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Effect of apolipoprotein E4 on clinical, neuroimaging, and biomarker measures in noncarrier participants in the Dominantly Inherited Alzheimer Network

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ABSTRACT

The apolipoprotein E ε4 allele (*APOE*4) is the major genetic risk factor for sporadic Alzheimer's disease (AD). *APOE*4 may have effects on cognition and brain atrophy years before the onset of symptomatic AD. We analyzed the effects of *APOE*4 in a unique cohort of young adults who had undergone comprehensive assessments as part of the Dominantly Inherited Alzheimer Network (DIAN), an international longitudinal study of individuals from families with autosomal dominant AD. We analyzed the effect of an *APOE*4 allele on cognitive measures, volumetric MRI, amyloid deposition, glucose metabolism, and on cerebrospinal fluid levels of AD biomarkers in 162 participants that did not carry the mutant gene (noncarriers). *APOE*4+ and *APOE*4− mutation noncarriers had similar performance on cognitive measures. Amyloid deposition began at an earlier age in *APOE*4+ participants, whereas hippocampal volume was similar between the groups. These preliminary findings are consistent with growing evidence that the APOE4 allele may exert effects in midlife years before symptom onset, promoting amyloid deposition before altering cognitive performance or brain structure.

1. Introduction

Alzheimer's disease (AD), the most common age-related progressive neurodegenerative disorder, typically becomes symptomatic in people older than age 65 years (late-onset AD [LOAD]); less commonly, symptom onset may be earlier. People with the much less common autosomal dominant form of AD (ADAD) typically develop symptoms at an early age, generally before age 60 years and as early as the third decade of life (e.g., Snider et al., 2005). The Dominantly Inherited Alzheimer Network observational study (DIAN-OBS) began in 2008 with funding from the National Institute of Aging. This international multicenter study supports the collection of longitudinal clinical, cognitive and biomarker data and tissue from over 500 families with ADAD worldwide (Morris et al., 2012). Importantly, family members are enrolled in ADAD whether or not they carry the ADAD-causing mutation. Only 17% of DIAN participants do know their mutation status, so many mutation noncarriers (NCs) participate in the study and undergo the same evaluations as mutation carriers, providing a unique cohort in which clinical, cognitive, and biomarker assessments are available in cognitively normal young adults.

Although the details of the pathogenic cascade that lead to AD are still under investigation, many studies have demonstrated a consistent pattern of changes in molecular biomarkers in both sporadic AD and ADAD; these changes may begin 20–25 years before the onset of symptoms. The DIAN study has been useful in this regard (Bateman et al., 2012; Benzinger et al., 2013; Cash et al.,

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2013; Fagan et al., 2014; Wang et al., 2015), as have large cohorts in sporadic AD, including the Alzheimer Disease Neuroimaging Initiative (ADNI, reviewed in the study by Weiner et al., 2017), the Knight Alzheimer Disease Research Center (Fagan et al., 2009; Morris et al., 2009; Vos et al., 2013), and several others (Epelbaum et al., 2017). The results of most, but not all, studies have been consistent with the amyloid hypothesis, demonstrating a temporal sequence with initial changes in the levels of amyloid beta peptide in cerebrospinal fluid (CSF), followed by changes in positron emission tomography (PET) amyloid imaging, then alterations in hippocampal volume, glucose metabolism, and CSF tau, and then subtle cognitive changes. Symptomatic onset occurs ~20 years after the first detection of changes in amyloid (Bateman et al., 2012; Jack et al., 2010). Some studies have suggested that cognitive performance early in life, decades before changes in amyloid biomarkers, can predict subsequent risk for symptomatic AD in late life. For example, the Nun Study (Riley et al., 2005) demonstrated a relationship between idea density in the second and third decades of life and presence of neuropathological AD in late life, suggesting that risk for AD or even AD pathogenic cascades may begin early in the life span.

The ε4 allele of apolipoprotein E (APOE4) remains the major genetic risk factor for sporadic AD (Burke and Roses, 1991; Corder et al., 1993; Strittmatter et al., 1993). Individuals homozygous for the ε4 allele have a greater than 10-fold higher risk of developing AD than those without an ε4 allele, although this effect is stronger in Caucasians than in Hispanics or African Americans (Farrer et al., 1997). APOE has two other isoforms: APOE3 and APOE2; the APOE2 allele may reduce the risk of AD (Talbot et al., 1994). The ε4 allele is associated with higher risk of both early-onset and late-onset sporadic AD, age-related cognitive impairment, and with cardiovascular disease and type II diabetes (El-Lebedy et al., 2016). The APOE4 allele can also accelerate development of cortical Aβ deposition and decreases in CSF Aβ42 levels in individuals who have ADAD (Lim et al., 2016), as well as in sporadic cases (Grimmer et al., 2010; Jack et al., 2013; Morris et al., 2010; Villemagne et al., 2011).

