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Role of family history for Alzheimer biomarker abnormalities in the adult children study

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Abstract

Objective—To assess whether family history (FH) of Alzheimer's disease (AD) alone influences AD biomarker abnormalities.

Design—Adult Children Study (ACS).

Setting—Washington University's Knight Alzheimer's Disease Research Center.

Participants—Cognitively normal middle to older age individuals with and without a FH for AD (n=269).

Main Outcome Measures—Clinical and cognitive measures, magnetic resonance imaging (MRI)-based brain volumes, diffusion tensor imaging (DTI)-based white matter microstructure, cerebrospinal fluid (CSF) biomarkers, and molecular imaging of cerebral fibrillar amyloid with positron emission tomography (PET) using the [^{11}C] benzothiazole tracer, Pittsburgh Compound-B (PIB).

Results—A positive FH for AD was associated with an age-related decrease of CSF Aβ_{42}; the ε4 allele of apolipoprotein E (APOE4) did not alter this effect. Age-adjusted CSF Aβ_{42} was decreased for individuals with APOE4 compared with those without, and the decrease was larger for individuals with a positive FH compared with those without. The variation of CSF tau and PIB mean cortical binding potential (MCBP) increased by age. For individuals younger than 55, an age-related increase in MCBP was associated with APOE4, but not FH. For individuals older than 55, a positive FH and a positive APOE4 implied the fastest age-related increase in MCBP. A positive FH was associated with decreased fractional anisotropy from DTI in the genu and splenium of the corpus callosum.

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Conclusion—Independent of APOE4, FH is associated with age-related change of several CSF, PIB and DTI biomarkers in cognitively normal middle to older age individuals, suggesting that non-APOE susceptibility genes for AD influence AD biomarkers.

Recent advances suggest that Alzheimer's disease (AD) has a lengthy period in which cerebral lesions gradually accumulate in the absence of symptoms, eventually causing sufficient synaptic and neuronal damage to result in symptomatic AD.[1–5] Since 2005, "Antecedent Biomarkers for AD: The Adult Children Study" (ACS) has enrolled a cohort of cognitively normal 43- to 76-year old individuals in an extensive study of biomarkers for AD prior to its symptomatic stages. In addition to clinical and cognitive measures, a broad spectrum of candidate antecedent biomarkers for AD were assessed, including magnetic resonance imaging (MRI)-based brain volumes, diffusion tensor imaging (DTI)-based measures of white matter microstructure, cerebrospinal fluid (CSF), and molecular imaging of cerebral fibrillar amyloid with positron emission tomography (PET) using the [^{11}C] benzothiazole tracer, Pittsburgh Compound-B (PIB). Because the ACS cohort is cognitively normal, changes in these well established biomarkers for AD likely represent the insidious pathogenesis of AD well before the development of symptoms, i.e., during the preclinical stage of AD.

The ACS cohort is stratified by family history (FH) for AD to genetically enrich the participants at risk of AD. Therefore, analysis on FH and biomarkers allows a linkage of biomarker abnormality to susceptibility genes for AD, especially non-APOE genes (i.e., PICALM, CR1, and CLU discovered from recent genome-wide association studie[6–7]) if the effect of FH is independent of APOE. Whereas several studies reported changes in isolated biomarkers with relatively small samples of elderly normal individuals with a FH of AD[8–10] or APOE4[11], the ACS facilitates a comprehensive analysis of both FH and APOE for a wide array of candidate antecedent biomarkers in cognitively normal middle to older age (43 to 76 y) individuals.

The objective of this report is to assess whether FH alone conveys AD risk beyond that of APOE4 by examining the influence of FH for AD, both together and independent of APOE4, on biomarker abnormalities using the baseline data of the ACS.

