.20, *SE* = 0.07, *t* = −2.96, *p* = .003** | **β = −0.22, *SE* = 0.04, *t* = −6.06, *p* < .001** | **β = −0.29, *SE* = 0.11, *t* = −2.46, *p* = .01** | β = −0.02, *SE* = 0.06, *t* = −0.34, *p* = .74 | β = −0.08, *SE* = 0.12, *t* = −0.64, *p* = .53 | β = −0.10, *SE* = 0.13, *t* = −0.74, *p* = .46 |
| EC | **β = −0.22, *SE* = 0.07, *t* = −2.95, *p* = .003** | **β = −0.16, *SE* = 0.04, *t* = −4.02, *p* < .001** | β = −0.19, *SE* = 0.13, *t* = −1.39, *p* = .16 | β = −0.06, *SE* = 0.07, *t* = −0.80, *p* = .43 | β = −0.25, *SE* = 0.13, *t* = −0.18, *p* = .85 | β = −0.33, *SE* = 0.15, *t* = −0.23, *p* = .82 |
| **Regional WMHs** | | | | | | |
| Frontal WMH | β = −0.06, *SE* = 0.07, *t* = −0.78, *p* = .43 | β = 0.03, *SE* = 0.4, *t* = 0.68, *p* = .49 | β = 0.03, *SE* = 0.13, *t* = 0.26, *p* = .79 | β = −0.08, *SE* = 0.07, *t* = −1.18, *p* = .24 | β = −0.01, *SE* = 0.13, *t* = −0.06, *p* = .95 | β = −0.09, *SE* = 0.15, *t* = −0.64, *p* = .53 |
| Temporal WMH | β = −0.01, *SE* = 0.08, *t* = −0.03, *p* = .98 | β = −0.03, *SE* = 0.04, *t* = −0.76, *p* = .44 | β = 0.08, *SE* = 0.14, *t* = 0.56, *p* = .58 | β = 0.03, *SE* = 0.07, *t* = 0.39, *p* = .70 | β = −0.11, *SE* = 0.14, *t* = −0.79, *p* = .43 | β = −0.08, *SE* = 0.15, *t* = −0.05, *p* = .60 |
| Parietal WMH | β = −0.01, *SE* = 0.08, *t* = −0.23, *p* = .84 | β = −0.02, *SE* = 0.04, *t* = −0.61, *p* = .54 | β = 0.03, *SE* = 0.13, *t* = 0.28, *p* = .78 | β = 0.01, *SE* = 0.07, *t* = 0.13, *p* = .89 | β = −0.06, *SE* = 0.13, *t* = −0.46, *p* = .65 | β = −0.05, *SE* = 0.15, *t* = −0.35, *p* = .72 |
| Occipital WMH | **β = 0.25, *SE* = 0.08, *t* = 3.10, *p* = .002** | **β = 0.10, *SE* = 0.04, *t* = 2.35, *p* = .019** | β = 0.05, *SE* = 0.15, *t* = 0.36, *p* = .72 | β = 0.15, *SE* = 0.08, *t* = 1.87, *p* = .06 | β = −0.05, *SE* = 0.15, *t* = −0.36, *p* = .72 | β = −0.20, *SE* = 0.16, *t* = −1.25 *p* = .21 |