The aim of this study was to look at the effect of APOE4 genotype on clinical, cognitive, and biomarker measures in the young cohort recruited for the DIAN-OBS, specifically focusing on those participants who did not carry an ADAD-causing mutation. We hypothesized that in these young NC DIAN-OBS participants, the presence of an APOE4 allele would affect brain structure and AD biomarkers in individuals many years before the possible development of AD symptoms.

2. Materials and methods

2.1. Participants

All participants in the DIAN-OBS have a parent or consanguineous relative with a known mutation causing symptomatic AD. Participants enrolled in the DIAN-OBS participate in all assessments whether or not they carry the ADAD-causing mutation that affects their family. Participants are enrolled in the DIAN-OBS at 1 of 20 current international study sites and undergo uniform longitudinal assessments including clinical, cognitive, genetic, neuroimaging, and fluid biomarker measures (Morris et al., 2012; Moulder et al., 2013). For this analysis, we included baseline assessments from 162 DIAN-OBS participants who had study visits between February 9, 2009, and June 21, 2016, and who met the inclusion criteria, which included 1) confirmed as not having an ADAD causing mutation (NC), 2) normal cognition, defined as having a Clinical Dementia Rating (CDR) of 0, 3) having one or zero *APOE*4 alleles, and 4) having clinical and cognitive testing, and 5) completed biomarker studies including PET amyloid imaging with [^{11}C]Pittsburgh Compound B Pittsburgh Compound B (PiB), glucose imaging with [^{18}F] fluorodeoxyglucose (FDG-PET), magnetic resonance imaging (MRI) and CSF levels of AD biomarkers amyloid beta peptide 42 ($A\beta_{42}$), total tau, and phosphorylated tau ($ptau_{181}$) from the time-locked semiannual data freeze (DIAN datafreeze 11). All participants provided informed consent for study participation; the study was approved by the Washington University Human Research Protection Office.

2.2. Clinical assessments

The CDR (Morris, 1993) was used for the clinical assessment. Family and medical history and physical and neurological examinations were completed on all participants. Clinicians completing the CDR and clinical assessment were blinded as to mutation status. All participants included in this analysis had a global CDR rating of 0, indicating no cognitive impairment, at the assessment within 1 year of the completion of cognitive, imaging, and biomarker measures. Assessments in the DIAN-OBS are performed every 3 years for participants with normal cognition; data presented here are from the baseline (initial) assessment.

2.3. Neuropsychological testing

All participants completed a battery of neuropsychological tests as previously described (Storandt et al., 2014). Measures included tests of semantic memory (category fluency for animals and vegetables and letter fluency), episodic memory (word list recall immediate and delayed, Wechsler Memory Scale (WMS-R) logical memory immediate and delayed), and associative learning (pair binding, with scores reported for correct identification of intact pairs, new pairs, and mixed pairs) and tests of processing speed and executive function (Trailmaking Test parts A and B, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution) and the Mini-Mental State Examination.

2.4. Brain imaging

2.4.1. Structural brain imaging with MRI

The Alzheimer's Disease Neuroimaging Initiative (ADNI) structural MRI protocol (Jack et al., 2008) was used for acquisition. Every site underwent quality control assessment to insure acquisition conformity. A 3-Tesla scanner was used to acquire T1-weighted images (1.1 × 1.1 × 1.2 mm voxels). Images were screened by the ADNI imaging core for protocol compliance and artifacts. All MRI sessions were processed using FreeSurfer 5.3 to define cortical and subcortical regions of interest (ROIs). Regional volumes were corrected for head size using a regression approach (Buckner et al., 2004). These ROIs were used for the processing of PET imaging data. We selected the total hippocampal volume for statistical analyses as this region has been shown before to be sensitive to AD pathophysiology (Dickerson et al., 2001; Fox et al., 1996; Gordon et al., 2016).

2.4.2. Metabolic and amyloid imaging with PET

Brain metabolism was analyzed with FDG-PET and amyloid was imaged with PiB. To account for differences in spatial resolution across PET scanners, a scanner-specific filter was applied to achieve a common spatial resolution (8 mm). Both FDG and PiB were processed using the FreeSurfer-derived ROIs (Su et al., 2013). Data for both modalities were converted to regional standardized uptake value ratios (SUVRs) using the cerebellar cortex as a reference. A regional spread function technique (Rousset et al., 1998; Su et al., 2015) was used to partial volume correct the data. Global amyloid deposition was summarized using the average of regions previously

shown to be sensitive to AD pathology (Su et al., 2013, 2015). In addition, we examined PiB SUVRs, FDG SUVRs, and cortical thickness in the precuneus as this region has been shown to be consistently affected in AD (Benzinger et al., 2013; La Joie et al., 2012).