METHODS

PARTICIPANTS

As of October, 2009, the ACS cohort included 269 community-living volunteers from the greater St. Louis metropolitan area. Recruitment primarily was through word-of-mouth and personal inquiries. A positive FH for AD is defined as at least one biological parent with age at onset for dementia of the Alzheimer type (DAT) below 80 y, and a negative FH is defined as both biological parents living to age 70 or greater without DAT. If a parent living to age 70 without DAT later developed DAT by age 80, the participant is reassigned to the positive FH group. About one-third of the participants were children of parents enrolled in longitudinal studies of the Washington University (WU) Alzheimer's Disease Research Center (ADRC). Eligibility criteria for the ACS were age 45 to 75 (two early enrollees were 43.47y and 76.42y), availability of an informant who knew the participant well, cognitively normal (defined as Clinical Dementia Rating (CDR)[12]=0), and willingness in principle to complete all procedures. Comorbid conditions, including depressive features short of major affective disorder, were acceptable if clinically stable at time of enrollment. Exclusion criteria included conditions such as end stage cancer or renal disease that would preclude longitudinal participation and/or confound cognitive assessment or membership in families with a dominantly inherited pattern of AD and/or a known causative mutation for AD. The WU Human Research Protection Office approved the study.

CLINICAL AND COGNITIVE ASSESSMENTS

The primary clinical assessment protocol is that of the National Alzheimer Coordinating Center Uniform Data Set (UDS).[13] Additional clinical information, such as an assessment of autobiographical memory using events in which the participant recently engaged,[14] also was obtained. The standard definitions and criteria (e.g., Diagnostic and Statistical Manual 4th ed.[15][DSM IV]) of the UDS for detection of dementia and its differential diagnosis were used.[16] The presence or absence of dementia and, when present, its severity was operationalized with the CDR. [12] The CDR is based on the judgment of an experienced clinician with informant information and examination of the participant, as to whether the individual performs accustomed activities at his or her previously attained level[17] and was completed independently of neuropsychological test results. The CDR is be highly reliable[18–20] and sensitive and accurate for even very mild cognitive decline caused by AD.[17, 21–22] The clinical assessment takes 90 minutes to complete.

Participants completed psychometric testing 1 to 2 weeks after they received the clinical assessment. The five cognitive domains assessed in the 2-hour battery are episodic memory (Wechsler Memory Scale III [WMS-III] Logical Memory I, II and Verbal Paired Associates I,[23] Free and Cued Selective Reminding[24]), working memory (WMS-III Letter-Number Sequencing, Auditory Consonant Trigrams,[25] Reading Span[26]), semantic knowledge (Wechsler Adult Intelligence Scale III [WAIS-III] Similarities and Information,[27] Animal Naming[28]), executive function and attention (Trailmaking Test A and B,[29] Simon Task,[30] Switching Task[31]), and visuospatial ability (WAIS III Block Design, [27] Benton Line Orientation,[32] Woodcock-Johnson Visual Relations[33]). The clinical and cognitive assessments are obtained at baseline and every 3 years thereafter except for participants age 65 y or older, when they are obtained annually.

CSF COLLECTION AND ANALYSIS

CSF (20–30 mL) was collected by routine lumber puncture (LP), free from any blood contamination in polypropylene tubes at 8:00 AM after overnight fasting as previously described. [34] The samples were analyzed for total tau, tau phosphorylated at threonine-181 ($ptau_{181}$), and amyloid beta(1–42) ($A\beta_{42}$) by commercial enzyme-linked immunosorbant assay (ELISA) (Innotest, Innogenetics, Ghent, Belgium). CSF $A\beta_{40}$ was assayed by ELISA as previously described.[35] For all CSF measures, samples were continuously kept on ice and assays were performed on sample aliquots after a single thaw following initial freezing.

IMAGE ACQUISITION AND PROCESSING

MRI scans were obtained on either a Sonata 1.5T, Vision 1.5T, or Trio 3.0T scanner (Siemens Corporation). Structural MRI processing steps are described in detail previously[36–38] and include motion correction, averaging across scans, atlas transformation, and inhomogeneity correction. Regional volumes were obtained via the Freesurfer image analysis suite (Version 4.1.0, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts). The regions-of-interest (ROIs) are detailed elsewhere.[37] A comparison between the Vision 1.5T and Trio 3T scanners of Freesurfer-derived volumes yielded an average intraclass correlation of 0.81.[37] Analysis was done on adjusted volumetric measures after regressing for the effect of scanner platform.

