Received: 23 June 2022 | Revised: 5 October 2022 | Accepted: 11 October 2022

DOI: 10.1002/dad2.12374

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Longitudinal CSF Alzheimer's disease biomarker changes from middle age to late adulthood

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Funding information
National Institutes of Health, Grant/Award Numbers: U19-AG033655, P30-AG066507

Abstract

Introduction: We examined longitudinal cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarker changes among cognitively normal individuals with 10.7 years follow-up, on average.

Methods: Analyses included 278 participants (*M* age = 57.5 years); 94 have progressed from normal cognition to mild cognitive impairment (MCI). Amyloid beta $(A\beta)_{42}/A\beta_{40}$, phosphorylated tau_{181} (p-tau_{181}), and total tau (t-tau) were measured using automated electrochemiluminescence assays.

Results: Apolipoprotein E (*APOE*) ε4 carriers had lower baseline $A\beta_{42}/A\beta_{40}$, but longitudinal $A\beta_{42}/A\beta_{40}$ decreases did not differ by *APOE* ε4 after accounting for $A\beta_{42}/A\beta_{40}$ positivity. Lower baseline $A\beta_{42}/A\beta_{40}$ was associated with greater increases in tau (more strongly in males), and *APOE* ε4 genotype was associated with greater tau increases after reaching $A\beta_{42}/A\beta_{40}$ positivity. Participants who progressed to MCI had more abnormal biomarker levels and greater tau increases prior to MCI symptom onset. Biomarkers were more abnormal among older adults, but unrelated to sex or education.

Discussion: Our results confirm accelerated biomarker changes during preclinical AD and highlight the important role of amyloid levels in tau accelerations.

KEYWORDS
amyloid, apolipoprotein E genotype, biomarkers, cerebrospinal fluid, preclinical Alzheimer's disease, tau

1 | BACKGROUND

The preclinical phase of Alzheimer's disease (AD) is characterized by the accumulation of amyloid plaques and neurofibrillary tangles years to decades before clinical symptoms emerge.[1] Despite significant advances in techniques for measuring these pathologies in vivo, current hypothetical models of biomarker trajectories are based largely on cross-sectional studies across the clinical disease spectrum or short-term evaluations (typically 2 to 5 years) of biomarker changes in older adults (baseline age = 70 years).[2] This limits understanding of longitudinal within-person biomarker changes during preclinical AD, especially from midlife. Addressing this gap is important, given clinical

RESEARCH IN CONTEXT

1. **Systematic review**: Traditional sources (e.g., PubMed) were used to review prior literature. Although hypothetical biomarker models of Alzheimer's disease (AD) describe biomarker changes during the preclinical phase of AD, these models are based primarily on cross-sectional and short-term longitudinal studies in older adults.
2. **Interpretation**: Our findings suggest that among cognitively normal, largely middle-aged individuals, lower levels of amyloid are associated with increases in tau (as measured in cerebrospinal fluid), while accelerations in tau are more closely linked to mild cognitive impairment symptom onset. They also suggest apolipoprotein E ε4 carriers have an earlier age of amyloid onset and higher rates of amyloid positivity, but no differences in amyloid rates of change over time.
3. **Future directions**: Future studies are needed to further address possible sex differences in AD biomarker trajectories. Additional longitudinal studies among more diverse groups of cognitively normal, middle-aged participants are needed to confirm the generalizability of these findings.

trials are increasingly targeting the earliest disease phases and using biomarkers for trial enrollment and outcomes.

This study's aim was to characterize longitudinal AD biomarker trajectories spanning an average of 10.7 years (max = 23 years) in 278 cognitively normal, primarily middle-aged individuals (*M* baseline age = 57.5 years). AD biomarkers were measured by cerebrospinal fluid (CSF) amyloid beta $(A\beta)_{42}/A\beta_{40}$, phosphorylated tau_{181} ($p\text{-}tau_{181}$), and total tau (t-tau). We examined the impact of demographics (age, sex, education) and apolipoprotein E (*APOE*) ε4 genotype on biomarker trajectories. We also examined associations among the biomarker measures, and tested the hypothesis that *APOE* ε4-related differences in biomarker trajectories are due to differences in amyloid positivity between *APOE* ε4 carriers and non-carriers, given *APOE* ε4 carriers accumulate amyloid earlier than non-carriers.[3–5] Furthermore, we explored interactions with sex, because prior studies have reported sex-related differences in AD biomarkers[6–8] and clinical outcomes.[9–12] Finally, given the sizeable number of individuals who progressed to mild cognitive impairment (MCI) or dementia ($n = 94$) during follow-up, we examined whether CSF biomarker trajectories differed with respect to clinical outcomes. The focus on middle-aged individuals is particularly important because AD pathology begins to develop in midlife,[5,13] and abnormal midlife levels of CSF amyloid and tau are associated with poorer cognitive outcomes.[11,14,15]

