APOE genotype and early β -amyloid accumulation in older adults without dementia

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ABSTRACT

Objective: To clarify associations between *APOE* ϵ 4 allele and age on longitudinal rates of β -amyloid ($A\beta$) accumulation within $A\beta+$ and $A\beta-$ older individuals without dementia.

Methods: We analyzed 595 older adults without dementia classified cross-sectionally as $A\beta-$ ($n = 325$) and $A\beta+$ ($n = 270$) using longitudinal florbetapir PET. The influence of age and *APOE* genotype on longitudinal accumulation of $A\beta$ was examined with linear mixed models.

Results: *APOE* ϵ 4 and older age were associated with higher risk of being classified as $A\beta+$ at baseline. The annual rate of $A\beta$ accumulation was significantly greater than zero for $A\beta- \epsilon$ 3 (0.0021 ± 0.0007 standardized uptake value ratio [SUVR] units) and $A\beta- \epsilon$ 4 (0.0044 ± 0.0010 SUVR units), as well as $A\beta+ \epsilon$ 3 (0.0141 ± 0.0019 SUVR units) and $A\beta+ \epsilon$ 4 (0.0126 ± 0.0018 SUVR units). $A\beta$ accumulation was significantly faster in $A\beta- \epsilon$ 4 compared to $A\beta- \epsilon$ 3 and $A\beta- \epsilon$ 2. Rates of $A\beta$ accumulation did not differ significantly between $A\beta+$ *APOE* groups. Older age was associated with higher rates of $A\beta$ accumulation in the $A\beta-$ group.

Conclusions: *APOE* ϵ 4 carriage and older age were predictors of longitudinal $A\beta$ accumulation within the $A\beta-$ group but not the $A\beta+$ group. *APOE* ϵ 2 carriage was protective against longitudinal $A\beta$ accumulation within the $A\beta-$ group. *APOE* genotype in conjunction with chronologic age may aid in participant selection for primary prevention trials aimed at halting $A\beta$ accumulation before abnormal levels are reached. *Neurology*® 2017;89:1028-1034

GLOSSARY

$A\beta$ = β -amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **MCI** = mild cognitive impairment; **SUVR** = standardized uptake value ratio.

Abnormal levels of β -amyloid ($A\beta+$) emerge many years before the clinical manifestation of Alzheimer disease (AD) dementia.¹ Characterizing the effect of early $A\beta$ in the stages preceding dementia has been critical for understanding disease development as well as for the design of prevention trials targeting clinically asymptomatic at-risk adults.²⁻⁴

The *APOE* ϵ 4 allele is the strongest genetic risk factor for AD dementia and is consistently linked to abnormal $A\beta$ aggregation.⁵⁻⁷ While ϵ 4 has been consistently associated with $A\beta+$ when measured cross-sectionally, the association between ϵ 4 and longitudinal rates of $A\beta$ accumulation remain unclear, especially after accounting for the strong association between *APOE* ϵ 4 and baseline $A\beta$.⁸ However, as rates of $A\beta$ accumulation reach a plateau at higher levels,⁹ it is possible that the effects of ϵ 4 on increasing $A\beta$ levels occur earlier, for example, in older adults whose absolute $A\beta$ levels have yet reached any threshold for abnormality ($A\beta-$). Thus, it is critical to examine factors that influence longitudinal $A\beta$ accumulation separately within $A\beta-$ and $A\beta+$ groups without dementia to establish the utility of these factors for identifying at-risk individuals as early as possible. In addition, the effect of the *APOE* ϵ 2 allele on

