ON-LINE APPENDIX

APOE ε4

APOE ε4 is the strongest known common genetic risk factor for sporadic AD. *APOE* ε4 increases the age-specific risk of developing AD in a dose-dependent manner compared with noncarriers, at least through ages 85–90 years,[1,2] and lowers the age of onset by up to 4–6 years for ε4 homozygotes relative to noncarriers.[1,3,4] Thus, ε4 status may be of importance diagnostically in the clinic, but it may also be important if medications are developed that affect carriers and noncarriers differently. Though it is not thought to increase synthesis of monomeric $A\beta_{1-42}$ ($A\beta$) in the brain,[5,6] ε4 nevertheless increases the burden of synaptotoxic oligomeric $A\beta$,[7-9] particularly near synapses, and this is hypothesized to facilitate its higher potency in producing AD. Several studies have examined the effects of ε4 on rates of hippocampal volume loss,[10-12] with a few also assessing the effects of $A\beta$,[13-16] but results have been inconsistent, and the effects across the diagnostic spectrum on cognitive rates of decline and rates of volume loss in multiple brain regions have not been well understood.

In follow-up analyses, we examined whether ε4 interacted with age to affect rates of structural or clinical decline in each diagnostic group, that is, the additional effect of an age × ε4 interaction implemented with an extra term $b_{AgeAPOE}A_iE_it_{ij}$ in Equation 1, and, separately, whether ε4 interacted with sex to affect the rates of structural or clinical decline, by including an extra term $b_{APOESex}E_iS_it_{ij}$ in Equation 1.

Interactions Among APOE ε4, Age, and Sex on Rates of Decline

For HC and MCI cohorts, there were no significant ε4 × age, ε4 × sex, or sex × age interactions on rates of structural or clinical decline.

In the AD cohort, the ε4 × age interaction was significant only for the entorhinal cortex, for which $b_{AgeAPOE} = -0.1\%/year^2$ (SE = 0.05, $P = .041$), indicating that the slowing in rate of decline with advancing age is attenuated in ε4 carriers compared with noncarriers. With the interaction term in the model, the sex effect remained significant, $b_{sex} = -0.57\%/year$ (SE = 0.22, $P = .009$), and the direct age effect also remained significant, $b_{Age} = 0.11\%/year^2$ (SE = 0.04, $P = .006$), but the direct ε4 effect remained insignificant, $b_{APOE} = -0.36\%/year$ (SE = 0.25, $P = .15$).

There were no significant ε4 × age interactions on cognitive measures, except for ADAS-Cog in MCI converters to AD for which $b_{AgeAPOE} = 0.28/year^2$ (SE = 0.10, $P = .006$). With the interaction term in the model, the sex effect remained significant, $b_{sex} = 1.55/year$ (SE = 0.51, $P = .002$), but the direct ε4 effect showed only a trend toward significance, $b_{APOE} = -1.06/year$ (SE = 0.57, $P = .063$).

A significant ε4 × sex effect was found only for ADAS-Cog in the AD cohort, for which $b_{APOESex} = 4.80/year$ (SE = 1.87, $P = .011$), indicating faster decline for women who are ε4 carriers compared with all others. With this term in the model, the direct *APOE* ε4 term remained insignificant, $b_{APOE} = -1.05\%/year$ (SE = 1.31, $P = .42$), but the direct sex term approached significance, $b_{sex} = -2.96/year$ (SE = 1.60, $P = .064$).

Rates of Decline for MCI-to-AD Converters

Because MCI is a heterogeneous condition, not necessarily prodromal AD, and *APOE* ε4 may have a selection effect for participants who are on an AD trajectory, we carried out an additional analysis restricted to MCI participants who converted to AD while being followed in the ADNI study.

On-line Table 1 shows the effects of age, *APOE* ε4 status, and sex on atrophy rates and clinical decline in the subset of MCI participants who converted to AD. The b_{APOE} term was found to be significant for the amygdala, inferior parietal cortex, and middle temporal cortex, approaching significance for the entorhinal cortex ($P = .060$) and the whole brain ($P = .064$); the b_{Sex} term was significant for the amygdala, entorhinal cortex, medial orbito-frontal cortex, and ADAS-Cog, approaching significance for the whole brain ($P = .063$).

Effects of APOE ε4 and Sex on Baseline CSF and Clinical Measures

There was insufficient power to assess ε4 × sex interactions on biomarker levels in the HC and AD groups (On-line Table 7 shows the number of participants in each category), but they could be explored in the MCI group, in which a trend toward significance was found for CSF $A\beta$ concentrations ($P = .08$, On-line Table 5*B*) and τ concentrations ($P = .12$). For $A\beta$ concentrations, subsequent analysis showed that the ε4 effect occurred only in men, with ε4 carriers having significantly lower values than noncarriers ($P = 3 \times 10^{-7}$, On-line Table 6*A*); in women, $A\beta$ concentrations were comparably lower for both carriers and noncarriers ($P = .498$); there was, however, only a trend toward a sex effect in ε4 noncarriers (lower concentrations for women, $P = .105$), whereas carriers had similarly low concentrations ($P = .91$). Thus, results in MCI suggest a potential interaction between sex and ε4 status on CSF $A\beta$ concentration, in which ε4-negative status does not confer the same advantage to women as it does to men. For τ concentrations, although the interaction effect was not significant, subsequent analysis showed that whereas there was a significant ε4 effect in both sexes (carriers had higher values, $P = .025$ for men and $P = .014$ for women, On-line Table 6*A*), the sex effect occurred only in ε4 carriers, in whom women had significantly higher concentrations than men ($P = .036$, On-line Table 6*B*, a pattern that also occurred in AD; $P = .019$); in noncarriers, τ concentrations were similarly low for both men and women ($P = .955$).

Interaction effects of ε4 × sex were found in AD for ADAS-Cog and MMSE, and in MCI for MMSE, only (On-line Table 5*B*). Subsequent analysis showed that there was an ε4 effect in AD for ADAS-Cog in men only, with carriers performing worse than noncarriers (On-line Table 6*A*). In women, there was no difference in performance on this measure as a function of ε4 status: both groups performed comparably to men with an ε4 allele. There was a sex effect in AD for MMSE for ε4 noncarriers only, with women performing more poorly. In MCI, women with ε4 performed more poorly than the other 3 groups (On-line Table 6*B*).

ADNI Database

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.ucla.edu). The ADNI was launched in

2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60 million, 5-year public-private partnership. The primary goal of the ADNI has been to test whether serial MRI, PET, other biologic markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California–San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from more than 50 sites across the United States and Canada. The initial goal of the ADNI was to recruit 800 adults, ages 55–90, to participate in the research, approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For up-to-date information, see www.adni-info.org.

Participants

The ADNI general eligibility criteria have been described elsewhere.[17] Briefly, participants are not depressed, have a modified Hachinski score of ≤4, and have a study partner able to provide an independent evaluation of functioning. HC participants have a CDR of 0. Participants with MCI have a subjective memory complaint, objective memory loss measured by education-adjusted scores on Wechsler Memory Scale Logical Memory II, a CDR of 0.5, preserved activities of daily living, and absence of dementia. Participants with AD have a CDR of 0.5 or 1.0 and meet National Institute of Neurological Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria for probable AD.