DTIs were collected at 3T for the assessment of white matter microstructural integrity (2×2×2mm voxels, TR=9900ms, TE=102ms, flip angle=90deg, b-values scaled up to 1400 maximum, using 23 diffusion encoding directions). Data were collected in two 6 minute runs. Quantitative images of mean diffusivity, fractional anisotropy, and axial and radial diffusivity for ROIs were computed as previously described.[39]

PET PIB imaging and analysis procedures have been reported elsewhere.[40] Brain PET imaging was conducted using a Siemens 961 HR ECAT PET scanner (CTI, Knoxville, KY) or a Siemens 962 HR+ ECAT PET scanner. Radiochemical synthesis of [^{11}C]PIB was carried out according to published literature.[41] After a transmission scan to measure attenuation, approximately 12 mCi of [^{11}C]PIB was administered intravenously simultaneous with initiation of a 60-minute dynamic PET scan in three dimensional mode (septa retracted; 24 × 5 seconds frames; 9 × 20 seconds frames; 10 × 1 minute frames). The measured attenuation factors, scatter correction and a ramp filter were employed to reconstruct the dynamic PET images. PIB image analysis was performed for specific ROIs as detailed previously.[40,42] The cerebellum was chosen as the reference region because of little specific binding of PIB.[41] The Logan analysis[42] yields a tracer distribution volume ratio (DVratio), resulting in estimates to the binding potential (BP) for each ROI: BP = DVratio – 1.[40] The BP values from the prefrontal cortex, gyrus rectus, lateral temporal, and precuneus ROIs were averaged to calculate a mean cortical binding potential (MCBP).[40]

ATTENTIONAL ASSESSMENT

A 2-hour attentional battery was administered, separate from the psychometric testing. The attentional control tasks were computation span,[43] letter rotation span,[44] Stroop,[45] and a process dissociation task.[45] The two span tasks involve participants making a series of true/false judgments, with the working memory component being to remember in order the parts of the stimulus across the judgments. The Stroop is a computerized color naming task, which includes 60 trials for the congruent (e.g., BLUE in BLUE), neutral (e.g., DEEP in BLUE), and incongruent conditions (e.g., RED in BLUE). The process dissociation task places recollection in direct conflict with familiarity via opposition procedures during retrieval.[46] A Consonant Vowel-Odd Even Switching (CVOE) task[47] was also administered.

GENOTYPING

DNA was extracted from peripheral blood samples using standard procedures. APOE genotyping was performed as previously described.[48]

STATISTICAL ANALYSIS

The analysis was done on ACS baseline data. Each marker was analyzed as a function of age, FH (yes or no) and APOE4 genotype (ε4 allele present or absent) by the Analysis of Covariance[49]. The interactive effects among these three risk factors were first tested and reported if confirmed. Otherwise independent effects of each risk factor were reported. Preliminary analysis suggested differential variances as a function of age (i.e., younger vs. older than 55), which were tested and then accommodated in the associational analyses with FH and APOE4 if confirmed. PROC MIXED/SAS[50] was used to implement these analyses. Satterthwaite's approximation[49] was used to estimate the denominator degrees of freedom in the approximate *F* or *t* tests.

RESULTS

Table 1 presents the demographics of the entire sample and subgroups with each modality of assessments. All 269 completed baseline clinical and psychometric assessments. 217 (81%) had a LP to obtain CSF, 206 (77%) completed PET PIB, 147 (55%) had a MRI, and 232 (86%) completed the attentional battery. One hundred and eight (40%) participants completed all baseline procedures (clinical, psychometric, attention, LP, MRI, PET PIB).