Editorial, page 986

Supplemental data
at Neurology.org

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

Table 1 Demographic and clinical characteristics

	A β - ϵ 2	A β - ϵ 3	A β - ϵ 4	p	A β + ϵ 2	A β + ϵ 3	A β + ϵ 4	p
No.	50	213	62		9	94	167	
No. (%) female	19 (38.0)	98 (46.0)	26 (41.9)	0.552	4 (44.4)	44 (46.8)	80 (47.9)	0.970
No. (%) diagnosed with MCI	24 (48.0)	97 (45.5)	31 (50.0)	0.811	3 (33.3)	59 (62.8)	128 (76.6)	0.003
Age (at baseline), y	73.58 (7.62)	72.98 (7.44)	69.53 (7.33)	0.003	75.97 (5.89)	76.67 (6.86)	72.71 (6.80)	0.000
No. of years of education, y	16.60 (2.81)	16.53 (2.54)	16.08 (2.60)	0.449	15.67 (2.74)	15.91 (2.88)	16.04 (2.83)	0.895
SUVr, gray matter cerebellum reference region	1.01 (0.05)	1.00 (0.05)	1.01 (0.05)	0.396	1.31 (0.11)	1.35 (0.18)	1.38 (0.16)	0.307
SUVr, composite reference region	0.73 (0.03)	0.74 (0.03)	0.75 (0.03)	0.012	0.93 (0.09)	0.96 (0.10)	0.98 (0.09)	0.153
Clinical Dementia Rating total score	0.25 (0.27)	0.23 (0.25)	0.25 (0.25)	0.838	0.17 (0.25)	0.31 (0.24)	0.38 (0.21)	0.002
Follow-up duration for PET scans, y	2.50 (0.51)	2.44 (0.50)	2.47 (0.50)	0.696	2.22 (0.44)	2.38 (0.49)	2.34 (0.48)	0.567

Abbreviations: A β = β -amyloid; MCI = mild cognitive impairment. SUVr = standardized uptake value ratio.

longitudinal rates of A β accumulation is also unclear. Although ϵ 2 carriers are less likely to develop AD dementia and more likely to be classified as A β - at baseline,^{1,10–13} the relative low frequency of the ϵ 2 allele has prevented previous studies from examining the effect of this protective factor on rates of longitudinal A β accumulation among participants without dementia.¹⁴

We therefore examined the effect of *APOE* genotype on rates of A β accumulation assessed using florbetapir PET imaging in 595 older adults who were cognitively normal or diagnosed with mild cognitive impairment (MCI). Importantly, the large sample size enabled exploration across multiple *APOE* groups (ϵ 2, ϵ 3, ϵ 4), rather than just between ϵ 4 carriers and noncarriers. We hypothesized that rates of A β accumulation would be fastest in ϵ 4 carriers and slowest in ϵ 2 carriers, and that an effect of *APOE* ϵ 4 on longitudinal rates of A β accumulation would only be present within the A β - group.

METHODS Participants. The process of recruitment and inclusion/exclusion criteria for the Alzheimer's Disease Neuroimaging Initiative (ADNI) has been described previously.¹⁵ ADNI participants were included in this study if they were clinically normal or had MCI during the visit closest to their first florbetapir PET, and had completed at least 2 florbetapir PET scans ($n = 595$; figure e-1 at Neurology.org). Given that florbetapir data was collected during the ADNI2 phase, approximately 15% of participants ($n = 89$) who had enrolled during the ADNI1 phase received their first PET scan many years following baseline enrollment into the study. We therefore used diagnosis closest to each participant's first PET scan rather than baseline diagnosis.

Standard protocol approvals, registrations, and patient consent. Institutional review boards of all participating

institutions of ADNI provided approval for the study. All participants at each site provided written informed consent.