MRI Processing

We preprocessed all MRI scans with the use of image correction procedures for site-specific distortion effects updated for recent scanner changes.[18] We quantified anatomical regional change in serial MRI with the use of Quarc,[19,20] a recently developed method from our laboratory. The longitudinal outcome measure of change with respect to baseline was calculated by directly registering each follow-up scan to the baseline scan. To evaluate baseline ROI measurements, we used a structural MRI postprocessing technique that automatically delineates subcortical[21] and cortical[22] ROIs. We analyzed data from all available time points that passed local quality control (total = 2244). The number of follow-up scans was reduced by approximately 15% primarily as the result of motion artifacts, change in scanner model, or change in radiofrequency coil, as described in Holland et al.[18]

Methodologic bias in image registration, leading to artifactually elevated effect sizes and reduced sample size estimates, remains a concern in the structural neuroimaging literature.[20] Several robust approaches to reducing or eliminating bias have been developed.[23,24] Our explicitly inverse-consistent approach[19] essentially eliminates potential bias by combining forward and reverse image registrations and has been assessed vis-à-vis other approaches.[20]

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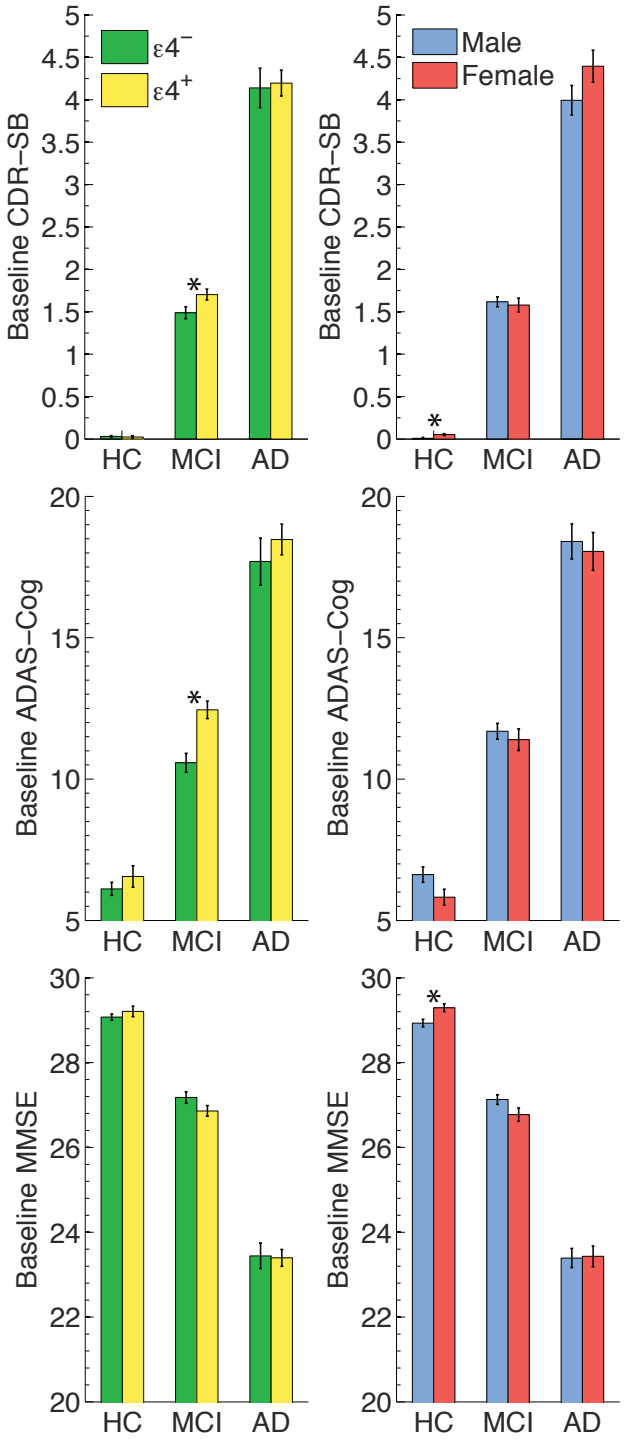
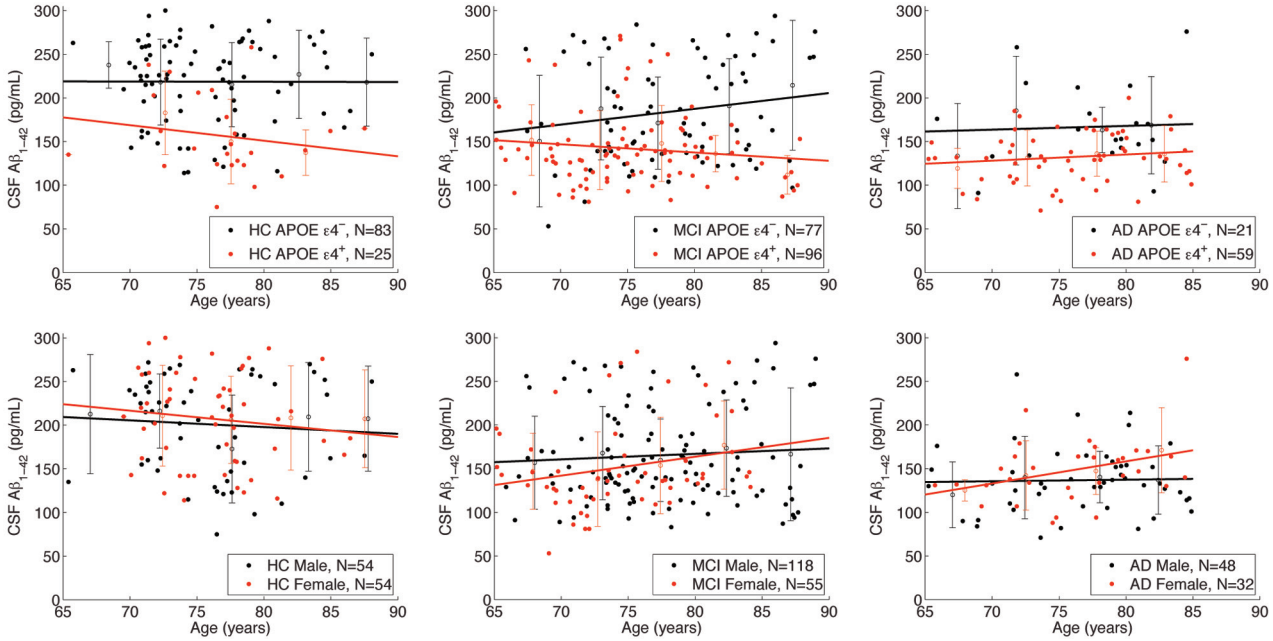
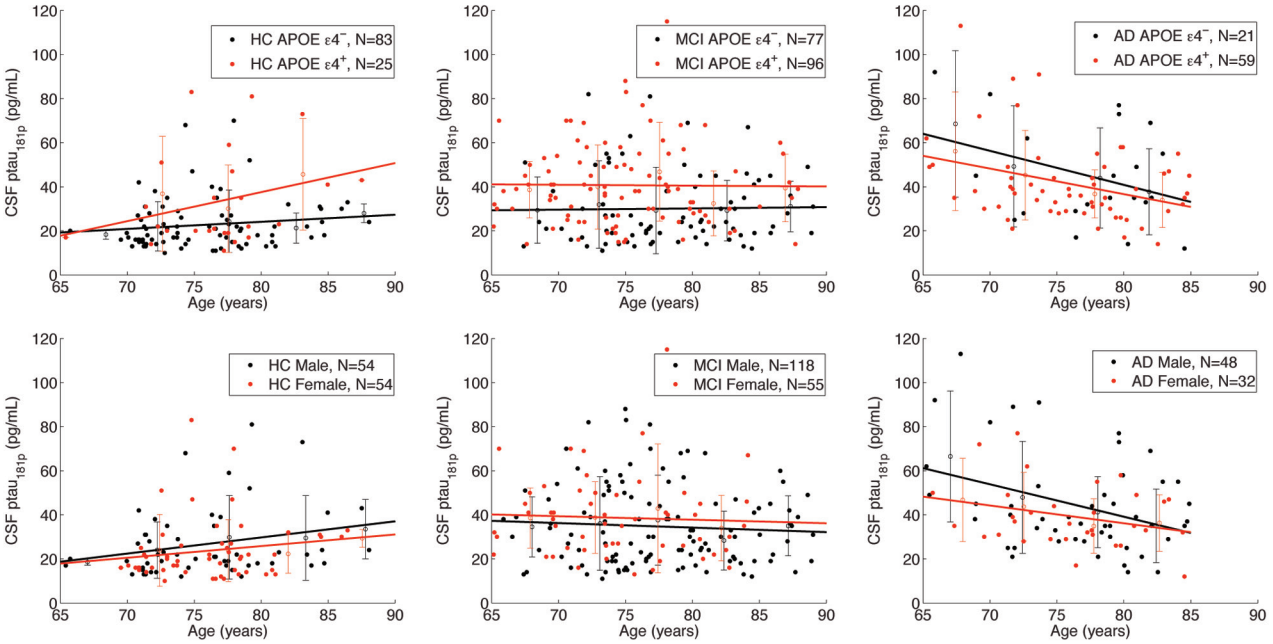