As shown in Figure 1, the mean level of CSF $A\beta_{42}$ decreased significantly with age at a rate of −7.76 pg/mL per year (SE=2.14 pg/mL, p=0.0004) in those with a positive FH but not in those without (p=0.35). The presence of an APOE4 allele did not alter the effect of FH on

the age-related decrease in CSF $A\beta_{42}$ (p=0.5). Those with an ε4 allele had lower levels of age-adjusted CSF $A\beta_{42}$ compared with those without (p<0.0001), and the decrease was larger if FH was positive compared with negative (F(1, 209)=5.29, p=0.02). Sensitivity analyses with multiple imputations[51] on CSF $A\beta_{42}$ confirmed these findings.

The variance increased among individuals age 55 or older when compared with the younger age group for CSF tau ($\chi^2(1) = 9.71$, p=0.002) and MCBP ($\chi^2(1) = 98.35$, p<.0001). Table 2 presents the estimated slope (per year of age) for MCBP and CSF tau on younger (<55 y) and older individuals (>=55 y) as a function of FH and APOE4. No significant effect of FH or APOE4 was found for CSF tau on the age-related rate of change, but individuals with a positive FH had a higher level of CSF tau than those otherwise (F(1,152)=4.60, p=0.03) at age 55. For individuals younger than 55, MCBP increased by age at a significantly faster pace for individuals with APOE4 compared with those without APOE4 (F(1, 62.4)=4.72, p=0.03), eventually leading to a higher level of MCBP for those with APOE4 compared to without (p=0.01). For individuals older than 55, a trend (p=0.09) was found to suggest a faster age-related increase of MCBP for individuals with APOE4 compared with those without APOE4. Individuals with a positive FH and a positive APOE4 had the largest age-related increase of MCBP (p<0.0001).

Brain volumes as determined by MRI decreased with age, but the difference was not statistically significant by FH (total cerebral brain volume F(1, 132)= 0.90, p=0.34; right hippocampal volume F(1, 139)=1.85, p=0.18; left hippocampal volume F(1, 139)= 0.31, p=0.58).

From a subsample of 165 participants who had DTI data, the age-adjusted mean level of fractional anisotropy was lower for individuals with a FH of AD when compared with those without in the genu (F(1,142)=3.91, p=0.05) and in the splenium (F(1,142)=4.12, p=0.04) of the corpus callosum. In the gyrus rectus, individuals with APOE4 had lower level of fractional anisotropy (F(1, 142)=4.75, p=0.03) and higher level of radial diffusivity (F(1, 142)=4.3, p=0.04) than those without APOE4. Age-related increase in radial diffusivity in the precuneus is faster if FH was positive compared with negative only among individuals with APOE4 (F(1,142)=4.67, p=0.03).

The mean performance level of auditory consonant trigrams decreased significantly with age at the rate of −0.411/year (SE=0.125, p=0.001) for these with a positive FH but not for those with a negative FH (p=0.52).

115 and 52 participants reported their mother and father's age of onset of DAT, respectively. An earlier mother's age of onset was correlated with larger reaction time difference between pure blocks and switched blocks of trials from the CVOE task[46] (Spearman r=−0.21, p=0.04), and an earlier father's age of onset was correlated with poorer performance in WAIS III Similarities (r=0.44, p=0.01).

Exploratory correlational analyses across the entire modalities of biomarkers confirmed those previously reported in the literature[52–54] Significant correlations between MCBP and CSF biomarkers (tau r=0.22, $ptau_{181}$ r=0.19, and CSF $A\beta_{42}$ r=−0.41) were observed in the entire ACS cohort. Some of these are potentially modulated by age, but not by FH. In the younger cohort (age <55 y), MCBP was not significantly correlated with CSF biomarkers or brain volumes. In the older cohort (age at least 55 y), however, MCBP was significantly correlated with CSF biomarkers ($A\beta_{42}$ r=−0.53, tau r=0.24, $ptau_{181}$ r=0.22). Further, CSF and imaging biomarkers were correlated with Stroop performance in the younger sample only in two occasions ($A\beta_{42}$ with greater interference in RTs r = −0.28, MCBP with Simon coefficient of variation (COV) r=0.31). In the older sample, however, CSF and imaging biomarkers were correlated with poorer performance across many attention measures (e.g.,