Outcome measures. Global summary measures extracted from florbetapir scans were downloaded directly from the LONI website (UCBERKELEYAV45_06_15_16.csv).¹⁶ Summed images 50–70 minutes postinjection were coregistered to each participant's MRI to enable alignment of FreeSurfer regions of interest. PET values were averaged across 4 large regions (frontal, cingulate, parietal, and lateral temporal). Standardized uptake value ratios (SUVr) were derived by dividing the cortical summary measure by the mean uptake from the reference region. While the whole cerebellum reference region is commonly used to assess A β cross-sectionally,^{16,17} recent data suggest that a larger composite region that incorporates cortical white matter may be superior for assessing longitudinal change in A β when measured with florbetapir PET.^{18,19} As such, we incorporated both reference regions for classification of individuals using previously published cutoffs for the composite (0.79) and the whole cerebellum reference regions (1.11) (figure e-2).^{18,20} Thus, participants were considered A β - only if they fell below both reference region cutoffs and A β + if they surpassed both cutoffs. Of the 656 participants without dementia with longitudinal florbetapir data available, 325 were classified as A β - across both cutoffs, 270 were classified as A β + across both cutoffs, and 61 were incongruently classified (figure e-2). As our aim was to understand how *APOE* genotype and age influence A β - and A β + groups, we excluded the 61 participants who were incongruently classified to reduce confounds related to misclassification. Of the 325 A β - participants, 178 completed 2 florbetapir scans and 147 completed 3 florbetapir PET scans. Of the 270 A β + participants, 175 completed 2 florbetapir scans and 95 completed 3 florbetapir PET scans. Each follow-up PET scan was separated by a median of 2 years. All longitudinal analyses predicting A β over time used the summary measure normalized by the composite reference region as the dependent variable.¹⁸

Statistical models. To examine the effect of *APOE* group on change in florbetapir SUVr over time, we conducted linear mixed effects models in the statistical program *R* v3.3.1 (lme4 package), with interactions between baseline age (centered) $\times$ time, diagnosis (cognitively normal vs MCI) $\times$ time, and *APOE* group $\times$ time specified as fixed factors. Time was coded as time relative to each participant's first florbetapir scan, and was expressed as years. Random intercepts and slopes were included. *APOE* group was divided into 3 levels: *APOE* ϵ 2 (comprising ϵ 2/ ϵ 2 and ϵ 2/ ϵ 3), *APOE* ϵ 3 (ϵ 3/ ϵ 3), and *APOE* ϵ 4 (comprising ϵ 4/

Table 2 Rates of β -amyloid ($A\beta$) accumulation for each $A\beta/APOE$ group, and contrast matrix comparing rates of $A\beta$ accumulation between groups (p values are listed)

	Slope estimates for each group		Contrast matrix between groups		
	Estimate (SE)	p	$\epsilon 2$	$\epsilon 3$	$\epsilon 4$
$A\beta-$					
$\epsilon 2$	0.0001 (0.0011)	0.952	—	0.079	0.002
$\epsilon 3$	0.0021 (0.0007)	0.001	0.079	—	0.033
$\epsilon 4$	0.0044 (0.0010)	<0.0001	0.002	0.033	—
$A\beta+$					
$\epsilon 2$	0.0081 (0.0050)	0.108	—	0.256	0.397
$\epsilon 3$	0.0141 (0.0019)	<0.0001	0.256	—	0.404
$\epsilon 4$	0.0126 (0.0018)	<0.0001	0.397	0.404	—

$\epsilon 4$, $\epsilon 3/\epsilon 4$, and $\epsilon 2/\epsilon 4$). Contrasts were formed to determine (1) whether accumulation over time within each $APOE$ group was significantly different from zero and (2) whether rates of accumulation were significantly different between $APOE$ groups. Analyses were conducted separately in $A\beta-$ and $A\beta+$ groups.

RESULTS $APOE$ $\epsilon 4$ carriers were more likely to be classified as $A\beta+$ at baseline whereas $APOE$ $\epsilon 2$ carriers were less likely to be classified as $A\beta+$ at baseline (72.9% of $\epsilon 4$ and 15.3% of $\epsilon 2$ were $A\beta+$, compared to 30.6% for $\epsilon 3$, $p < 0.001$). Older age was also associated with a greater likelihood of $A\beta+$ classification at baseline ($p = 0.003$).