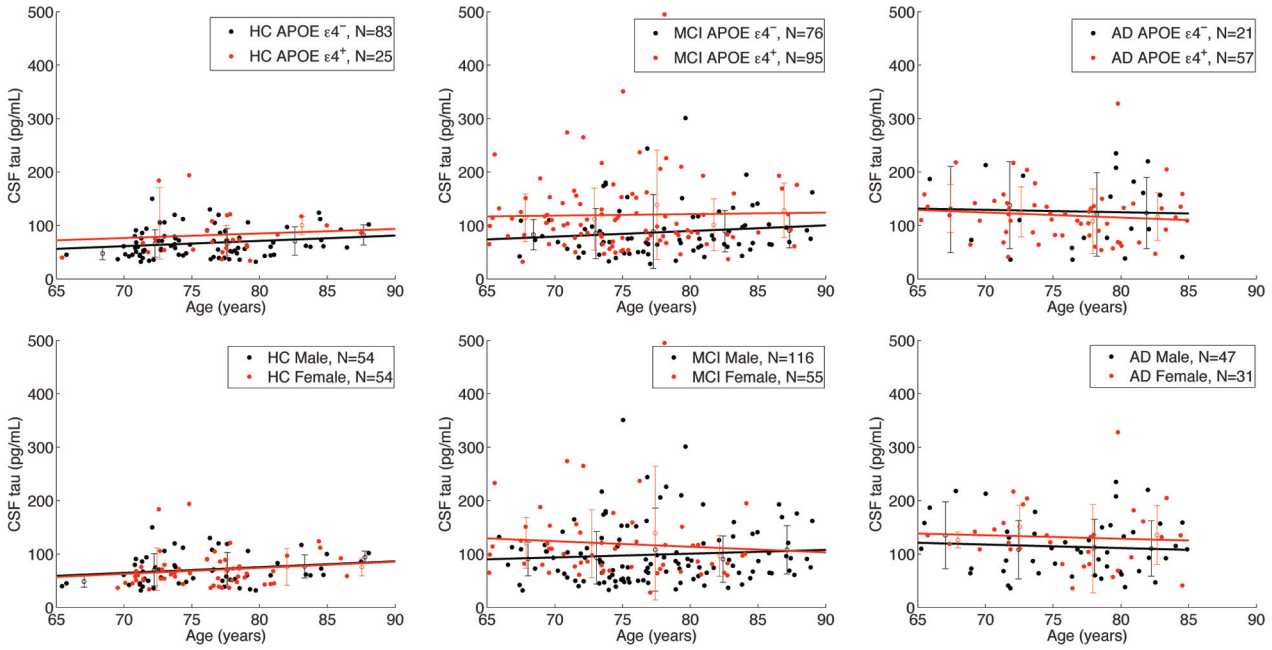
ON-LINE FIG 1. Baseline cognitive performance, measured with CDR-SB, ADAS-Cog, and MMSE, by $\varepsilon 4$ status (left) and sex (right) for the HC, MCI, and AD cohorts. *Significant differences. Also see On-line Table 5*A*.



ON-LINE FIG 2. Top row shows baseline CSF Aβ_{1-42} values for HC, MCI, and AD participants, with respect to age, categorized by *APOE* $\varepsilon 4$ status (upper row) and sex (lower row). Open circles with error bars are means for successive 5-year age ranges; closed circles represent individual participants. Lines are generalized linear model fits to the data. The linear fits show that regardless of diagnosis, *APOE* $\varepsilon 4^+$ had consistently lower CSF Aβ than *APOE* $\varepsilon 4^-$. For the HC and MCI *APOE* $\varepsilon 4^+$ participants, the linear fits suggest an increase in Aβ burden with age (lower CSF Aβ), becoming independent of age for the AD cohort. For the *APOE* $\varepsilon 4^-$ HCs, Aβ burden appears to be independent of age. Unexpectedly, the Aβ burden appeared to be greater for younger compared with older *APOE* $\varepsilon 4^-$ MCI participants, but the positive slope (1.8 pg/[mL year], SE = 1.2) was not significantly different from zero ($P = .15$). The negative slope is also not significant (−0.9 pg/[mL year], SE = 0.7), but the difference between slopes approaches significance: $P = .058$.



ON-LINE FIG 3. See On-line Fig 1, but for baseline CSF p-τ. The negative p-τ slope for AD *APOE* $\varepsilon 4^+$ (−1.2 pg/[mL year], SE = 0.4) is significant: $P = .01$.



ON-LINE FIG 4. See On-line Fig 1, but for baseline CSF τ.