$A\beta_{42}$ with task switching COV r = −0.22 and interference errors r = −0.20; MCBP with task switching COV r =0.19, interference RT r=0.17 and errors r =0.19, incongruent errors r=0.19, and with Simon COV r=0.17). Brain volumetric measures were also correlated with attentional and working memory measures (e.g., total cerebral brain volume with rotation span r = 0.22; left hippocampal volume with rotation span r=0.35) in the older sample. Because of a large number of correlations assessed across all modalities of markers, these findings were subject to a higher false positive rate (than 5%). Therefore they were preliminary and will only serve to generate scientific hypotheses that need to be critically tested in future studies.

Analyses were repeated on the subgroup of individuals who completed all procedures. The findings were consistent with the reported statistics, although a severe loss of statistical power resulted in losses of statistical significance.

DISCUSSION

FH for AD as a risk factor for AD and cognitive decline has been well documented[55–57] many times jointly with APOE4 genotypes. Several studies reported reduced gray matter volume[8] and brain glucose metabolism[9] as well as increased semantic memory activation[10] in normal individuals with a maternal history of AD. These reports, however, focused mostly on a small number of biomarkers assessed on the elderly population aged 65 or older. We reported the influence of FH for AD for a wide array of candidate antecedent biomarkers in the ACS cohort of cognitively normal middle to older age (43 to 76 y) individuals. In addition to clinical and cognitive measures, we analyzed MRI-based brain volumes, DTI-based estimates of white matter microstructure, biofluid assays, and molecular imaging of fibrillar amyloid measure with PET PIB.

No difference was found on cognitive and clinical measures as a function of FH of AD among cognitively normal ACS individuals. The only possible exception comes from the performance on the auditory consonant trigrams,[25] and the difference is no longer significant after multiplicity adjustment.

FH for AD, however, was associated with several CSF and imaging biomarkers in the cognitively normal ACS cohort, suggesting their potential role as antecedent biomarkers of AD. These findings support the design of the ACS that genetically enriched the sample of cognitively normal individuals at risk of AD by FH, and are consistent with recently reported meta-analysis of DTI[58]. The current results point to the likelihood of non-APOE susceptibility genes for AD, consistent with recent reports of multiple risk genes (*PICALM*, *CR1*, and *CLU*) of AD from several genome-wide association studies.[6–7]

Together, our data across a wide spectrum of biomarkers on a cohort of cognitively normal middle to old age (from 43 to 76 years) individuals, albeit cross sectional, suggest that AD has a lengthy period during which cerebral lesions gradually accumulate in the absence of symptoms (i.e., preclinical AD). Eventually these lesions are expected to cause sufficient synaptic and neuronal damage to result in symptomatic AD. More specifically, among cognitively normal middle to old age individuals, age-related changes in brain $A\beta_{42}$ metabolism as well as local microstructural characteristics of water diffusion in certain brain regions are influenced by FH of AD, suggesting that they are likely early events in AD pathogenesis. Significant disruptions in CSF tau and $ptau_{181}$ metabolism, reflecting other changes in the structural integrity of axonal tracts, likely occur after brain $A\beta_{42}$ initially aggregates and then increases as amyloid accumulates. Interestingly, CSF $A\beta_{42}$ and MCBP are correlated with several of the attentional measures. These correlations suggest that

antecedent biomarker changes likely have a deleterious effect on neuronal and attentional integrity.