In general, $APOE$ $\epsilon 4$ carriers were significantly younger compared to $\epsilon 2$ and $\epsilon 3$ groups (table 1). Specifically, the $A\beta-$ $\epsilon 4$ group was younger than the $A\beta-$ $\epsilon 2$ ($p = 0.005$) and $A\beta-$ $\epsilon 3$ groups ($p = 0.001$). Similarly, the $A\beta+$ $\epsilon 4$ group was significantly

younger than the $A\beta+$ $\epsilon 3$ group ($p < 0.001$), but not the $A\beta+$ $\epsilon 2$ group ($p = 0.161$). Groups based on joint $A\beta$ and $APOE$ status did not differ significantly on any other demographic or clinical characteristic (table 1).

In the $A\beta-$ group, $\epsilon 4$ carriers and $\epsilon 3$ homozygotes showed rates of $A\beta$ accumulation significantly greater than zero (table 2). There was no significant increase in $A\beta$ over time in $A\beta-$ $\epsilon 2$ carriers. The rate of $A\beta$ accumulation in $A\beta-$ $\epsilon 4$ carriers was significantly faster than in $A\beta-$ $\epsilon 3$ homozygotes and $A\beta-$ $\epsilon 2$ carriers (table 2, figure 1). Among $A\beta-$ adults, the interaction between diagnosis and time was insignificant, suggesting no difference in the rate of $A\beta$ accumulation between cognitively normal and MCI $A\beta-$ groups (table 3). The difference between the $A\beta-$ $\epsilon 4$ and $\epsilon 3$ groups remained significant after

Figure 1 Effect of $APOE$ genotype on β -amyloid ($A\beta$) accumulation over time

Overall, rates of $A\beta$ accumulation are greater in the $A\beta+$ (B) group compared to the $A\beta-$ (A) group, regardless of $APOE$ group. Within the $A\beta-$ participants, the $APOE$ $\epsilon 4$ group shows the greatest rates of $A\beta$ accumulation. SUVR = standardized uptake value ratio.

Table 3 Results from linear mixed model examining longitudinal accumulation of β -amyloid ($A\beta$) among $A\beta$ – and $A\beta$ + older adults without dementia in relation to *APOE* genotype (*APOE* ϵ 3 as the reference group)

	<i>Aβ</i> – older adults		<i>Aβ</i> + older adults	
	Estimate (SE)	p	Estimate (SE)	p
Intercept	0.7331 (0.0049)	0.000	0.9558 (0.0122)	0.000
Age	–0.0008 (0.0002)	0.000	0.0017 (0.0009)	0.051
Diagnosis	0.0023 (0.0031)	0.461	0.0347 (0.0130)	0.008
<i>APOE</i> ϵ 2	–0.0020 (0.0043)	0.645	–0.0210 (0.0330)	0.526
<i>APOE</i> ϵ 4	0.0075 (0.0040)	0.064	0.0181 (0.0126)	0.152
Time	0.0023 (0.0014)	0.089	0.0141 (0.0019)	0.000
Time $\times$ age	0.0002 (0.0001)	0.008	–0.0002 (0.0001)	0.068
Time $\times$ diagnosis	–0.0002 (0.0009)	0.811	–0.0048 (0.0019)	0.014
Time $\times$ <i>APOE</i> ϵ 2	–0.0020 (0.0012)	0.079	–0.0060 (0.0053)	0.256
Time $\times$ <i>APOE</i> ϵ 4	0.0023 (0.0011)	0.033	–0.0016 (0.0019)	0.404

The time $\times$ *APOE* ϵ 2 term reflects the difference in slopes between the *APOE* ϵ 2 and *APOE* ϵ 3 groups. Likewise, the time $\times$ *APOE* ϵ 4 term reflects the difference in slopes between the *APOE* ϵ 4 and *APOE* ϵ 3 groups. Age is centered at 75 years.

exclusion of the 5 ϵ 4 homozygotes ($\beta = 0.002$, $p = 0.041$). Baseline age was significantly associated with $A\beta$ accumulation, such that older $A\beta$ – participants showed faster rates of accumulation independent of *APOE* genotype (table 3). Examination of a 3-way interaction among *APOE* ϵ 4, age, and time was not significant ($p = 0.926$), suggesting that the effects of *APOE* genotype and age were additive rather than synergistic.