On-line Table 1: Direct effects of age, *APOE* ε4, and sex on rates of change in individuals with MCI who converted to dementia within the 3-year follow-up period

Measure	b_0	b_{Cog}	b_{Edu}	b_{Age} (SE; *P*)	b_{APOE} (SE; *P*)	b_{Sex} (SE; *P*)
Hippocampus	−2.43[a]	−0.09[a]	−0.01	0.01 (.03; 0.8)	−0.22 (.33; .5)	−0.41 (.31; .2)
Amygdala	−2.10[a]	−0.09[a]	−0.04	0.03 (.03; .2)	−0.99[a] (.33; .003)	−1.07[a] (.31; 5×10^{-4})
Entorhinal	−2.27[a]	−0.03	0.00	0.05[a] (.02; .026)	−0.47 (.25; .060)	−0.77[a] (.23; .001)
Inferior parietal	−1.15[a]	−0.06[a]	0.02	0.06[a] (.02; .002)	−0.57[a] (.24; .017)	−0.30 (.22; .2)
Middle temporal	−1.80[a]	−0.09[a]	0.03	0.08[a] (.02; .002)	−0.64[a] (.28; .023)	−0.39 (.26; .1)
Med-orbito-frontal	−0.77[a]	−0.03	0.05	0.01 (.02; .5)	−0.13 (.19; .5)	−0.46[a] (.17; .008)
Whole brain	−0.82[a]	−0.02	0.02	0.02 (.01; .070)	−0.25 (.13; .064)	−0.23 (.12; .063)
CDR-SB	1.21[a]	–	−0.02	0.01 (0.01; .3)	0.09 (.17; .6)	0.23 (.16; .1)
ADAS-Cog	2.53[a]	–	0.01	−0.01 (0.05; .8)	−0.58 (.56; .3)	1.41[a] (.52; .007)
MMSE	−1.72[a]	–	0.01	0.03 (0.03; .3)	−0.11 (.30; .7)	−0.20 (.29; .5)

Note:—b-Values are coefficients in Equation 1; for structural measures, units are annual thickness or volume change as a percentage of baseline size (%/year), and for cognitive measures they are annual score change, per ADAS-Cog unit in the case of b_{Cog}, and per year in the case of b_{Edu} and b_{Age}. Med-orbito-frontal indicates medial orbito-frontal cortex.

ROIs: $N = 110$; mean age = 75.77 years; mean ADAS-Cog = 13.06; mean years education = 15.66. Clinical: $N = 139$; mean age = 76.23 years; mean years education = 15.63. SE indicates standard error. $P = P$ value for significance of b−coefficients.

[a] Values significant at $P \leq .05$.

On-line Table 2*A*: Direct effects of age, *APOE* ε4, and sex on rates of change in HC participants with CSF data

HC Measure $N = 95/107$[b]	b_0	b_{Cog}	b_{Edu}	b_{Age}	p_{Age}	b_{APOE}	p_{APOE}	b_{Sex}	p_{Sex}
Hippocampus	−0.7358[a]	−0.0396	−0.0304	−0.0426[a]	0.0054	−0.1318	0.4420	−0.1321	0.3806
Amygdala	−0.3995[a]	0.0133	−0.0343	−0.0189	0.3381	−0.5853[a]	0.0085	−0.4322[a]	0.0267
Entorhinal	−0.4545[a]	0.0088	−0.0248	−0.0261	0.1900	−0.4328	0.0539	−0.3905[a]	0.0478
Inferior parietal	−0.4625[a]	−0.0015	0.0076	0.0078	0.5433	−0.2011	0.1609	0.0801	0.5250
Middle temporal	−0.6826[a]	−0.0098	−0.0039	0.0273[a]	0.0466	−0.2521	0.1010	0.1012	0.4533
Med-orbito-frontal	−0.4509[a]	−0.0180	−0.0063	0.0067	0.5736	−0.1502	0.2558	−0.0326	0.7782
Whole brain	−0.3639[a]	0.0073	0.0009	0.0121	0.1302	−0.1573	0.0796	−0.0301	0.7020
CDR-SB	0.0571	–	0.0045	−0.0002	0.9621	0.1159[a]	0.0461	0.0027	0.9572
ADAS-Cog	−0.4802[a]	–	−0.0084	0.0264	0.3314	0.4185	0.1631	0.1300	0.6140
MMSE	−0.0506	–	−0.0311	−0.0138	0.1906	−0.1073	0.3571	0.0027	0.9785

Note:—See On-line Table 1 for units and key.

[a] Values significant at $P \leq .05$.

[b] Number of participants in ROI analyses/number in clinical analyses.

On-line Table 2*B*: Direct effects of age, *APOE* ε4, and sex on rates of change in participants with MCI with CSF data

MCI Measure $N = 147/169$[b]	b_0	b_{Cog}	b_{Edu}	b_{Age}	p_{Age}	b_{APOE}	p_{APOE}	b_{Sex}	p_{Sex}
Hippocampus	−2.0205[a]	−0.1192[a]	0.0058	−0.0126	0.6110	−0.3303	0.2462	−0.3598	0.2228
Amygdala	−1.7862[a]	−0.1390	0.0451	0.0621[a]	0.0076	−0.7454[a]	0.0054	−0.8419[a]	0.0025
Entorhinal	−1.9059[a]	−0.1111[a]	−0.0221	0.0456[a]	0.0270	−0.2784	0.2401	−0.6526[a]	0.0080
Inferior parietal	−1.0310[a]	−0.0792[a]	0.0075	0.0562[a]	0.0009	−0.1823	0.3494	−0.5099[a]	0.0118
Middle temporal	−1.5571[a]	−0.1101[a]	−0.0178	0.0640[a]	0.0022	−0.0327	0.8911	−0.8062[a]	0.0012
Med-orbito-frontal	−0.8515[a]	−0.0488[a]	0.0443	0.0166	0.2156	0.2145	0.1643	−0.4547[a]	0.0046
Whole brain	−0.7901[a]	−0.0411[a]	0.0139	0.0231[a]	0.0181	0.0153	0.8917	−0.2848[a]	0.0148
CDR-SB	0.4798[a]	–	0.0101	0.0246	0.0581	0.4252[a]	0.0040	0.3408[a]	0.0326
ADAS-Cog	0.2702	–	0.0205	0.0551	0.1751	0.9146[a]	0.0484	1.8267[a]	0.0003
MMSE	−0.2088	–	−0.0097	−0.0255	0.3315	−0.9983[a]			

Note:—See On-line Table 1 for units and key.

[a] Values significant at $P \leq .05$.

[b] Number of participants in ROI analyses/number in clinical analyses.