2.5. Biochemical analysis

Cerebrospinal fluid was collected by lumbar puncture in the morning after overnight fasting using standard protocols (Fagan et al., 2014). Levels of $A\beta_{42}$, total tau, and tau phosphorylated at threonine 181 ($ptau_{181}$) were measured using a multiplex bead-based immunoassay (AlzBio3, Fujirebio, Ghent, Belgium).

2.6. Statistical analysis

We conducted a cross-sectional mixed effects analysis of covariance at participant baseline visit to test if clinical, cognitive, imaging, and biomarker variables were different between the *APOE*4− and *APOE*4+ groups, as well as males and females. Family of origin was the random effect. Age was a covariate in the analyses because it is known to be a risk factor for NCs. Age was centered in all analyses to the mean of all participants. All tests were conducted at the 95% confidence level (alpha = 0.05) using PROC MIXED in SAS 9.4. Raw *p* values, not corrected for multiple comparisons, are provided; given the 23 comparisons performed, no findings were significant when corrected for multiple comparisons.

3. Results

3.1. Demographic characteristics

A total of 162 participants met eligibility criteria. Measures were obtained during a 2- to 4-day visit to a DIAN-OBS site. In a few cases, PET imaging was not performed during the visit; we excluded any PET data from the analysis if obtained more than 1 year from the other measures. The participants ranged in age from 19 to 69 years; mean age for all participants was 38.77 ± 11.68 years. Overall, there were 60.5% females and 39.5% males. The most common *APOE* genotype was *APOE*3/3; most of the participants who had an *APOE*4 allele were heterozygotes. Because of the limited number of participants with each specific *APOE* genotype, analyses were conducted comparing those with one *APOE*4 allele (*APOE*4+, 31.0% of the sample) to those who did not have an *APOE*4 allele (*APOE*4−, 69.0% of the sample). As shown in Table 1, *APOE*4+ and *APOE*4− groups had a similar age and gender distribution, although the *APOE*4− group was slightly younger than the *APOE*4+ group. There was a similar distribution of males and females in both groups and a similar distribution of ADAD-causing mutations (overall 66.7% were from families with a *PSEN1* mutation; 21.6% from families with an *APP* mutation, and 11.7% from families with a *PSEN2* mutation). Note that participants included in this analysis did not themselves carry the ADAD-causing mutation.

Table 1
Demographic features and genotype

	*APOE*4−	*APOE*4+
	Mean ± S.D. (Range)	Mean ± S.D. (Range)
	n = 118	n = 44
Age at clinical assessment (y)	37.18 ± 10.54 (19–66)	43.05 ± 11.38 (19–69)
Female/male (% female)	72/46 (61.0%)	26/18 (59.1%)
APOE genotype distribution	*APOE3/3*: 100 *APOE2/3*: 17 *APOE2/2*: 1	*APOE3/4*: 44
Family mutation distribution	*PSEN1*: 81 (68.6%) *PSEN2*: 11 (9.3%) *APP*: 26 (22.0%)	*PSEN1*: 27 (61.4%) *PSEN2*: 8 (18.2%) *APP*: 9 (20.4%)

Key: APOE, apolipoprotein E.
The table provides basic demographic information for the sample. Although the participants included here did not have an ADAD-causing mutation, the ADAD-causing mutation in the family is reported as this was included as a random effect in the statistical analysis to account for within and among family variability as families are clustered by mutation.

3.2. Effect of APOE4 alone on cognitive performance, imaging, or biomarker measures

Results of the cognitive, imaging, and biomarker measures are shown in Table 2. *APOE*4+ and *APOE*4− groups performed very similarly in most tests, although the *APOE4*− group generally had slightly superior scores in most cognitive tests. *APOE*4− participants performed slightly but significantly better than *APOE*4+ participants in the Mini-Mental State Examination and in one test of associative memory (identification of new/novel pairs in the pair-binding test) and in one of three tests of semantic fluency (category fluency vegetables) but not in two other similar tests (category fluency for animals and a letter fluency test). There were no significant differences between *APOE*4+ and *APOE*4− participants on volumetric MRI measures for the two regions most affected early in AD (precuneus and hippocampus) or in amyloid deposition (measured by binding to PiB) or on glucose metabolism in the precuneus. There were no differences between *APOE*4+ and *APOE*4− participants in levels of CSF biomarkers of AD pathology (Table 3).

3.3. Effect of APOE4 and age on cognitive performance

Because the participants in this cross-sectional study included a broad age range (19–69 years), we included age as a covariate in the analysis. Age did not have an effect on most of the cognitive test scores, with the exception of two speeded tasks, (WAIS-R digit symbol [Wechsler, 1981] and Trailmaking A), where increasing age was associated with slightly poorer scores. Age did not have an effect on category or letter fluency in our sample.