We additionally examined the proportion of $A\beta$ – participants who progressed to an $A\beta$ + classification at follow-up. At the first follow-up scan (i.e., ~ 2 years postbaseline), 7/325 (2.2%) $A\beta$ – progressed to $A\beta$ + and there were no differences between *APOE* groups in progression rates (ϵ 2 = 1/50; ϵ 3 = 5/213; ϵ 4 = 1/62), $\chi^2 = 0.21$, $p = 0.902$. At the second follow-up scan (i.e., ~ 4 years postbaseline), 7/147 (4.8%) $A\beta$ – were classified as $A\beta$ +, with a higher proportion of progressors in the *APOE* ϵ 4 group (14%; 4/29) compared to the ϵ 2 (4%; 1/25) and ϵ 3 groups (2%, 2/93), $\chi^2 = 6.21$, $p = 0.045$.

In the $A\beta$ + group, ϵ 4 carriers and ϵ 3 homozygotes showed rates of $A\beta$ accumulation that were significantly greater than zero (table 2; figure 1). $A\beta$ accumulation in $A\beta$ + ϵ 2 carriers did not reach statistical significance (table 2). However, there were no statistically significant group differences in $A\beta$ accumulation between $A\beta$ + *APOE* groups (table 2; figure 1). Within the $A\beta$ + group, the cognitively normal group showed significantly faster rates of $A\beta$ accumulation than $A\beta$ + MCIs (figure 2, table 3). However, inclusion of a 3-way interaction among diagnosis, *APOE* genotype, and time was not significant ($p = 0.210$), suggesting that the pattern of $A\beta$

accumulation across *APOE* groups did not differ by diagnosis (figure 2).

Given that $A\beta$ – ϵ 4 shows greater continuous levels of baseline $A\beta$ compared to other $A\beta$ – groups (table 1), it is possible that slightly elevated values within the $A\beta$ – range account for the effect of ϵ 4 within the $A\beta$ – group. We therefore examined the simultaneous effect of *APOE* group and continuous levels of $A\beta$ at baseline on $A\beta$ accumulation over time within the $A\beta$ – group. These analyses revealed that both ϵ 4 and baseline $A\beta$ were independently associated with $A\beta$ accumulation within the $A\beta$ – group (e-Methods, figure e-3, table e-1).

DISCUSSION We aimed to determine whether *APOE* genotype and age were associated with rates of $A\beta$ accumulation in individuals without a clinical diagnosis of AD dementia. Consistent with previous reports, we found that the *APOE* ϵ 4 allele and older age were associated with a greater likelihood of being classified as $A\beta$ + at baseline.^{1,10,21} Importantly though, we observed that *APOE* ϵ 4 carriers showed faster rates of $A\beta$ accumulation when compared to ϵ 3 and ϵ 2 groups, but only in $A\beta$ – adults. Furthermore, *APOE* ϵ 2 carriers were more likely to be $A\beta$ – and showed the slowest rates of $A\beta$ accumulation in the $A\beta$ – group. Older age was associated with increased rates of $A\beta$ accumulation, and this effect was independent of the effect of *APOE*. When taken together, these results highlight that through serial assessment of $A\beta$ using florbetapir PET imaging, subtle but significant increases in $A\beta$ over time are present among $A\beta$ – older adults with established AD risk factors (i.e., ϵ 4 and older age), and that the protective effect

Figure 2 Annual rate of change in β -amyloid ($A\beta$), by *APOE* and diagnostic group

Error bars represent standard error. A similar pattern related to *APOE* group is present between normal controls and mild cognitive impairment (MCI) groups, such that there is an effect of *APOE* ϵ 4 only among participants who are $A\beta$ - at baseline.

of ϵ 2 against AD dementia may be mediated by slower rates of $A\beta$ accumulation.