On-line Table 2*C*: Direct effects of age, *APOE* ε4, and sex on rates of change in participants with AD with CSF data

AD Measure $N = 65/78$[b]	b_0	b_{Cog}	b_{Edu}	b_{Age}	p_{Age}	b_{APOE}	p_{APOE}	b_{Sex}	p_{Sex}
Hippocampus	−2.3602[a]	−0.0697	−0.0101	0.0345	0.3242	−0.9650[a]	0.0345	−0.7228	0.0665
Amygdala	−2.3926[a]	−0.0394	−0.0337	0.0240	0.5046	−0.9151	0.0513	−0.9114[a]	0.0245
Entorhinal	−2.1663[a]	−0.0474	−0.0697	0.0514[a]	0.0387	−0.8120[a]	0.0122	−0.6985[a]	0.0119
Inferior parietal	−1.5070[a]	−0.0903[a]	−0.0105	0.1350[a]	0.0000	−0.3966	0.2019	−0.8234[a]	0.0024
Middle temporal	−2.3257[a]	−0.1318[a]	−0.0496	0.1559[a]	0.0000	−0.3848	0.2761	−0.9883[a]	0.0014
Med-orbito-frontal	−0.8551[a]	0.0034	−0.0293	0.0480[a]	0.0091	0.1746	0.4642	−0.8418[a]	0.0000
Whole brain	−0.7822[a]	−0.0517[a]	−0.0019	0.0530[a]	0.0000	−0.2498	0.1220	−0.5332[a]	0.0001
CDR-SB	1.4401[a]	–	0.1595[a]	0.0268	0.4030	−0.1134	0.7815	0.5184	0.1328
ADAS-Cog	2.9904[a]	–	0.3394	−0.0947	0.3921	0.2238	0.8742	1.4690	0.2190
MMSE	−1.9407[a]	–	−0.1458	0.1104	0.0874	0.2789	0.7342	−0.2064	0.7659

Note:—See On-line Table 1 for units and key.

[a] Values significant at $P \leq .05$.

[b] Number of participants in ROI analyses/number in clinical analyses.

On-line Table 3*A*: Direct effects of age, *APOE* ε4, sex, and Aβ on rates of change in HC

HC Measure $N = 95/107^b$	b_0	b_{Cog}	b_{Edu}	b_{Age}	p_{Age}	b_{APOE}	p_{APOE}	b_{Sex}	p_{Sex}	$b_{A\beta}$	$p_{A\beta}$
Hippocampus	−0.7717[a]	−0.0336	−0.0306	−0.0418[a]	0.0062	−0.0215	0.9118	−0.1128	0.4545	0.0019	0.2347
Amygdala	−0.4557[a]	0.0224	−0.0344	−0.0176	0.3679	−0.4155	0.0966	−0.4018[a]	0.0387	0.0029	0.1574
Entorhinal	−0.4699[a]	0.0114	−0.0249	−0.0258	0.1967	−0.3856	0.1311	−0.3821	0.0542	0.0008	0.6991
Inferior parietal	−0.4901[a]	0.0032	0.0075	0.0084	0.5094	−0.1170	0.4726	0.0950	0.4524	0.0014	0.2799
Middle temporal	−0.7105[a]	−0.0051	−0.0040	0.0279[a]	0.0410	−0.1666	0.3386	0.1163	0.3895	0.0015	0.3050
Med-orbito-frontal	−0.4772[a]	−0.0132	−0.0063	0.0073	0.5364	−0.0696	0.6418	−0.0185	0.8737	0.0014	0.2555
Whole brain	−0.3784[a]	0.0098	0.0008	0.0124	0.1196	−0.1128	0.2681	−0.0222	0.7792	0.0008	0.3601
CDR-SB	0.0680	–	0.0043	−0.0004	0.9428	0.0734	0.2605	0.0007	0.9884	−0.0007	0.1658
ADAS-Cog	−0.4801[a]	–	−0.0084	0.0264	0.3314	0.4180	0.2190	0.1300	0.6141	0.0000	0.9976
MMSE	−0.0861	–	−0.0297	−0.0140	0.1762	0.0317	0.8066	0.0083	0.9321	0.0022[a]	0.0238

Note:—See On-line Table 1 for units and key.

[a] Values significant at $P \leq .05$.

[b] Number of participants in ROI analyses/number in clinical analyses.

On-line Table 3*B*: Direct effects of age, *APOE* ε4, sex, and Aβ on rates of change in MCI

MCI Measure $N = 147/169^b$	b_0	b_{Cog}	b_{Edu}	b_{Age}	p_{Age}	b_{APOE}	p_{APOE}	b_{Sex}	p_{Sex}	$b_{A\beta}$	$p_{A\beta}$
Hippocampus	−2.1172[a]	−0.1144[a]	0.0080	−0.0160	0.5144	−0.1625	0.5860	−0.3466	0.2352	0.0047	0.0886
Amygdala	−1.8958[a]	−0.1332[a]	0.0470	0.0580[a]	0.0112	−0.5520[a]	0.0470	−0.8269[a]	0.0024	0.0054[a]	0.0352
Entorhinal	−2.0113[a]	−0.1058[a]	−0.0199	0.0419[a]	0.0395	−0.0931	0.7061	−0.6389[a]	0.0083	0.0051[a]	0.0243
Inferior parietal	−1.0569[a]	−0.0779[a]	0.0080	0.0553[a]	0.0011	−0.1373	0.5041	−0.5058[a]	0.0121	0.0013	0.5002
Middle temporal	−1.6065[a]	−0.1077[a]	−0.0167	0.0622[a]	0.0028	0.0530	0.8332	−0.7996[a]	0.0012	0.0024	0.2984
Med-orbito-frontal	−0.8462[a]	−0.0491[a]	0.0442	0.0168	0.2119	0.2051	0.2102	−0.4555[a]	0.0046	−0.0003	0.8633
Whole brain	−0.7859[a]	−0.0413[a]	0.0138	0.0233[a]	0.0180	0.0080	0.9467	−0.2855[a]	0.0147	−0.0002	0.8482
CDR-SB	0.5464[a]	–	0.0070	0.0250	0.0505	0.3107[a]	0.0487	0.3170[a]	0.0442	−0.0027	0.0584
ADAS-Cog	0.5043	–	0.0115	0.0567	0.1577	0.5060	0.3072	1.7476[a]	0.0004	−0.0095[a]	0.0344
MMSE	−0.3697	–	−0.0028	−0.0262	0.3108	−0.7185[a]	0.0237	−0.5836	0.0656	0.0065[a]	0.0234

Note:—See On-line Table 1 for units and key.

[a] Values significant at $P \leq .05$.

[b] Number of participants in ROI analyses/number in clinical analyses.