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



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

| | ε4vε2 | ε4vε3 | ε4vε24 | ε3vε2 | ε24vε3 | ε24vε2 |
|---|---|---|---|---|---|---|
| AV-45 | **β = 0.16, *SE* = 0.03, *t* = 4.91, *p* < .001** | **β = 0.07, *SE* = 0.02, *t* = 3.83, *p* < .001** | β = 0.03, *SE* = 0.06, *t* = 0.52, *p* = .60 | **β = 0.08, *SE* = 0.03, *t* = 2.75, *p* = .006** | β = 0.04, *SE* = 0.06, *t* = 0.66, *p* = .51 | β = 0.12, *SE* = 0.07, *t* = 1.85, *p* = .064 |
| pTau | β = 0.02, *SE* = 0.02, *t* = 1.23, *p* = .22 | **β = −0.05, *SE* = 0.01, *t* = −4.76, *p* < .001** | β = 0.03, *SE* = 0.02, *t* = 1.27, *p* = .21 | β = 0.03, *SE* = 0.02, *t* = 1.62, *p* = .11 | β = 0.38, *SE* = 0.22, *t* = 1.73 *p* = .08 | β = 0.45, *SE* = 0.24, *t* = 1.90, *p* = .06 |
| Total WMH | **β = 0.08, *SE* = 0.01, *t* = 9.29, *p* < .001** | **β = 0.06, *SE* = 0.01, *t* = 10.42, *p* < .001** | β = 0.03, *SE* = 0.01, *t* = 2.13, *p* = .03 | **β = 0.03, *SE* = 0.01, *t* = 3.24, *p* = .001** | β = 0.02, *SE* = 0.02, *t* = 1.17, *p* = .24 | **β = 0.05, *SE* = 0.02, *t* = 2.61 *p* = .009** |
| Ventricle | **β = 0.08, *SE* = 0.01, *t* = 16.04, *p* < .001** | **β = 0.06, *SE* = 0.01, *t* = 20.92, *p* < .001** | **β = 0.02, *SE* = 0.01, *t* = 2.57, *p* = .010** | **β = 0.02, *SE* = 0.01, *t* = 3.53, *p* < .001** | **β = 0.04, *SE* = 0.01, *t* = 3.94, *p* < .001** | **β = 0.05, *SE* = 0.01, *t* = 5.25, *p* < .001** |
| HC | **β = −0.14, *SE* = 0.01, *t* = −15.37, *p* < .001** | **β = −0.09, *SE* = 0.01, *t* = −17.59, *p* < .001** | **β = −0.05, *SE* = 0.02, *t* = −3.19, *p* = .001** | **β = −0.04, *SE* = 0.01, *t* = −5.13, *p* < .001** | **β = −0.04, *SE* = 0.02, *t* = −2.48, *p* = .013** | **β = −0.08, *SE* = 0.02, *t* = −4.73, *p* < .001** |
| EC | **β = −0.14, *SE* = 0.02, *t* = −7.42, *p* < .001** | **β = −0.11, *SE* = 0.01, *t* = −9.87, *p* < .001** | β = −0.05, *SE* = 0.03, *t* = −1.43, *p* = .15 | β = 0.03, *SE* = 0.02, *t* = 1.53, *p* = .13 | β = −0.06, *SE* = 0.03, *t* = −1.84, *p* = .065 | **β = −0.09, *SE* = 0.04, *t* = −2.43, *p* = .015** |
| **Regional WMHs** | | | | | | |
| Frontal | **β = 0.07, *SE* = 0.01, *t* = 8.09, *p* < .001** | **β = 0.05, *SE* = 0.01, *t* = 9.11, *p* < .001** | β = 0.01, *SE* = 0.02, *t* = 0.65, *p* = .52 | **β = 0.02, *SE* = 0.01, *t* = 2.80, *p* = .005** | β = 0.04, *SE* = 0.02, *t* = 2.25, *p* = .024 | **β = 0.06, *SE* = 0.02, *t* = 3.39, *p* < .001** |
| Temporal | **β = 0.07, *SE* = 0.01, *t* = 6.41, *p* < .001** | **β = 0.03, *SE* = 0.01, *t* = 4.76, *p* < .001** | **β = 0.05, *SE* = 0.02, *t* = 2.68, *p* < .001** | **β = 0.04, *SE* = 0.01, *t* = 3.74, *p* < .001** | β = 0.02, *SE* = 0.02, *t* = 1.20, *p* = .23 | β = 0.01, *SE* = 0.02, *t* = 0.67, *p* = .50 |
| Parietal | **β = 0.08, *SE* = 0.01, *t* = 9.09, *p* < .001** | **β = 0.05, *SE* = 0.01, *t* = 10.23, *p* < .001** | **β = 0.05, *SE* = 0.02, *t* = 2.91, *p* = .003** | **β = 0.03, *SE* = 0.01, *t* = 3.14, *p* = .002** | β = 0.01, *SE* = 0.02, *t* = 0.33, *p* = .75 | β = 0.03, *SE* = 0.02, *t* = 1.78, *p* = .07 |
| Occipital | **β = 0.13, *SE* = 0.01, *t* = 9.67, *p* < .001** | **β = 0.08, *SE* = 0.01, *t* = 10.35, *p* < .001** | **β = 0.07, *SE* = 0.02, *t* = 2.62, *p* = .009** | **β = 0.05, *SE* = 0.01, *t* = 3.69, *p* < .001** | β = 0.02, *SE* = 0.02, *t* = 0.65, *p* = .51 | **β = 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.

