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ORIGINAL RESEARCH

Apolipoprotein E ε4 Does Not Modulate Amyloid-β–Associated Neurodegeneration in Preclinical Alzheimer Disease

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BACKGROUND AND PURPOSE: Among cognitively healthy older individuals, the relationship among the 2 hallmark proteins of AD (Aβ and τ *APOE* ε4) and neurodegeneration is not well-understood. Here, we investigated the relationship between Aβ, p-τ, and *APOE* ε4 on longitudinal brain atrophy in preclinical AD.

MATERIALS AND METHODS: We examined 107 cognitively healthy older adults who underwent longitudinal MR imaging and baseline lumbar puncture. Within the same linear mixed-effects model, we concurrently investigated main and interactive effects between the *APOE* ε4 genotype and CSF Aβ_{1-42}, CSF p-τ and CSF Aβ_{1-42}, and the *APOE* ε4 genotype and CSF p-τ on entorhinal cortex atrophy rate. We also examined the relationship of *APOE* ε4, CSF p-τ, and CSF Aβ_{1-42} on the atrophy rate of other AD-vulnerable neuroanatomic regions.

RESULTS: The full model with main and interactive effects demonstrated a significant interaction only between CSF p-τ and CSF Aβ_{1-42} on entorhinal cortex atrophy rate, indicating elevated atrophy with time in individuals with increased CSF p-τ and decreased CSF Aβ_{1-42}. The *APOE* ε4 genotype was significantly and specifically associated with CSF Aβ_{1-42}. However, the interaction between the *APOE* ε4 genotype and either CSF Aβ_{1-42} or CSF p-τ on entorhinal cortex atrophy rate was not significant. We found similar results in other AD-vulnerable regions.

CONCLUSIONS: On the basis of our findings and building on prior experimental evidence, we propose a model of the pathogenic cascade underlying preclinical AD in which *APOE* ε4 primarily influences the pathology of Alzheimer disease via Aβ-related mechanisms, and in turn, Aβ-associated neurodegeneration occurs only in the presence of p-τ.

ABBREVIATIONS: Aβ = amyloid-β; AD =Alzheimer disease; *APOE* ε4 = ε4 allele of *apolipoprotein E*; HC = healthy controls; p-τ = phospho-τ_{181p}; SE = standard error of the mean

BRAIN

ORIGINAL RESEARCH

Converging biochemical, molecular, and genetic evidence indicates that Aβ plays a central role in the neurodegenerative process underlying AD.[1] The presence of Aβ initiates loss of dendritic spines and synapses[2] and contributes to the dysfunction of neuronal networks.[3] Reports based on mouse models suggest that multiple factors influence Aβ-associated toxicity. The ε4 allele of *APOE* ε4, the most important genetic risk factor for late-onset AD,[4] accelerates the onset of Aβ deposition into plaques[5] and decreases the transport of Aβ across the blood-brain barrier.[6] Reductions in τ, another hallmark protein of AD pathology, protect against Aβ-induced neuronal dysfunction,[7] while the presence of τ potentiates Aβ-associated synapotoxicity.[8]

In humans, evidence from genetic-at-risk cohorts and neuropathologic findings in clinically healthy older individuals suggest that the pathobiologic process underlying AD begins years before the onset of cognitive deficits or dementia symptoms.[9] Biomarker studies in cognitively asymptomatic older

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Table 1: Demographic, clinical, and imaging data for all older HC in this study, as assessed by P-τ and Aβ status

	P-τ−/Aβ− (n = 46)	P-τ−/Aβ+ (n = 20)	P-τ+/Aβ− (n = 19)	P-τ+/Aβ+ (n = 21)	*P* Value
Age (yr) (mean) (SE)	74.3 (0.6)	74.9 (1.1)	78.0 (1.4)	78.2 (1.0)	.02[a]
Female (%)	24	31	29	38	.59[b]
Education (yr) (mean) (SE)	15.5 (0.4)	14.8 (0.8)	15.5 (0.4)	16.7 (0.6)	.34[a]
Baseline MMSE (mean) (SE)	29.1 (0.1)	29.1 (0.2)	28.8 (0.3)	29.3 (0.2)	.46[a]
Entorhinal cortex APC (mean) (SE)	−0.6 (0.15)	−0.6 (0.18)	−0.6 (0.18)	−1.2 (0.25)	.005[c]
AD-vulnerable ROI APC (mean) (SE)	−0.6 (0.08)	−0.5 (0.11)	−0.7 (0.14)	−1.1 (0.14)	.002[c]

Note:—MMSE indicates Mini-Mental State Examination; APC = annualized percentage change.
[a] Derived from analysis of variance.
[b] Derived from a χ^2 test.
[c] Derived from linear mixed-effects models (please see text for details).