An increasing number of studies now show significantly increased rates of $A\beta$ accumulation in $A\beta$ + older adults without dementia; however, the rate at which $A\beta$ accumulates over time in $A\beta$ - older adults is less clear, with multiple studies reporting no significant increases at the group level.^{8,9,22} The lack of significant group level increases among $A\beta$ - older adults may, in part, be due to insufficient follow-up, as well as heterogeneity across $A\beta$ - participants, such that some participants show accumulation whereas others remain stable. Identification of factors that explain variable rates of $A\beta$ accumulation among $A\beta$ - older participants is increasingly relevant as the field moves towards interventions that attempt to delay clinical impairment by targeting $A\beta$ as early as possible,^{23,24} especially by targeting the $A\beta$ protein before deposition into fibrillar $A\beta$ plaques.²⁵ Our results suggest that this variability among $A\beta$ - adults can be explained in part by *APOE* genotype and older age. Thus, consideration of both *APOE* genotype and age could aid in the selection of $A\beta$ - adults at greatest risk of future $A\beta$ accumulation.

Despite the strong mechanistic link between *APOE* ϵ 4 and $A\beta$, the effect of ϵ 4 on longitudinal rates of $A\beta$ accumulation using in vivo biomarkers has remained unclear in previous studies. Recent work examining 2 large cohorts without dementia revealed that while ϵ 4 is strongly associated with

$A\beta$ + at baseline, there was no additional effect of ϵ 4 on longitudinal rates of $A\beta$ accumulation when considering the combined group of $A\beta$ - and $A\beta$ + participants.⁸ However, it is noteworthy that there is a nonlinear association between baseline $A\beta$ and longitudinal change in $A\beta$, with a positive relationship in $A\beta$ - adults (e.g., within the $A\beta$ - range, higher continuous levels of $A\beta$ predict greater rates $A\beta$ accumulation) whereas a plateau or even a negative association is observed in $A\beta$ + adults (e.g., within the $A\beta$ + range, higher continuous levels of $A\beta$ become uncoupled from rates of $A\beta$ accumulation).⁹ This decoupling between baseline and longitudinal change in $A\beta$ as a function of overall $A\beta$ magnitude implies that rates of $A\beta$ accumulation can be differentially relevant depending on an individual's disease stage. Specifically, a faster rate of $A\beta$ accumulation in $A\beta$ - adults may indicate the very early stages of AD pathophysiology. Conversely, a steady rate of $A\beta$ accumulation in $A\beta$ + adults may suggest a later disease stage as these participants reach an $A\beta$ plateau. Given this dissociation, it is critical to examine risk factors that predict $A\beta$ accumulation separately within $A\beta$ - and $A\beta$ + groups. In doing so, we identified an association between ϵ 4 and $A\beta$ accumulation, such that among $A\beta$ - adults, *APOE* ϵ 4 was associated with increased rates of $A\beta$ accumulation, whereas in $A\beta$ + adults, there was no difference across *APOE* genotypes in rates of $A\beta$ accumulation. The differential relationship between ϵ 4 and future $A\beta$

accumulation highlights that the *APOE* $\epsilon 4$ allele provides additional information about risk of further accumulation specifically among $A\beta^-$ participants.

The *APOE* $\epsilon 2$ allele is a strong protective genetic factor against AD dementia.^{11,26} Our results suggest that this protection is at least in part mediated by slower rates of $A\beta$ accumulation. Specifically, we found that $\epsilon 2$ carriers were the only group to not show significantly greater rates of accumulation than zero in both $A\beta^-$ and $A\beta^+$ groups. This pattern is consistent with previous reports that have shown that when compared to the $\epsilon 3$ allele, the $\epsilon 2$ allele is associated with increased neuroprotection against AD, through an increased rate of $A\beta$ clearance.⁵ It will be important to establish whether $A\beta^+$ $\epsilon 2$ carriers without dementia are also at lower risk of progressing to AD dementia, which may be due to the slower rates of accumulation in this group even though they have surpassed the $A\beta^+$ threshold. However, our analyses investigating the effects of $\epsilon 2$ within the $A\beta^+$ group were greatly limited by sample size ($n = 9$) and warrant further research. Nevertheless, a lack of significant $A\beta$ accumulation was also present in the 50 $A\beta^-$ $\epsilon 2$ carriers, which lends support to the hypothesis that slower rates of $A\beta$ accumulation may explain the effects of $\epsilon 2$ on lowering the risk of AD dementia.