The only significant interactions between age and APOE4 status on cognitive testing was on the pair-binding associative learning tasks (pair binding—mixed). When we looked more closely at the effect of age and *APOE4* status, as shown in Fig. 1, we found that older *APOE4*+ participants tended to perform better than younger *APOE4*+ participants, whereas performance in *APOE*4− was largely stable with age. There were no other significant interactions for age with cognitive performance.

3.4. Age-related changes in brain structure and amyloid deposition in APOE4 carriers and noncarriers

Age was associated with an increase in amyloid deposition in precuneus and in the averaged global amyloid deposition regions (raw $p = 0.0022$ and $p = 0.0232$, respectively) and with a decline in glucose metabolism in the precuneus ($p = 0.0346$). As shown in Fig. 2A and B, there was a significant interaction between age and *APOE*4 status on amyloid deposition in both precuneus ($p = 0.0024$) and in the pooled cortical regions ($p = 0.0209$), with the *APOE*4+ participants having more rapid amyloid accumulation. The slopes began to diverge around 30–40 years of age, but this effect disappeared when we repeated the analysis without including those over the age of 50 years, so the older members of the cohort are driving this finding. There was no significant interaction between age and *APOE*4 for glucose metabolism.

Table 2
Clinical, cognitive, and imaging features by *APOE4* group

Cognitive test (range)	*APOE4*−	n	*APOE4*+	n	Raw *p* values		
	Mean ± S.D. (Range)		Mean ± S.D. (Range)		*APOE4*+ vs. *APOE4*−	Age	Age and *APOE4*
MMSE (0–30)	29.1 ± 0.9 (26–30)	117	28.8 ± 1.3 (25–30)	44	**0.0209**	0.3939	0.3636
Word list recall—immediate (0–16)	6.1 ± 2.0 (1–11)	117	5.6 ±1.8 (2–9)	44	0.4084	0.3639	0.9033
Word list recall—delayed (0–16)	3.6 ± 2.2 (0–13)	116	3.0 ± 1.9 (0–7)	44	0.7268	0.1501	0.2512
WMS-R logical memory—immediate (0–25)	15.3 ± 3.9 (6–24)	117	14.0 ± 4.0 (5–23)	44	0.7268	0.1501	0.2512
WMS-R logical memory—delayed (0–25)	14.4 ± 4.1 (3–24)	117	12.9 ± 4.3 (3–22)	44	0.1887	0.4649	0.8343
Pair binding—mixed (0–12)	8.0 ± 3.0 (1–12)	115	7.4 ± 3.2 (0–12)	43	0.1589	0.5453	**0.0341**
WAIS-R digit symbol (0–93)	61.8 ± 12.2 (35–93)	117	59.9 ± 9.8 (39–83)	43	0.6741	**0.0106**	0.2288
Trailmaking A (0–150 s)	21.3 ± 6.0 (11–38)	116	22.8 ± 6.5 (14–48)	44	0.6672	**0.0240**	0.9616
Trailmaking B (0–300 s)	57.2 ± 23.0 (28–149)	117	57.3 ± 22.7 (27–125)	44	0.6647	0.1267	0.8079
Category fluency—animals	22.6 ± 5.2 (11–36)	117	21.7 ± 5.3 (10–34)	44	0.3781	0.1750	0.5533
Category fluency—vegetables	15.5 ± 3.5 (4–24)	117	15.0 ± 3.9 (8–28)	44	**0.0351**	0.5503	0.9651
Category fluency—letter	39.8 ± 10.8 (15–65)	117	40.1 ± 11.4 (24–69)	44	0.3347	0.7210	0.3191
MRI volumes	Mean ± S.D. (range)	n	Mean ± S.D. (range)	n			
Precuneus thickness (mm)	2.37 ± 0.13 (2.05–2.68)	107	2.36 ± 0.12 (2.12–2.67)	37	0.2154	**0.0022**	0.0567
Hippocampal volume (mm^3)	8823.1 ± 806.6 (6886.1–10,699.5)	110	8740.1 ± 741.6 (6805.2–10,385.6)	39	0.7104	**0.0232**	**0.0280**
PET Measures (SUVR)	Mean ± S.D. (range)	n	Mean ± S.D. (range)	n			
PiB precuneus	1.12 ± 0.09 (0.89–1.30)	100	1.18 ± 0.15 (0.99–3.12)	35	0.5900	**0.0168**	**0.0024**
PiB global cortical amyloid deposition	1.04 ± 0.07 (0.85–1.21)	100	1.06 ± 0.08 (0.89–1.66)	35	0.7422	**0.0227**	**0.0209**
FDG precuneus	1.89 ± 0.15 (1.51–2.44)	97	1.90 ± 0.17 (1.58–2.44)	35	0.2043	**0.0346**	0.6904