Table 2: Demographic, clinical, and imaging data for all older HC in this study, as assessed by *APOE* ε4 and Aβ status

	ε4−/Aβ− (n = 61)	ε4−/Aβ+ (n = 21)	ε4+/Aβ− (n = 5)	ε4+/Aβ+ (n = 20)	*P* Value
Age (yr) (mean) (SE)	75.7 (0.7)	76.2 (0.9)	71.7 (2.5)	77.1 (1.3)	.56[a]
Female (%)	54	54	20	35	.23[b]
Education (yr) (mean) (SE)	15.6 (0.3)	15.9 (0.6)	15 (1.1)	15.6 (0.8)	.98[a]
Baseline MMSE (mean) (SE)	29.1 (0.1)	29.4 (0.2)	28.6 (0.9)	29 (0.2)	.73[a]
Entorhinal cortex APC (mean) (SE)	−0.57 (0.13)	−0.67 (0.17)	−0.43 (0.30)	−1.17 (0.28)	.35[c]
AD-vulnerable ROI APC (mean) (SE)	−0.6 (0.07)	−0.78 (0.14)	−0.65 (0.23)	−1.0 (0.16)	.28[c]

Note:—MMSE indicates Mini-Mental State Examination; APC = annualized percentage change.
[a] Derived from analysis of variance.
[b] Derived from a χ^2 test.
[c] Derived from linear mixed-effects models (please see text for details).

adults have demonstrated significant relationships between structural MR imaging measures of brain atrophy and CSF Aβ levels,[10-12] enabling identification of clinically healthy individuals who may be in a presymptomatic or preclinical stage of AD.[13]

Recent evidence from our laboratory indicates that in clinically healthy older individuals and those with mild cognitive impairment, Aβ-associated volume loss occurs only in the presence of p-τ.[14] However, it is unknown whether *APOE* ε4 and CSF p-τ concurrently modulate the effect of CSF Aβ on longitudinal brain atrophy in preclinical AD. In this study, we investigated whether concurrent interactions between decreased CSF Aβ_{1-42} and *APOE* ε4 and between decreased CSF Aβ_{1-42} and increased CSF p-τ are associated with increased brain atrophy in cognitively healthy older individuals.

Materials and Methods

Selection of participants and analysis methods for MR imaging and CSF biomarkers are briefly summarized here, with details provided in the On-line Appendix.

We evaluated participants who were clinically diagnosed at baseline as cognitively and clinically healthy controls (global Clinical Dementia Rating = 0) from the Alzheimer Disease Neuroimaging Initiative. A total of 115 cognitively healthy older individuals had undergone longitudinal MR imaging, CSF lumbar puncture, and *APOE* ε4 genotyping. Of these individuals, we restricted our analyses to those participants (n = 107) with quality-assured baseline and at least 1 follow-up MR imaging (6 months to 3.5 years; 10% with 6-month follow-up, 15% with 12-month follow-up, 34% with 23-month follow-up, and 41% with 36-month follow-up) available as of December 2011. We classified all participants on the basis of the presence ("carriers") and absence ("noncarriers") of at least 1 *APOE* ε4 allele (Tables 1 and 2). Using recently proposed CSF cutoffs,[15] we also classified all participants on the basis of high (>23 pg/mL, "positive") and low (<23 pg/mL, "negative") p-τ levels, and on low (<192 pg/mL, "positive") and high (>192 pg/mL, "negative") Aβ_{1-42} levels (Tables 1 and 2).