For CSF tau and MCBP, we also observed increased variability as a function of age, which was further accompanied by an accelerated age-related increase. This finding, although cross sectional, is consistent with several longitudinal studies in which an accelerated cognitive decline [59–60] preceding the onset of DAT was reported. Whereas cognitive changes might be later events in the neurodegenerative sequence prior to the onset of DAT, changes in CSF and PIB biomarkers have the potential to capture the earliest possible antecedent events.

This study has several limitations. First, the ACS is an observational study on a convenience sample. Unobserved factors could contribute to the differences of subgroups with each modality of measures. The interpretation of the findings thus has the standard limitations of observational studies. Second, a lack of longitudinal data on biomarkers prevents us from understanding the cascade of early events in AD pathogenesis. The ongoing longitudinal follow-up of clinical and biomarker measures on the ACS cohort will provide much more insight to the preclinical progression of AD.

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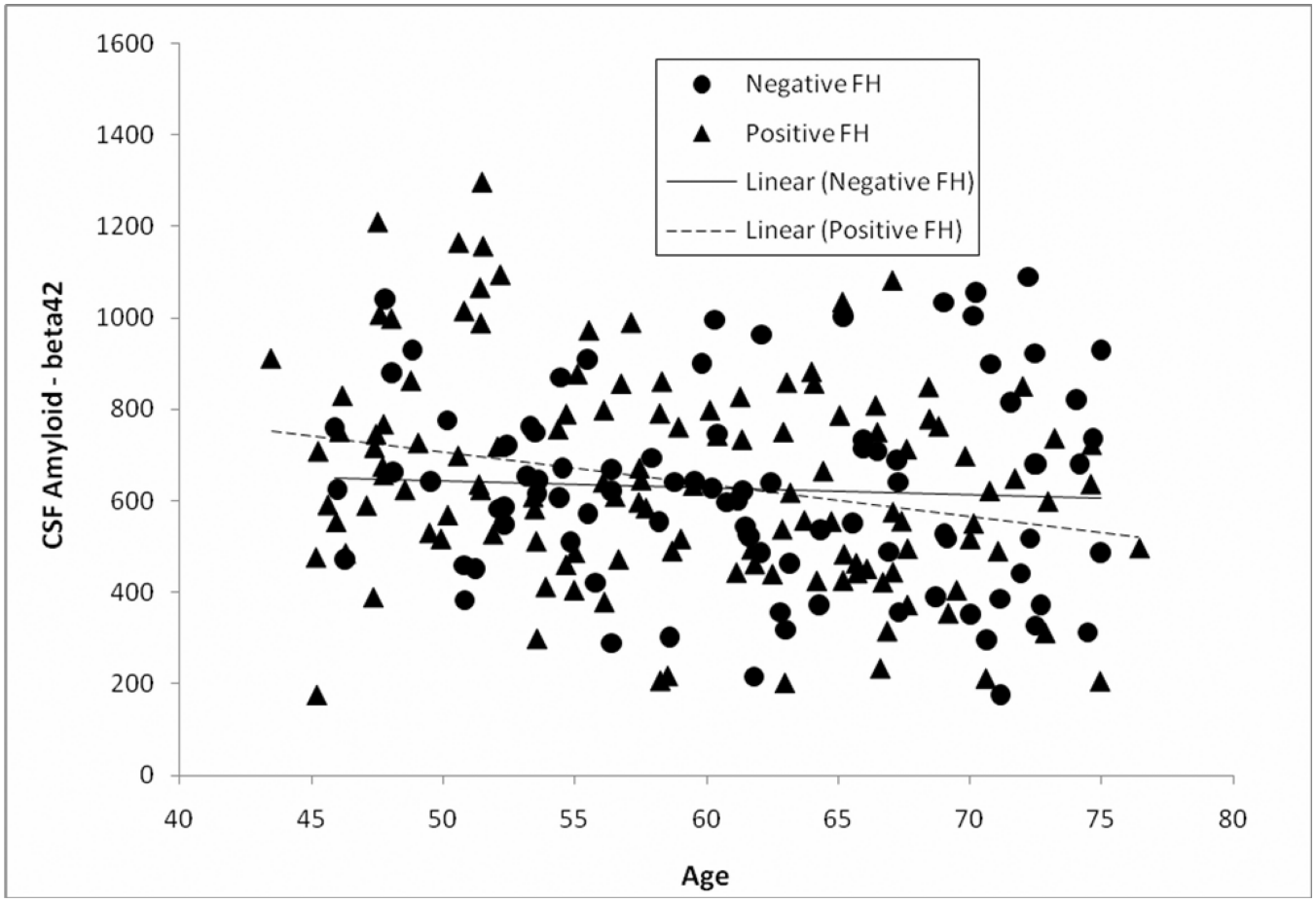