Key: APOE, apolipoprotein E; FDG, fluorodeoxyglucose; MMSE, Mini-Mental State Examination; SUVR, standardized uptake value ratio; WMS-R, Wechsler Memory Scale; WAIS-R, Wechsler Adult Intelligence Scale-Revised.
Sample sizes vary by variable because for a variety of reasons; not all data were available for every participant. Raw *p* values shown are from the cross-sectional mixed effects analysis of covariance to test if clinical, cognitive, imaging, and biomarker variables were different between the *APOE4*− and *APOE4*+ groups, with centered age as a covariate. Values shown in BOLD are those that achieved significance ($p < 0.05$) in this exploratory study; note that these are raw *p* values that were not corrected for multiple comparisons; no findings were significant when corrected for the 23 comparisons performed. For cognitive testing, higher scores indicate better performance except for the timed tasks, Trailmaking A and Trailmaking B, where lower scores indicate better performance.

As expected, age was related to MRI volumetric measures, with an age-associated decrease in precuneus thickness ($p = 0.0022$) and hippocampal volume ($p = 0.0232$). There was a significant interaction between age and presence of an *APOE4* allele for hippocampal volume ($p = 0.0280$), but this interaction did not achieve statistical significance for precuneus thickness ($p = 0.0567$, see Fig. 2 C and D). Somewhat surprisingly, the trend was for a stronger effect of age on precuneus thickness and hippocampal volume in the *APOE4*− group.

3.5. Age effects on CSF biomarkers

As expected, there was an effect of age on CSF total tau ($p = 0.0044$) in all participants, but there was no effect of age on CSF $A\beta_{42}$ or on levels of ptau, and no interactions between age and APOE4 status. As shown in Fig. 3A, tau seemed to increase slowly with age in both *APOE4* groups.

4. Discussion

This study provides a cross-sectional analysis of a robust data set from a unique cohort of 162 cognitively normal adults ranging in age from 19–69 years that enables analysis of the effects of one *APOE4* allele on cognitive testing, brain structure and function, and biomarkers for AD. This is the first study to include cognitive, fluid, and imaging biomarkers in a young cohort. We found that cognitive performance, brain structure, and glucose metabolism were very similar between young *APOE4*+ and *APOE4*− individuals. We did not see an effect of APOE4 on fluid biomarkers, but did observe an increase in amyloid deposition with age as measured by PET imaging.

The lack of an effect of *APOE4* on cognitive performance is consistent with several other reports (Deary et al., 2002; Reiman et al., 2005, 2004; Turic et al., 2001; Wright et al., 2003; Yu et al., 2000), but in contrast to other studies that reported better performance on some measures for *APOE4* carriers in young adults (Alexander et al., 2007; Puttonen et al., 2003). These findings in young adults are in contrast to studies in older adults, where the presence of an *APOE4* allele has been associated with poorer cognitive performance even in the absence of dementia or mild cognitive impairment (reviewed in the study by Wisdom et al., 2011). The association of age with performance on speeded tasks (Trailmaking A and B) was consistent with prior studies (Tombaugh, 2004). The interaction between age and the presence of an *APOE4*

Table 3
CSF measures by *APOE4* group

CSF measures (pg/mL)	*APOE4*−	n	*APOE4*+	n	*p* Values		
	Mean ± S.D. [95% CI]		Mean ± S.D. [95% CI]		*APOE4*+ vs. *APOE4*−	Age	Age and *APOE4*
$A\beta_{42}$ (pg/mL)	448 ± 144 [416–478]	89	435 ± 141 [387–482]	37	0.7458	0.2418	0.2852
Total tau (pg/mL)	56 ± 22 [51–61]	89	57 ± 25 [49–66]	39	0.7526	**0.0044**	0.6071
ptau (pg/mL)	29 ± 10 [27–31]	89	29 ± 8 [26–31]	39	0.4762	0.3777	0.9673

Key: APOE, apolipoprotein E; CSF, cerebrospinal fluid.
Values are shown for each group with 95% confidence intervals. *p* values shown are from the cross-sectional mixed effects analysis of covariance to test if clinical, cognitive, imaging, and biomarker variables were different between the *APOE4*− and *APOE4*+ groups, with centered age as a covariate. Values shown in BOLD are those that achieved significance ($p < 0.05$).