We examined 417 T1-weighted MR images. We performed quantitative surface-based analysis of all MR images by using an automated region-of-interest labeling technique[16] and primarily focused on entorhinal cortex, a medial temporal lobe region that is selectively affected in the earliest stages of AD.[17-20] To additionally investigate neuroanatomic regions that are involved in the later stages of the disease process[17,18] and to minimize multiple comparisons, we averaged longitudinal volume change in the temporal pole, parahippocampal gyrus, inferior temporal gyrus, banks of the superior temporal sulcus, inferior parietal lobule, amygdala, and hippocampus to create an "AD-vulnerable" region of interest (Fig 1). Using an automated method developed in our laboratory,[21] we assessed longitudinal subregional change in gray matter volume (atrophy) on serial MR images.

We asked whether p-τ and *APOE* ε4 independently influence Aβ-associated neurodegeneration. To investigate this question, we examined the main and interactive effects of CSF Aβ_{1-42} and *APOE* ε4, and CSF Aβ_{1-42} and CSF p-τ on entorhinal cortex atrophy rate in a mixed-effects model, covarying for the effects of age and sex, specifically

$$\Delta v = \beta_0 \times \Delta t + \beta_1 APOE\ \varepsilon 4\_status \times \Delta t + \beta_2 CSF\_A\beta_{1-42}\_status \times \Delta t + \beta_3 CSF\_p\text{-}\tau\_status \times \Delta t + \beta_4[APOE\varepsilon 4\_status \times CSF\_A\beta_{1-42}\_status \times \Delta t] + \beta_5[CSF\_p\text{-}\tau\_status \times CSF\_A\beta_{1-42}\_status \times \Delta t] + covariates \times \Delta t + \varepsilon.$$

Here, Δv is entorhinal cortex atrophy (millimeters) and Δt is the change in time from baseline MR imaging (in years). Using the same

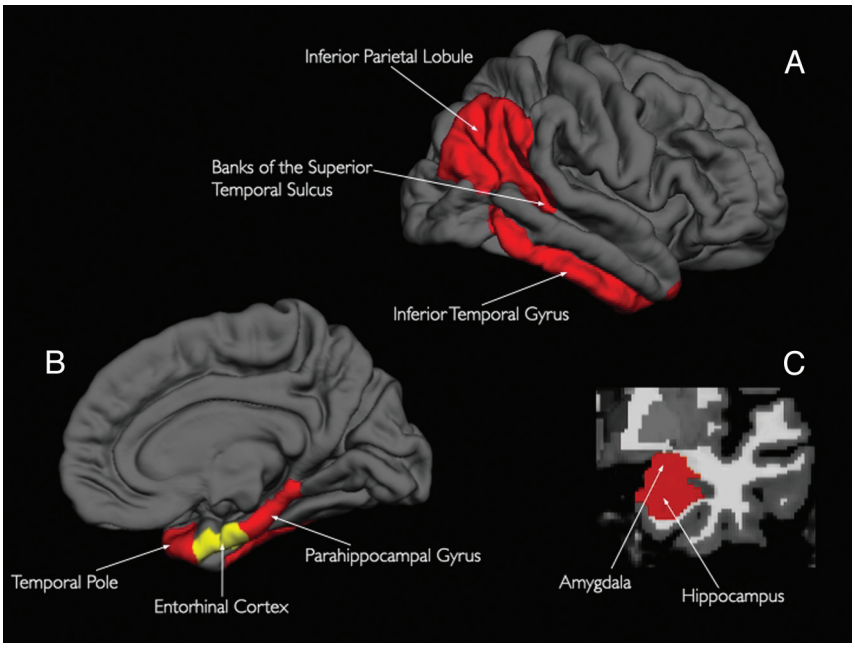

Fig 1. 3D representations of the neuroanatomic regions examined in the current study (only 1 hemisphere is shown). All of the neocortical regions are visible in the lateral (*A*) and medial (*B*) views of the gray matter surface, and the 2 non-neocortical regions (ie, the hippocampus and amygdala, *C*) are visible in the coronal view of a T1-weighted MR image. Regions illustrated in red constitute the AD-vulnerable region of interest (for further details please see text).