On-line Table 3*C*: Direct effects of age, *APOE* ε4, sex, and Aβ on rates of change in AD

AD Measure $N = 65/78^b$	b_0	b_{Cog}	b_{Edu}	b_{Age}	p_{Age}	b_{APOE}	p_{APOE}	b_{Sex}	p_{Sex}	$b_{A\beta}$	$p_{A\beta}$
Hippocampus	−2.3223[a]	−0.0703	−0.0083	0.0359	0.3073	−1.0322[a]	0.0352	−0.6933	0.0838	−0.0020	0.7077
Amygdala	−2.5179[a]	−0.0376	−0.0395	0.0193	0.5906	−0.6934	0.1655	−1.0075[a]	0.0141	0.0067	0.2303
Entorhinal	−2.2334[a]	−0.0467	−0.0727	0.0489[a]	0.0476	−0.6958[a]	0.0430	−0.7477[a]	0.0076	0.0035	0.3555
Inferior parietal	−1.5753[a]	−0.0894[a]	−0.0138	0.1324[a]	0.0000	−0.2762	0.4039	−0.8751[a]	0.0014	0.0037	0.3216
Middle temporal	−2.4393[a]	−0.1301[a]	−0.0552	0.1515[a]	0.0000	−0.1863	0.6179	−1.0725[a]	0.0005	0.0060	0.1485
Med-orbito-frontal	−0.9168[a]	0.0038	−0.0311	0.0453[a]	0.0121	0.2836	0.2597	−0.8911[a]	0.0000	0.0032	0.2443
Whole brain	−0.7956[a]	−0.0516[a]	−0.0025	0.0525[a]	0.0000	−0.2260	0.1934	−0.5438[a]	0.0002	0.0007	0.7119
CDR-SB	1.6222[a]	–	0.1646[a]	0.0337	0.2861	−0.4198	0.3349	0.6277	0.0678	−0.0087	0.0741
ADAS-Cog	3.5894[a]	–	0.3557	−0.0717	0.5115	−0.7730	0.6076	1.8108	0.1279	−0.0284	0.0939
MMSE	−2.0679[a]	–	−0.1492	0.1054	0.1053	0.4935	0.5801	−0.2846	0.6863	0.0062	0.5386

Note:—See On-line Table 1 for units and key.

[a] Values significant at $P \leq .05$.

[b] Number of participants in ROI analyses/number in clinical analyses.

On-line Table 4*A*: Direct effects of age, *APOE* ε4, sex, Aβ, and p-τ on rates of change in HC

HC Measure $N = 95/107^b$	b_0	b_{Cog}	b_{Edu}	b_{Age}	p_{Age}	b_{APOE}	p_{APOE}	b_{Sex}	p_{Sex}	$b_{A\beta}$	$p_{A\beta}$	b_{Ptau}	p_{Ptau}
Hippocampus	−0.771[a]	−0.034	−0.030	−0.041[a]	0.0080	−0.0196	0.9197	−0.1149	0.4472	0.0018	0.2833	−0.0011	0.8495
Amygdala	−0.450[a]	0.022	−0.027	−0.011	0.5607	−0.3933	0.1082	−0.4261[a]	0.0255	0.0017	0.4081	−0.0123	0.0796
Entorhinal	−0.464[a]	0.011	−0.020	−0.022	0.2849	−0.3715	0.1432	−0.4001[a]	0.0429	0.0000	0.9823	−0.0081	0.2665
Inferior parietal	−0.491[a]	0.003	0.006	0.007	0.5749	−0.1209	0.4571	0.0994	0.4319	0.0016	0.2397	0.0022	0.6329
Middle temporal	−0.713[a]	−0.005	−0.007	0.026	0.0634	−0.1737	0.3184	0.1248	0.3570	0.0018	0.2183	0.0041	0.4084
Med-orbito-frontal	−0.480[a]	−0.013	−0.009	0.005	0.6645	−0.0749	0.6139	−0.0108	0.9255	0.0018	0.1652	0.0042	0.3299
Whole brain	−0.378[a]	0.010	0.001	0.013	0.1167	−0.1118	0.2731	−0.0234	0.7677	0.0007	0.4206	−0.0006	0.8326
CDR-SB	0.062	–	0.002	−0.003	0.5852	0.0681	0.2850	0.0125	0.7974	−0.0003	0.5975	0.0042	0.0279
ADAS-Cog	−0.497[a]	–	−0.015	0.020	0.4717	0.4071	0.2273	0.1639	0.5238	0.0012	0.6646	0.0118	0.2479
MMSE	−0.094	–	−0.033	−0.017	0.1017	0.0246	0.8481	0.0253	0.7957	0.0028[a]	0.0074	0.0059	0.1274

Note:—See On-line Table 1 for units and key.

[a] Values significant at $P \leq .05$.

[b] Number of participants in ROI analyses/number in clinical analyses.

On-line Table 4*B*: Direct effects of age, *APOE* ε4, sex, Aβ, and p-τ on rates of change in MCI

MCI Measure $N = 147/169^b$	b_0	b_{Cog}	b_{Edu}	b_{Age}	p_{Age}	b_{APOE}	p_{APOE}	b_{Sex}	p_{Sex}	$b_{A\beta}$	$p_{A\beta}$	b_{Ptau}	p_{Ptau}
Hippocampus	−2.124[a]	−0.113[a]	0.008	−0.017	0.4999	−0.1521	0.6103	−0.3452	0.2360	0.0041	0.1733	−0.0044	0.6113
Amygdala	−1.932[a]	−0.125[a]	0.045	0.055[a]	0.0139	−0.5005	0.0653	−0.8184[a]	0.0021	0.0024	0.3692	−0.0219	0.0055
Entorhinal	−2.044[a]	−0.098[a]	−0.022	0.040[a]	0.0467	−0.0449	0.8524	−0.6323[a]	0.0074	0.0024	0.3269	−0.0201	0.0042
Inferior parietal	−1.064[a]	−0.076[a]	0.008	0.055[a]	0.0013	−0.1269	0.5369	−0.5042[a]	0.0121	0.0007	0.7490	−0.0045	0.4492
Middle temporal	−1.627[a]	−0.103[a]	−0.018	0.061[a]	0.0033	0.0831	0.7391	−0.7955[a]	0.0011	0.0006	0.8194	−0.0133	0.0667
Med-orbito-frontal	−0.846[a]	−0.049[a]	0.044	0.017	0.2126	0.2051	0.2111	−0.4555[a]	0.0046	−0.0003	0.8725	0.0000	0.9960
Whole brain	−0.784[a]	−0.042[a]	0.014	0.024[a]	0.0172	0.0048	0.9682	−0.2860[a]	0.0146	0.0000	0.9840	0.0014	0.6950
CDR-SB	0.561[a]	–	0.007	0.025[a]	0.0492	0.2855	0.0706	0.3170[a]	0.0428	−0.0019	0.2091	0.0055	0.2316
ADAS-Cog	0.599	–	0.015	0.056	0.1527	0.3390	0.4881	1.7498	0.0003	−0.0046	0.3350	0.0361	0.0121
MMSE	−0.419	–	−0.005	−0.026	0.3041	−0.6325[a]	0.0447	−0.5839	0.0610	0.0040	0.1998	−0.0186	0.0458

Note:—See On-line Table 1 for units and key.

[a] Values significant at $P \leq .05$.

[b] Number of participants in ROI analyses/number in clinical analyses.