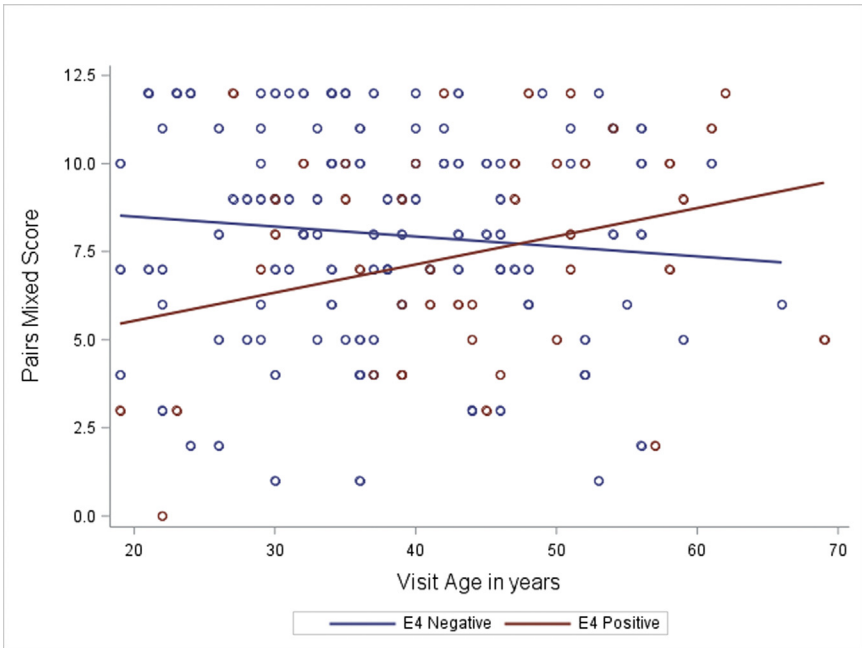

Fig. 1. Changes in performance on pair-binding associative learning task by age and *APOE4* status. Scores on the mixed item subtest (number of 12 mixed pairs correctly identified) plotted against age. Each circle represents scores from a single participant, with *APOE4*− participants in blue circles and line, and *APOE4*+ participants, red circles and lines, with age at time of testing on the horizontal axis. The best fit for each group is shown in the solid lines. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

allele on an associative learning task (pair-binding score for mixed pairs) is difficult to interpret given the abnormal distribution of test scores (Fig. 1).

We did not see differences in brain structure between *APOE4*+ and *APOE4*− individuals, but our analysis was limited to hippocampal volume and thickness of the precuneus and did not include participants under the age of 19 years. As expected, increasing age did have an effect on brain structure, with decreases in hippocampal volume and precuneus thickness with age. We did not find more rapid atrophy of brain structures in the *APOE*4+ participants, but instead found the age-related decline in hippocampal volume was more pronounced in the *APOE*4− group (Fig. 2D), with a similar trend in the precuneus (Fig. 2C). This is in contrast to many studies suggesting more rapid atrophy of these structures in *APOE*4+ participants (Cherbuin et al., 2007) although other studies have had similar findings, showing no significant differences between cognitively normal *APOE*4 homozygotes and those without an *APOE*4 allele across the life span (Habes et al., 2016; Reiman et al., 1998). The average age of cognitively normal participants in those studies was older than the cohort studied here and could have included participants with very mild or not yet symptomatic AD, so it is possible that *APOE4*-related atrophy begins later in the AD pathogenic cascade. Our findings are consistent with a prior report showing that NCs of *APOE*4 have more pronounced age-related atrophy (Gonneaud et al., 2016). This may also be consistent with the idea that *APOE*4 may have an antagonistic pleiotropic effect, with benefits on brain structure early in life. In the largest study to date on the effects of *APOE* alleles on brain structure and cognition in children (Chang et al., 2016), children with an *APOE*4 allele (*APOE*3/4 heterozygotes) had larger volumes in some brain regions (hippocampi, occipital, and frontal cortical areas) than those who were homozygous for *APOE*3.

Some but not all studies have found a significant decrease in glucose metabolism in young adults who carry an *APOE*4 allele. Reiman et al., found that glucose metabolism was reduced in frontal, temporal, and parietal lobes and in the cingulate cortex in cognitively normal young adults with an *APOE4* allele (Reiman et al., 1996, 2005). We observed an association of glucose metabolism with age in the precuneus, but there was no interaction of *APOE4* status with glucose metabolism or with age. This may reflect differences in the cohort or in the areas sampled but we note one other study has also found that *APOE*4 does not affect glucose metabolism in cognitively normal adults across the life span (Gonneaud et al., 2016).

We did not see differences between *APOE*4+ and *APOE*4− participants in amyloid deposition in the precuneus or in pooled cortical regions, but we did observe a correlation between amyloid deposition and age and an increased slope of amyloid accumulation with age in *APOE*4+ participants (Fig. 2A and B). Amyloid deposition in precuneus and in cortex overall was stable with age for *APOE*4 NCs, whereas *APOE*4 carriers had increasing amyloid deposition with age, consistent with prior reports in older cohorts (Liu et al., 2016; Rowe et al., 2010). Our findings suggest that *APOE*4 effects on amyloid accumulation may begin relatively early in life, perhaps around age 30–40 years, consistent with other reports that included a younger cohort (Gonneaud et al., 2016, 2017) and with autopsy studies showing amyloid beta deposition in individuals aged 40–49 years who have an *APOE*4 allele (Pletnikova et al., 2015). A meta-analysis of 55 studies also suggested that amyloid accumulation in *APOE*4+ participants might begin slightly before age 40 years, although less than 5% of participants in the pooled studies were under the age of 40 years (Jansen et al., 2015). Our findings differ somewhat from the recent report by Gonneaud et al. (Gonneaud et al., 2017), who showed a linear increase in florbetapir binding with age in participants aged 20–60 years and only a marginal effect of *APOE*4. The study reported here has a larger sample size (162 young participants here vs. 76 in the study by Gonneaud) and used PiB rather than florbetapir. The suggestion of