Figure 1.
CSF Amyloid-beta42 as a functions of age and family history.
(See Table 1 for the sample size and demographics of the subgroup)

Table 1

Characteristics of ACS Cohort at Baseline

	Family history of AD, N=160					No family history of AD, n=109				
	Clinical N=160	**CSF N=126**	**Imaging N=128**	**Attention N=136**	**All N=55**	**Clinical N=109**	**CSF N=91**	**Imaging N=94**	**Attention N=96**	**All N=53**
N: age<=54/age >=55	54/106	46/80	40/88	45/91	18/37	30/79	26/65	26/68	23/73	14/39
Female: (%)	73.13	72.22	74.22	75.74	85.45	63.30	61.54	62.77	61.46	69.81
MMSE: Mean (SD)	29.22 (1.11)	29.31 (1.02)	29.30 (1.04)	29.23 (1.12)	29.25 (1.09)	29.25 (1.10)	29.20 (1.16)	29.23 (1.09)	29.26 (1.07)	29.19 (1.18)
Education: Mean (SD)	15.99 (2.34)	16.15 (2.33)	16.03 (2.35)	15.91 (2.33)	16.00 (2.15)	16.11 (2.67)	16.15 (2.64)	16.14 (2.71)	16.02 (2.70)	15.94 (2.60)
APOE4 + (%)	49.38	49.21	48.44	49.26	56.36	23.58	26.37	25.53	25.00	33.96

Abbreviations: APOE4, apolipoprotein E4; APOE4 +, presence of an APOE4 allele; MMSE, Mini mental state examination; Imaging, MRI or PIB PET.

Table 2

Estimated slope (per year of age, 95% confidence interval) for MCBP and CSF tau on younger (<55 y) and older (>=55 y) individuals as a function of FH and APOE4

FH	APOE4	MCBP: Age<55 y (95% CI)	MCBP: Age>=55 y (95% CI)	tau (pg/mL): Age<55 y (95% CI)	tau (pg/mL): Age>=55 y (95% CI)
−	−	−0.0008 (−0.0087, 0.0071)	0.0067 (0.0016, 0.0118)	4.08 (−8.67, 16.83)	5.62 (0.59, 10.65)
−	+	0.0133 (0.0021, 0.0244)	0.0086 (0.0007, 0.0165)	−18.92 (−39.35, 1.52)	7.75 (0.42, 15.07)
+	−	0.0028 (−0.0038, 0.0095)	0.0033 (−0.0029, 0.0095)	2.15 (−8.30, 12.60)	1.25 (−4.22, 6.71)
+	+	0.0065 (0.0006, 0.0123)	0.0126 (0.0063, 0.0188)	5.18 (−4.54, 14.91)	5.04 (−1.04, 11.12)

The model for each biomarker included all terms FH, APOE4, younger age(=age for individuals younger than 55 y and 0 otherwise), older age (=age for individuals at least 55 y and 0 otherwise), and all their interactions. Significant terms for MCBP are APOE4*(younger age) (p=0.03), older age (p<0.0001), younger age (p=0.01), and APOE4 (p=0.01). Significant terms for CSF tau are FH (p=0.03) and older age (p=0.002). See Table 1 for the sample sizes and demographic characteristics of subgroups.