On-line Table 4*C*: Direct effects of age, *APOE* ε4, sex, Aβ, and p-τ on rates of change in AD

AD Measure $N = 65/78^b$	b_0	b_{Cog}	b_{Edu}	b_{Age}	p_{Age}	b_{APOE}	p_{APOE}	b_{Sex}	p_{Sex}	$b_{A\beta}$	$p_{A\beta}$	b_{Ptau}	p_{Ptau}
Hippocampus	−2.308[a]	−0.069	−0.007	0.031	0.4222	−1.0478[a]	0.0338	−0.7020	0.0810	−0.0024	0.6668	−0.0032	0.7739
Amygdala	−2.435[a]	−0.029	−0.030	−0.012	0.7592	−0.7882	0.1069	−1.0607[a]	0.0081	0.0043	0.4374	−0.0203	0.0667
Entorhinal	−2.161[a]	−0.038	−0.064	0.018	0.4953	−0.7828[a]	0.0162	−0.8052[a]	0.0024	0.0014	0.7027	**−0.0196**	0.0075
Inferior parietal	−1.538[a]	−0.085[a]	−0.010	0.119[a]	0.0000	−0.3182	0.3378	−0.8993[a]	0.0010	0.0027	0.4833	−0.0088	0.2442
Middle temporal	−2.393[a]	−0.125[a]	−0.050	0.135[a]	0.0000	−0.2397	0.5202	−1.1014[a]	0.0004	0.0048	0.2623	−0.0110	0.1934
Med-orbito-frontal	−0.906[a]	0.005	−0.030	0.041[a]	0.0427	0.2720	0.2807	−0.9024[a]	0.0000	0.0029	0.3053	−0.0028	0.6183
Whole brain	−0.793[a]	−0.051[a]	−0.002	0.051[a]	0.0003	−0.2290	0.1898	−0.5460[a]	0.0002	0.0006	0.7486	−0.0007	0.8650
CDR-SB	1.595[a]	–	0.165[a]	0.041	0.2326	−0.3879	0.3762	0.6390	0.0629	−0.0080	0.1112	0.0052	0.5899
ADAS-Cog	3.484[a]	–	0.357	−0.043	0.7131	−0.6498	0.6676	1.8531	0.1184	−0.0257	0.1409	0.0200	0.5472
MMSE	−2.054[a]	–	−0.149	0.102	0.1500	0.4773	0.5962	−0.2903	0.6809	0.0058	0.5750	−0.0026	0.8972

Note:—See On-line Table 1 for units and key.

[a] Values significant at $P \leq .05$.

[b] Number of participants in ROI analyses/number in clinical analyses.

On-line Table 5*A*: Expected baseline CSF and cognitive values for each cohort: Effects of *APOE* and sex

	$\varepsilon4^-$ (SE)	$\varepsilon4^+$ (SE)	*P*	Male (SE)	Female (SE)	*P*
Aβ						
HC	218.63 (5.17)	156.57 (9.48)	$<10^{-6}$[a]	205.20 (6.39)	203.57 (6.45)	.9
MCI	183.17 (5.67)	142.57 (5.11)	$<10^{-6}$[a]	163.40 (4.59)	155.08 (6.76)	.3
AD	166.27 (7.47)	132.46 (4.46)	2×10^{-4}[a]	136.33 (4.94)	148.85 (6.05)	.11
p-τ						
HC	22.97 (1.53)	32.79 (2.80)	.003[a]	26.12 (1.89)	24.30 (1.90)	.5
MCI	30.27 (2.01)	40.68 (1.81)	3×10^{-4}[a]	35.12 (1.62)	37.94 (2.39)	.3
AD	46.19 (4.06)	40.93 (2.42)	.3	44.48 (2.68)	39.06 (3.29)	.2
τ						
HC	66.93 (3.28)	81.57 (6.01)	.038[a]	69.97 (4.05)	70.60 (4.09)	.9
MCI	87.43 (6.93)	120.40 (6.24)	9×10^{-4}[a]	99.41 (5.62)	118.89 (8.20)	.060
AD	127.02 (12.19)	118.31 (7.40)	.5	113.67 (8.15)	131.24 (10.03)	.2
CDR-SB						
HC	0.03 (0.01)	0.02 (0.01)	.7	0.01 (0.01)	0.05 (0.01)	.006[a]
MCI	1.49 (0.07)	1.70 (0.07)	.031[a]	1.62 (0.06)	1.58 (0.08)	.7
AD	4.14 (0.23)	4.20 (0.15)	.8	3.99 (0.17)	4.40 (0.19)	.1
ADAS-Cog						
HC	6.12 (0.23)	6.56 (0.38)	.3	6.62 (0.27)	5.83 (0.28)	.052
MCI	10.58 (0.34)	12.45 (0.31)	9×10^{-5}[a]	11.69 (0.28)	11.39 (0.39)	.5
AD	17.70 (0.83)	18.48 (0.54)	.4	18.40 (0.62)	18.05 (0.67)	.7
MMSE						
HC	29.07 (0.08)	29.21 (0.12)	.4	28.93 (0.09)	29.29 (0.09)	.007[a]
MCI	27.18 (0.14)	26.86 (0.13)	.1	27.13 (0.11)	26.77 (0.16)	.072
AD	23.44 (0.30)	23.40 (0.20)	.9	23.39 (0.23)	23.43(0.25)	0.9

Note:—Units are pg/mL for CSF values. All values for *APOE* $\varepsilon4$ effects (left half of table) are covaried for age and sex; all values for sex effects (right half of table) are covaried for age and *APOE*; clinical values are additionally covaried for education.

SE indicates standard error; $P = P$ value for paired comparisons (significance of the effect, ie, the difference in the expected values).

[a] Differences significant at $P < .05$.

See print Fig 3 and On-line Fig 1. Numbers of participants are in On-line Table 7.

On-line Table 5*B*: Expected baseline CSF and cognitive values for each cohort: Direct and interaction effects of *APOE* and sex

	$\varepsilon4^-$	SE	$\varepsilon4^+$	SE	*P*	Male	SE	Female	SE	*P*	*P* $\varepsilon4 \times$ *Sex*
Aβ											
HC	218.69	5.20	157.20	9.53	1×10^{-7}[a]	205.36	6.42	203.80	6.48	.9	.785
MCI	181.78	5.64	142.27	5.08	6×10^{-7}[a]	162.88	4.57	153.70	6.72	.3	.083
AD	166.59	7.48	132.46	4.46	2×10^{-4}[a]	136.40	4.95	148.95	6.06	.113	.366
p-τ											
HC	23.00	1.53	33.14	2.81	.002[a]	26.21	1.89	24.43	1.91	.5	.605
MCI	30.15	2.01	40.65	1.81	2×10^{-4}[a]	35.08	1.63	37.82	2.39	.3	.675
AD	45.90	4.02	40.93	2.40	.3	44.41	2.66	38.97	3.26	.2	.123
τ											
HC	67.25	3.21	84.97	5.88	.009[a]	70.81	3.96	71.83	4.00	.9	.018[a]
MCI	85.91	6.90	120.07	6.21	3×10^{-4}[a]	98.84	5.60	117.40	8.16	.063	.120
AD	126.07	11.99	118.33	7.28	.6	113.48	8.02	130.93	9.87	.2	.067
CDR-SB											
HC	0.03	0.01	0.01	0.01	.3	0.01	0.01	0.05	0.01	.014[a]	.628
MCI	1.49	0.07	1.73	0.07	.012[a]	1.62	0.06	1.63	0.08	.9	.631
AD	4.12	0.23	4.58	0.15	.102	3.99	0.17	4.97	0.19	2×10^{-4}[a]	.117
ADAS-Cog											
HC	6.12	0.23	6.26	0.38	.7	6.62	0.27	5.66	0.28	.015	.556
MCI	10.57	0.34	12.15	0.31	6×10^{-4}[a]	11.69	0.28	10.92	0.39	.110	.485
AD	17.54	0.81	21.14	0.53	3×10^{-4}[a]	18.33	0.60	22.09	0.65	4×10^{-5}[a]	.004[a]
MMSE											
HC	29.07	0.08	29.17	0.12	.5	28.93	0.09	29.27	0.09	.009[a]	.535
MCI	27.19	0.14	27.17	0.13	.9	27.13	0.11	27.25	0.16	.5	.044[a]
AD	23.48	0.30	22.64	0.20	.021[a]	23.41	0.22	22.30	0.24	9×10^{-4}[a]	.018[a]

Note:—See On-line Table 5*A* for units and key.