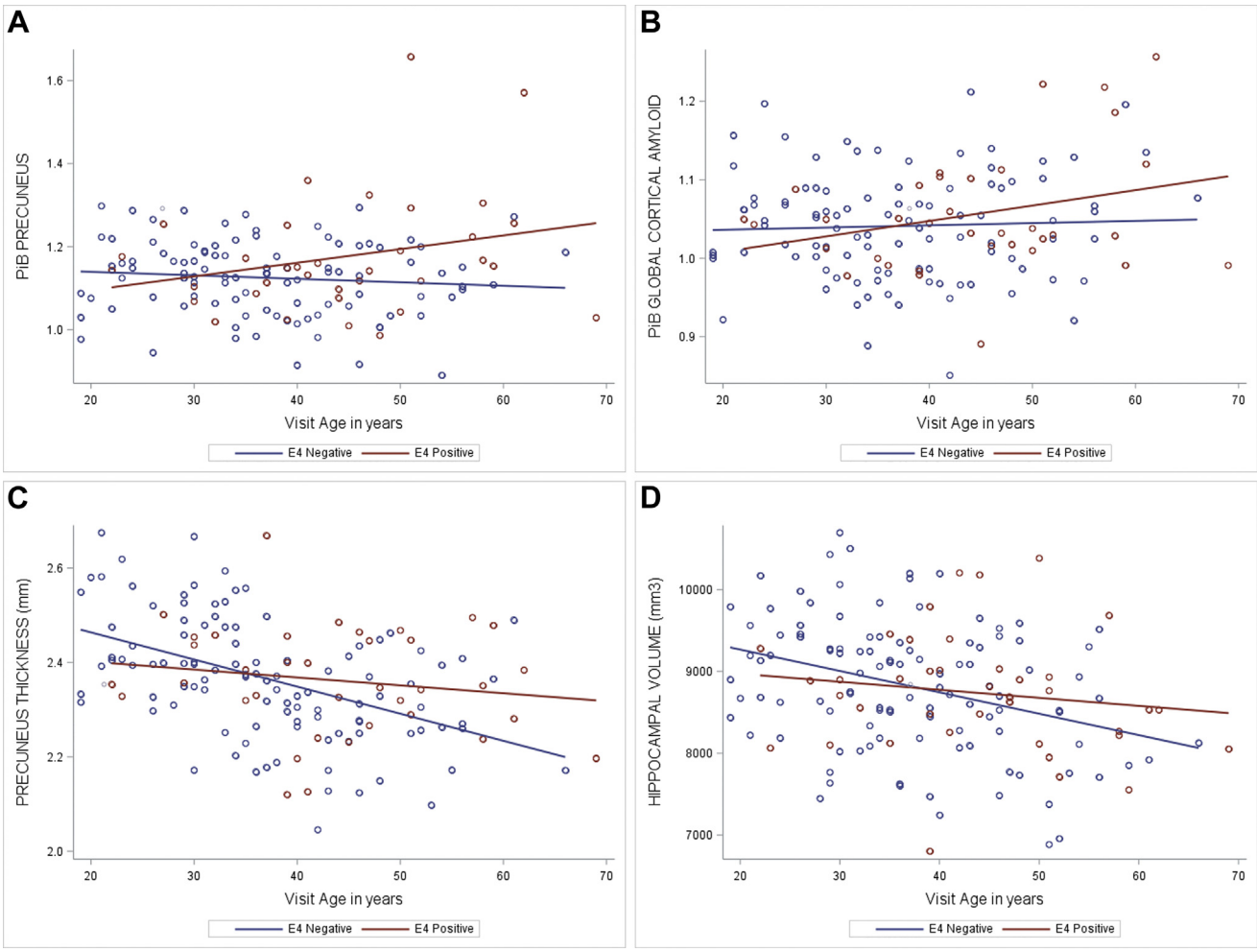

Fig. 2. Interactions between age and *APOE* status for amyloid deposition and volumetric MRI. Amyloid plaque load as measured by PET amyloid imaging with [^{11}C]Pittsburgh Compound B Pittsburgh Compound B in the precuneus (A) and in an average of six cortical regions (B) plotted over time versus age for *APOE4*– (blue circles and line) and *APOE4*+ (red circles and line) participants. (C) Thickness of the precuneus (mm) plotted against age and (D) hippocampal volume (mm^3) plotted against age. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

an interaction between age and *APOE*4 differs from the findings of Jack et al. who observed no interaction between age and *APOE*4 when looking at amyloidosis in a cohort aged 50–89 years (Jack et al., 2014). These results must be interpreted with caution, however, as the increase in amyloid deposition in the *APOE4*+ group is not observed when participants over the age of 50 years (n = 26) are excluded from the analysis, so this finding is driven by the older participants.