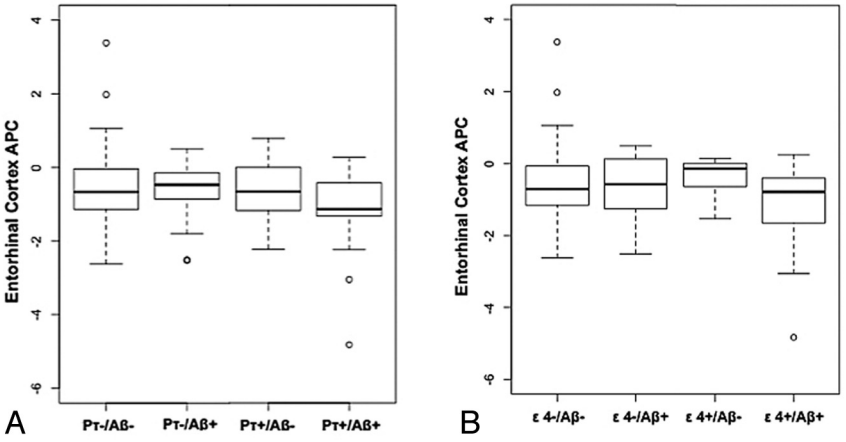

Fig 2. Box-and-whisker plots for all healthy control participants illustrating entorhinal cortex atrophy rate, measured as annualized percentage change (APC) based on CSF p-τ and CSF Aβ status (*A*) and ε4 genotype and CSF Aβ status (*B*). For each plot, thick black lines show the median value. Regions above and below the black line show the upper and lower quartiles, respectively. The dashed lines extend to the minimum and maximum values with outliers shown as open circles. As illustrated in *A*, the pτ+/Aβ+ HC demonstrate the largest cortical atrophy rate (ie, more negative percentage change). In comparison as noted in *B*, the ε4+/Aβ+ HC show equivalent rates of atrophy compared with the other groups.

linear mixed-effects framework, we also investigated the main and interactive effects of CSF Aβ_{1-42} and *APOE* ε4, and CSF Aβ_{1-42} and CSF p-τ on the atrophy rate in the AD-vulnerable region of interest.

Results

Results from the full model with both interactive terms showed that the interaction between CSF Aβ_{1-42} and CSF p-τ status on entorhinal cortex atrophy rate was significant ($\beta_5 = -0.39$, SE = 0.14, $P = .005$), indicating elevated atrophy with time in individuals with positive CSF p-τ and positive CSF Aβ_{1-42} status (Fig 2*A*) as previously reported.[14] In contrast, the interaction between CSF Aβ_{1-42} and *APOE* ε4 on entorhinal cortex atrophy rate was not significant ($\beta_4 = -0.17$, SE = 0.18, $P = .35$). With both interaction terms in the model, the main effects of *APOE* ε4, CSF Aβ_{1-42} status, and CSF p-τ status were not significant. Follow-up analyses demonstrated that positive CSF Aβ_{1-42} status was associated with an elevated entorhinal cortex atrophy rate only among CSF p-τ–positive individuals (β-coefficient = −0.32, SE = 0.11, $P = .008$). There was no association between positive CSF Aβ_{1-42} status and entorhinal cortex atrophy rate among CSF p-τ–negative individuals (β-coefficient = 0.10, SE = 0.08, $P = .23$) (Fig 2*A*). There was no association between positive CSF Aβ_{1-42} status and entorhinal cortex atrophy rate either among *APOE* ε4 carriers (β-coefficient = −0.11, SE = 0.19, $P = .58$) or noncarriers (β-coefficient = −0.02, SE = 0.08, $P = .76$) (Fig 2*B*).

Similar results were obtained when examining the association of CSF protein and *APOE* ε4 status on the atrophy rate in the AD-vulnerable region of interest: The interaction of CSF

$A\beta_{1-42}$ and CSF p-τ status on the AD-vulnerable region-of-interest atrophy rate was significant (β-coefficient = −0.34, SE = 0.11, P = .002), but the interaction of CSF $A\beta_{1-42}$ and *APOE* ε4 was not (β-coefficient = −0.15, SE = 0.14, P = .28). None of the main effects of *APOE* ε4, CSF $A\beta_{1-42}$ status, and CSF p-τ were significant with both interaction terms in the model. Follow-up analyses demonstrated that positive CSF $A\beta_{1-42}$ status was associated with an elevated AD-vulnerable region-of-interest atrophy rate among CSF p-τ–positive individuals (β-coefficient = −0.30, SE = 0.09, P = .001) but not among CSF p-τ–negative individuals (β-coefficient = 0.03, SE = 0.07, P = .61). There was no association between positive CSF $A\beta_{1-42}$ status and atrophy rate in the AD-vulnerable region of interest either in *APOE* ε4 carriers (β-coefficient = −0.19, SE = 0.13, P = .09) or noncarriers (β-coefficient = −0.06, SE = 0.07, P = .38).