We found that among older adults without dementia who underwent PET imaging at 3 time-points (mean follow-up of 4 years), 4.7% of $A\beta^-$ adults progressed to $A\beta^+$, and 57% of $A\beta^-$ adults who progressed to $A\beta^+$ were $\epsilon 4$ carriers. This is consistent with a previous study that reported that 3.1% of $A\beta^-$ adults progressed to $A\beta^+$ after 2.5 years, and 70% of those who progressed were $\epsilon 4$ carriers.²² However, our results are at odds with another study that reported a much higher rate of progression from $A\beta^-$ to $A\beta^+$ (13% per year), and did not find any association with *APOE* genotype.²⁷ Given the small numbers that result when examining the incidence of surpassing the $A\beta^+$ cutoff, and inconsistent results across studies, additional research is needed to investigate incidence of progressing to $A\beta^+$ among $A\beta^-$ adults without dementia. It is likely that these estimates will be influenced by differences across cohorts or methodologic factors (e.g., amyloid PET tracer, choice of cutoffs used to define $A\beta^-$). For instance, given our exclusion of ambiguous cases (i.e., participants with inconsistent $A\beta$ classification across reference regions), we are likely underestimating the prevalence of progression from $A\beta^-$ to $A\beta^+$ in our study. Given these considerations, and that surpassing a study-defined $A\beta$ cutoff is somewhat arbitrary, it may be more insightful to examine $A\beta$ accumulation over time as a continuous measure rather than

as an event that occurs when the $A\beta^+$ threshold is crossed.

Several caveats need to be considered when interpreting the results of our study. First, we focused on a single global summary measure of $A\beta$ while regional measures may be more sensitive during the early stages of accumulation.²⁸ Second, we combined cognitively normal and MCI groups to enable examination across a large sample of $A\beta^-$ and $A\beta^+$ older adults divided by *APOE* genotype. Although the associations we identified between *APOE* and $A\beta$ accumulation appear consistent across diagnosis, it will be important for future studies with larger sample sizes to determine whether the *APOE* effect on $A\beta$ accumulation is affected by clinical diagnosis. We did not examine the role of vascular risk factors in influencing $A\beta$ accumulation, which may account for the effect of *APOE* $\epsilon 4$ or add independent information regarding risk of future $A\beta$ positivity, as suggested by previous cross-sectional data.²⁹ Finally, while we found significant associations between $A\beta$ accumulation and *APOE* genotype, these annual rates of increase are small, making it unlikely that rates of $A\beta$ accumulation will be used as an endpoint in clinical trials that utilize short follow-ups. Despite this, the association between *APOE* $\epsilon 4$ and $A\beta$ accumulation among $A\beta^-$ adults suggest that considering $\epsilon 4$ status for enrichment in clinical trials will improve the likelihood of including $A\beta^-$ adults at greater risk for AD pathophysiologic processes.

These caveats notwithstanding, the ability to measure the effect of $\epsilon 4$ on increasing rates of $A\beta$ accumulation in $A\beta^-$ older adults suggests that very early disease processes can be detected with serial assessment of PET imaging. As such, *APOE* $\epsilon 4$ carriers may be an ideal population for primary prevention trials that aim to halt $A\beta$ accumulation before abnormal levels are reached.

AUTHOR CONTRIBUTIONS

Study concept and design: Y.Y.L., E.C.M. Data analysis and interpretation: Y.Y.L., E.C.M. Writing of manuscript: Y.Y.L., E.C.M. Critical revision of the manuscript for important intellectual content: Y.Y.L., E.C.M.

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DISCLOSURE

Y. Lim currently serves as a consultant for Biogen and Cogstate Ltd. E. Mormino has also served as a consultant for Biogen and Eli Lilly. Go to Neurology.org for full disclosures.

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