We did not see effects of APOE4 genotype on any of the CSF measures of AD pathology, but did observe a slight increase in CSF tau with increasing age, consistent with some prior studies (Paternico et al., 2012; Sjogren et al., 2001; Sutphen et al., 2015). Age did not have a significant effect on CSF levels of ptau or Aβ_{42}, in contrast to some prior studies (Popp et al., 2010; Shoji et al., 2001; Sjogren et al., 2001). We did not observe an interaction between age and *APOE*4 status for CSF levels of Aβ_{42} (Fig. 3B); this is in contrast to findings in a much larger pooled cohort study that analyzed 1233 healthy control subjects, 40–84 years old, where *APOE4*+ individuals had higher CSF tau and lower Aβ_{42}, starting in their 40s (Toledo et al., 2015).

This study has several limitations. Owing to sample size considerations, no measures achieved significance when corrected for multiple comparisons so findings must be considered exploratory. The participants studied here all have family members with an ADAD mutation, so may not reflect the general population. The study is cross-sectional, so lacks longitudinal data. The goal of this exploratory study was to assess all available measures. It will be important to reassess these findings as longitudinal data become available from this cohort.

Our findings overall support the growing literature on the preclinical stages of AD. The exploratory findings here are in line with growing evidence that cerebral amyloid accumulation may begin in middle age, perhaps as early as age 30–40 years and that the presence of an *APOE*4 allele may accelerate amyloid deposition (Gonneaud et al., 2016, 2017). Changes in CSF Aβ_{42} are thought to precede amyloid deposition, but we did not detect an age- or *APOE*-dependent effect on CSF Aβ_{42}. We did not see effects of *APOE4* on cognitive performance or brain atrophy, making it more likely that the effects of *APOE*4 early in disease are associated with amyloid metabolism or deposition. This highlights the need for larger

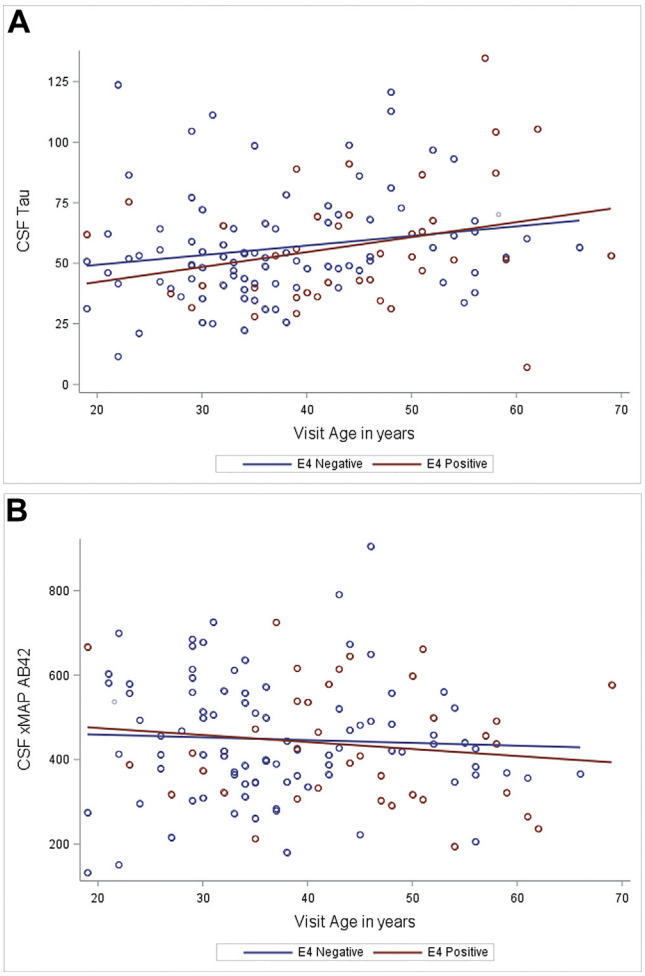

Fig. 3. (A) CSF total tau levels plotted against age at time of CSF sampling for *APOE*4+ participants (red circles and line) and *APOE*4− participants (blue circles and line). (B) CSF Aβ_{42} levels plotted against age at time of CSF sampling for *APOE*4+ participants (red circles and line) and *APOE*4− participants (blue circles and line). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

longitudinal studies that include imaging and fluid biomarkers in both young and older adults.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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