We also examined the possibility that *APOE* ε4 modulates AD-associated neurodegeneration via p-τ–related mechanisms. Using the same linear mixed-effects model framework described above, we concurrently examined the main and interactive effects of *APOE* ε4 and CSF p-τ, CSF $A\beta_{1-42}$ and *APOE* ε4, and CSF $A\beta_{1-42}$ and CSF p-τ on the atrophy rate of entorhinal cortex and the AD-vulnerable region of interest. We did not find a significant interaction between *APOE* ε4 and CSF p-τ either on the atrophy rate of entorhinal cortex (β-coefficient = −0.04, SE = 0.18, P = .78) or the AD-vulnerable region of interest (β-coefficient = 0.19, SE = 0.15, P = .18). Most important, even within this triple interaction model, the only significant effect was the interaction between CSF $A\beta_{1-42}$ and CSF p-τ on the atrophy rate of entorhinal cortex (β-coefficient = −0.38, SE = 0.15, P = .01) and the AD-vulnerable region of interest (β-coefficient = −0.41, SE = 0.12, P = .001).

Finally, although our results did not demonstrate a significant interaction between *APOE* ε4 and CSF $A\beta_{1-42}$ on longitudinal brain atrophy among HC, we examined whether the presence of *APOE* ε4 is associated with decreased CSF $A\beta_{1-42}$ and increased CSF p-τ by using a generalized linear model, covarying for age and sex, specifically

$$\text{Logit}([\text{CSF\_A}\beta_{1-42}\text{\_status or CSF\_p-}\tau\text{\_status}]) = \beta_0 + \beta_1 APOE\ \varepsilon4\text{\_status} + \beta_2\text{Age} + \beta_3\text{Sex}.$$

We found a significant relationship between *APOE* ε4 status and positive CSF $A\beta_{1-42}$ status (β-coefficient = 0.40, SE = 0.07, $P = 4.82 \times 10^{-7}$), indicating increased Aβ deposition in ε4 carriers. In contrast, there was no relationship between *APOE* ε4 carriers and positive CSF p-τ status (β-coefficient = 0.05, SE = 0.09, P = .55).

Discussion

In this study, we show that in cognitively healthy older individuals, though the presence of the ε4 allele is specifically associated with Aβ deposition, *APOE* ε4 does not affect Aβ-associated volume loss. In contrast, we found that p-τ modulates Aβ-associated neurodegeneration in clinically healthy individuals, as previously reported.[14] These findings, in conjunction with recent experimental observations,[22,23] support a conceptual model of the pathogenic cascade underlying preclinical AD (Fig 3), in which *APOE* ε4 primarily influences Alzheimer pathology via Aβ-related mechanisms; and in turn, Aβ-associated neurodegeneration occurs only in the presence of p-τ. This model provides a representation of the disease process that can be assessed with currently validated biomarkers, not a comprehensive framework of all pathologic processes occurring in the earliest stages of AD. As such, it can be expanded to include future findings such as mechanistic details regarding the effect of genetic susceptibility loci on AD-associated neurodegeneration.

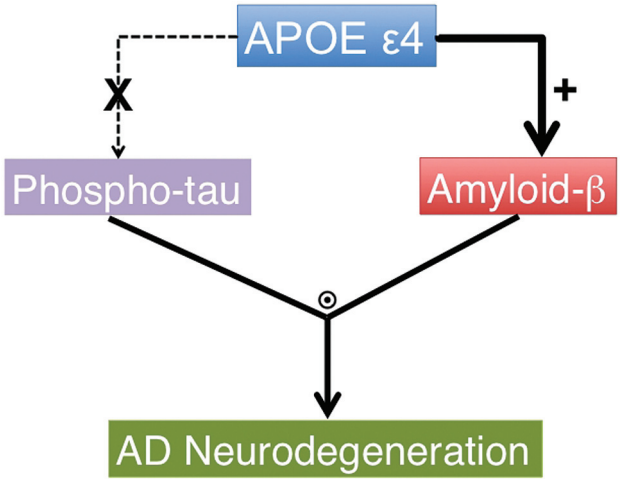

Fig 3. A conceptual model of AD-associated neurodegeneration in the preclinical phase of the disease process based on data from our mixed-effects models (please see text for details). The thickness of the arrows illustrates the magnitude of effect. The circle with a dot inside illustrates an interactive effect, the plus sign illustrates a positive effect, and X illustrates no significant effect.