[a] Differences significant at $P < .05$.

Along with the direct effects, $\varepsilon4 \times$ sex effects are additionally modeled; p−value for $\varepsilon4 \times$ sex gives the significance of the interaction term alone.

On-line Table 6*A*: Baseline CSF and cognitive values: male and female *APOE* effects

	Male					Female				
	$\varepsilon4^-$	SE	$\varepsilon4^+$	SE	*P*	$\varepsilon4^-$	SE	$\varepsilon4^+$	SE	*P*
Aβ										
HC	220.60	7.52	154.72	11.75	2×10^{-5}[a]	217.09	7.22	158.97	16.14	.002[a]
MCI	190.47	6.45	140.82	6.29	3×10^{-7}[a]	158.86	11.44	147.42	8.65	.498
AD	156.97	10.06	129.27	6.13	.023[a]	178.96	10.97	137.93	6.33	.004[a]
p-τ										
HC	24.22	2.37	32.58	3.70	.067	21.78	1.99	33.67	4.45	.018[a]
MCI	29.95	2.32	39.38	2.26	.005[a]	29.25	4.03	44.06	3.05	.015[a]
AD	52.31	5.75	41.23	3.51	.107	35.09	4.97	40.89	2.87	.340
τ										
HC	70.38	4.65	71.64	7.26	.886	64.07	4.47	98.54	10.00	.003[a]
MCI	87.02	7.35	110.58	7.16	.025[a]	82.02	15.85	140.99	11.98	.014[a]
AD	134.84	14.52	105.50	8.98	.093	111.76	21.08	138.13	12.43	.310
CDR-SB										
HC	0.01	0.01	0.00	0.01	.515	0.05	0.02	0.06	0.03	.841
MCI	1.48	0.09	1.73	0.08	.049[a]	1.45	0.11	1.70	0.10	.135
AD	3.68	0.34	4.09	0.21	.317	4.61	0.31	4.33	0.21	.476
ADAS-Cog										
HC	6.53	0.29	6.69	0.49	.783	5.69	0.36	6.38	0.59	.323
MCI	10.78	0.40	12.40	0.37	.004[a]	9.96	0.60	12.72	0.55	.003[a]
AD	15.94	1.13	19.45	0.70	.012[a]	19.33	1.17	17.32	0.81	.174
MMSE										
HC	29.00	0.11	29.05	0.18	.816	29.14	0.10	29.36	0.17	.273
MCI	27.16	0.17	27.13	0.16	.889	27.16	0.23	26.41	0.21	.030[a]
AD	24.07	0.44	23.17	0.28	.091	22.78	0.41	23.68	0.28	.082

Note:—This table shows the results of modeling the effects of *APOE* $\varepsilon4$ on baseline values, independently in men and in women. Units are pg/mL for CSF values. All values are covaried for age; clinical values are additionally covaried for education.

SE indicates standard error; $P = P$ value for paired comparisons (significance of the effect, ie, the difference in the expected values).

[a] Differences significant at $P < .05$.

Numbers of participants are shown in On-line Table 7.

On-line Table 6*B*: Baseline CSF and cognitive values: *APOE* $\varepsilon4^-$ and *APOE* $\varepsilon4^+$ sex effects

	$\varepsilon4^-$					$\varepsilon4^+$				
	Male	SE	Female	SE	*P*	Male	SE	Female	SE	*P*
Aβ										
HC	220.44	7.69	217.15	7.16	.756	155.72	11.68	157.60	15.58	.924
MCI	190.06	7.63	165.33	13.00	.105	142.51	5.27	141.45	6.96	.910
AD	157.02	13.33	182.59	17.00	.258	128.84	4.86	137.32	5.87	.273
p-τ										
HC	24.02	1.80	21.63	1.67	.334	32.98	5.31	34.58	7.08	.859
MCI	29.88	2.20	31.23	3.75	.758	39.29	2.38	43.17	3.14	.363
AD	51.21	5.92	34.79	7.55	.108	41.96	2.96	40.52	3.58	.759
τ										
HC	70.20	4.15	63.63	3.86	.251	72.80	10.03	99.46	13.37	.127
MCI	87.96	6.49	88.67	10.96	.955	107.50	8.87	140.94	11.62	.036[a]
AD	134.47	19.88	111.87	25.35	.497	105.89	8.35	137.72	10.15	.019[a]
CDR-SB										
HC	0.01	0.01	0.05	0.01	.031[a]	0.00	0.02	0.05	0.02	.088
MCI	1.49	0.08	1.50	0.12	.924	1.73	0.08	1.64	0.11	.552
AD	3.72	0.32	4.68	0.32	.052	4.11	0.21	4.26	0.23	.633
ADAS-Cog										
HC	6.62	0.30	5.57	0.31	.021[a]	6.68	0.62	6.45	0.63	.798
MCI	10.89	0.40	10.23	0.56	.335	12.36	0.40	12.39	0.54	.965
AD	15.74	1.19	19.58	1.19	.036[a]	19.43	0.70	17.32	0.79	.055
MMSE										
HC	28.92	0.11	29.25	0.11	.038[a]	28.95	0.17	29.43	0.18	.063
MCI	27.09	0.16	27.15	0.23	.826	27.21	0.16	26.38	0.21	.003[a]
AD	24.12	0.43	22.70	0.44	.036[a]	23.12	0.26	23.75	0.29	.121

Note:—See On-line Table 6*A* for units and key. This table shows the results of modeling the effects of sex on baseline values, independently in $\varepsilon4$ noncarriers and in carriers.

[a] Differences significant at $P < .05$.

On-line Table 7: Number of participants with baseline CSF and cognitive data

	Male		Female	
	$\varepsilon4^-$	$\varepsilon4^+$	$\varepsilon4^-$	$\varepsilon4^+$
CSF[a]				
HC	39	16	45	9
MCI	58[c]	61[d]	20	35
AD	13	35[e]	8	24[f]
Cog[b]				
HC	84	30	79	29
MCI	106	122	54	66
AD	24[g]	60	23	49

[a]CSF: Aβ, p-τ, and τ.
[b] Cog: CDR-SB, ADAS-Cog, and MMSE.
[c–f] For τ. [c]57, [d]60, [e]34, [f]23.
[g] For ADAS-Cog: 23.