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they did not exhibit an increased rate of change longitudinally. The protective effect of the ε2 also resulted in reduced accumulation of Aβ compared to those with ε3. These findings are consistent with past reports that the ε4 is associated with increased Aβ, whereas the ε2 is associated with lower Aβ (11,12). Additionally, this study observed opposite ε4 and ε2 effects in rate of accumulation of Aβ, indicating the detrimental effect of ε4 and protective effect of ε2 on rate of amyloid accumulation. The finding of increased baseline ε2ε4 Aβ, but lack of longitudinal differences indicates that the change over time in this group is similar to that of all other groups. The heightened Aβ at baseline compared to ε2 and ε3 may reduce resiliency to other brain changes observed longitudinally.

Interestingly, although ε4 had increased pTau levels at baseline compared to ε2 and ε3, 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 Aβ (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, ε4 had increased occipital WMHs over both ε2 and ε3. The ε4 profile showed increased rates of WMH accumulation compared to ε2 and ε3 for total burden and for all regions, and more than ε2ε4 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 ε4 profile are exhibiting WMH burden that is associated with progression to dementia. The ε2 profile showed lower rates of WMH accumulation compared to ε3 for total burden and at all regions, and compared to ε2ε4 for total WMH accumulation and frontal and occipital regions. These findings are consistent with cross-sectional findings showing the protective effects of ε2 (23) and detrimental effects of ε4 (24,25). Extending on this research, the current study also observed that the ε2 offers protection against WMH accumulation over time. With respect to the ε2ε4, this group showed less WMH accumulation compared to ε4, no difference compared to ε3, but more than ε2 at total, frontal, and occipital regions. They showed a similar pattern of WMH change to that of ε3, indicating that the ε2ε4 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 ε2ε4 having larger ventricles compared to both ε3 and ε4. This slightly larger ventricle volume at baseline may be associated with the limited sample size of the ε2ε4. This baseline difference was followed by the ε2ε4 having increased ventricle volume over time compared to ε2 and ε3, but slightly lower rate of change compared to ε4. These findings suggest that the ε2ε4 genotype has a detrimental risk toward overall atrophy as measured by ventricle volumes. The ε4 profile had increased ventricle volume rate of change compared to both ε3 and ε2, and ε2 had less ventricle volume increases than ε3. That is, ε4 has a negative influence on ventricle volume, whereas ε2 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 ε4 and ε2ε4 had reduced whole brain volume compared to both ε2 and ε3. Neither ε2 versus ε3 nor ε4 versus ε2ε4 differed in rate of whole brain volume change. Taken together, an increase in ventricular volume and reduction in whole brain volume suggest that the ε2ε4 genotype is associated with overall atrophy similar to that observed in those with ε4.

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 ε4 profile had increased HC atrophy compared to all other groups (16), and increased EC atrophy compared to ε2 and ε3 (14). Rate of change in HC volume was significantly different between all APOE profiles. The ε2ε4 exhibited increased HC atrophy over time compared to ε2 and ε3, but lower rate of change compared to ε4. These findings suggest that the ε2ε4 genotype has a detrimental risk toward HC atrophy, a known marker of AD disease staging (44). The ε4 profile had increased HC atrophy over time compared to both ε3 and ε2, and ε2 had less HC atrophy increases than ε3. That is, ε4 has a negative influence, whereas ε2 offers protection toward minimizing HC atrophy that occurs over time. Rate of atrophy change in the EC was increased in ε4 compared to ε2 and ε3, and ε2ε4 compared to ε2. As the ε2ε4 did not differ from ε3 or ε4 but was slightly increased compared to ε2, we can interpret this finding as the ε2ε4 profile exhibiting an intermediate rate of change between ε3 and ε4.

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

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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 ε2 offers and the detrimental effects from the ε4 toward neurodegeneration and pathologies. Furthermore, the observation of the detrimental effect of ε2ε4 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 ε4 status, and may offer greater chances of successful techniques to prevent AD. Given that people who have the ε2ε4 genotype can expect to have increased atrophy, they should be considered (alongside those with an ε4 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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