These findings provide important insights into the preclinical stage of AD. Although several studies in cognitively asymptomatic older individuals have demonstrated a significant relationship among *APOE* ε4 genotype, Aβ deposition, and neurodegeneration,[10-12,24-26] there has been limited evaluation of the role of p-τ in modulating these relationships. Our findings indicate that in clinically healthy older individuals, Aβ deposition by itself, either in ε4 carriers or noncarriers, is not associated with volume loss; the presence of p-τ represents a critical link among the *APOE* ε4 genotype, Aβ deposition, and neurodegeneration. Consistent with prior reports,[27,28] our results illustrate that the ε4 allele primarily affects AD in an indirect fashion via Aβ. In contrast, these findings do not support a role for *APOE* ε4 either in affecting intracranial p-τ levels or modulating AD pathology via p-τ–related mechanisms.

From a quantitative neuroimaging perspective, our results demonstrate the feasibility of using automated MR imaging–based measures of longitudinal brain atrophy as an in vivo biomarker even at the preclinical stage of the disease process. Building on prior neuroimaging studies in cognitively healthy older adults,[10-12,24-26] these findings indicate that volume loss can be detected in older individuals testing positive for both Aβ and p-τ. Furthermore, the pattern of atrophy detected in this study is consistent with previous neuropathologic studies demonstrating neuronal loss within entorhinal cortex in the earliest stages of AD.[19,20] Taken together, these findings suggest that the regionally specific volume loss occurring in a subset of cognitively healthy older adults is neuropathologically consistent with early AD.

This study has limitations. One concern is that CSF biomarkers provide an indirect assessment of amyloid and neurofibrillary pathology and may not fully reflect the pathologic processes underlying Alzheimer disease. Another limitation is that we primarily focused on the *APOE* $\varepsilon 4$ genotype and CSF biomarkers of the 2 pathologic hallmarks of AD. Additional genetic and cellular markers may also interact with Aβ to predict neurodegeneration in cognitively healthy elders. Finally, the individuals examined here may represent a group of highly selected, generally healthy older adults who are motivated to participate in research studies. These findings therefore need to be further validated on an independent community-based cohort of older individuals who would be more representative of the general older population.

Clinically, these results indicate that a biomarker profile evaluating both Aβ and p-τ may better identify those older individuals who are at an elevated risk of progressing to eventual dementia than either biomarker by itself. Consistent with prior clinical observations from our laboratory,[29] our current findings suggest that early intervention trials should take into account both the p-τ and Aβ status of participants because older individuals with increased CSF p-τ and decreased CSF $A\beta_{1-42}$ levels are likely to have significantly elevated rates of volume loss compared with individuals with normal CSF p-τ and decreased CSF $A\beta_{1-42}$ levels. Finally, in addition to the current emphasis on Aβ, our findings identify the need for developing novel therapies that target *APOE*- and τ-related processes. It is likely that a complex interplay between multiple genetic and molecular entities determines AD pathogenesis.[30,31] As such, targeting "upstream" events such as neuronal lipids and cholesterol transporters that interact with *APOE* in $\varepsilon 4$ carriers with normal AD biomarker levels as well as "downstream" events such as τ phosphorylation and aggregation in older individuals with both decreased CSF $A\beta_{1-42}$ and increased CSF p-τ levels may represent additionally beneficial treatment strategies.

Conclusions

We show that in cognitively healthy older individuals, p-τ modulates the effect of Aβ on neurodegeneration. In contrast, although the presence of the $\varepsilon 4$ allele is specifically associated with Aβ deposition, *APOE* $\varepsilon 4$ does not influence Aβ-associated volume loss. These findings provide important insights into the pathogenic cascade underlying preclinical AD and illustrate the importance of examining both Aβ and p-τ in secondary prevention trials.

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