2 | METHODS

2.1 | Study design and participant selection

Data were derived from the BIOCARD study, which was designed to identify variables among cognitively normal individuals that predict subsequent development of cognitive decline and dementia. As described previously,[16] the study was initiated in 1995 at the National Institutes of Health (NIH). Between 1995 and 2005, 349 cognitively normal, primarily middle-aged ($M = 57.3$ years, standard deviation = 10.4) participants were enrolled after providing written informed consent. By design, 75% of the cohort had a first-degree relative with AD dementia. While at the NIH, participants completed comprehensive clinical and cognitive assessments annually; CSF and other biomarkers were obtained approximately every 2 years. The study was stopped in 2005 and re-established in 2009 at Johns Hopkins University (JHU), and annual clinical and cognitive assessments and collection of blood specimens were reinitiated. The biennial collection of CSF was reinitiated in 2015. Participants have undergone repeated visits over a long period of time and longitudinal data collection is ongoing (see supporting information Text S1 for additional details, including a study timeline). This study was approved by the JHU Institutional Review Board.

These analyses included 278 participants who were cognitively normal at their "baseline" CSF measure (i.e., first available). Participants were excluded for the following reasons: (1) 26 had not yet re-enrolled or had withdrawn, (2) 21 had an estimated age of MCI clinical symptom onset at or prior to their first CSF measure, and (3) 24 did not have CSF collected.

2.2 | Clinical assessments

Annual assessments include physical and neurological examinations, record of medication use, behavioral and mood assessments, family history of dementia, history of symptom onset, a neuropsychological test battery, and the Clinical Dementia Rating (CDR[17]) based on a semi-structured interview. Consensus diagnoses used in study analyses (see Albert et al.[16] and Text S1) involved first establishing a syndromic diagnosis (normal, MCI, dementia, impaired-not-MCI) based on (1) clinical data (medical, neurological, and psychiatric status), (2) reports of changes in cognition (based on the CDR), and (3) decline in cognitive test performance. Second, for participants with cognitive impairment, the likely syndromic etiology (/etiologies) was determined based on the neurologic, medical, and psychiatric information collected (without knowledge of biomarker measures). These consensus diagnoses follow the recommendations of the National Institute on Aging/Alzheimer's Association working group reports for the diagnosis of MCI[18] and AD dementia.[19] The estimated age of MCI clinical symptom onset was established separately, based primarily on the CDR interview.

For these analyses, we created a dichotomous indicator variable for follow-up diagnosis, reflecting each participant's last (i.e., most recent)

diagnosis (remain normal = 0, progress from normal cognition to MCI or dementia = 1).

2.3 | Cerebrospinal fluid biomarker measures

CSF samples used in these analyses were collected over time while the study was at the NIH (1995-2005) and JHU (since 2015; see Text S2 in supporting information for CSF measures across sites). CSF was collected via lumbar puncture after an overnight fast. Samples were aliquoted into polypropylene cryotubes that were kept on dry ice and immediately transferred to a −80°C freezer for long-term storage. Samples were thawed for the first time since collection to measure $A\beta_{40}$, $A\beta_{42}$, p-tau_{181}, and t-tau using fully automated electrochemiluminescence assays (Lumipulse G1200 platform; Fujirebio Diagnostics, Inc.; for coefficients of variation, see Greenberg et al.[11]). The present analyses used the $A\beta_{42}/A\beta_{40}$ ratio (vs. $A\beta_{42}$ alone) to account for individual differences in total $A\beta$ production (as measured by $A\beta_{40}$) and reduce the impact of pre-analytic variables.[20–23] The three main outcome variables were $A\beta_{42}/A\beta_{40}$, p-tau_{181}, and t-tau. See Text S3 in supporting information for the p-$tau_{181}/(A\beta_{42}/A\beta_{40})$ and t-tau/$(A\beta_{42}/A\beta_{40})$ ratio results.

2.4 | *APOE* genotype

APOE genotypes were determined by restriction endonuclease digestion of polymerase chain reaction amplified genomic DNA (performed by Athena Diagnostics, Worcester, MA). Genotypes were coded dichotomously (*APOE* ε4 non-carriers = 0, carriers = 1).

2.5 | Statistical analyses

Group differences in descriptive statistics were compared using *t* tests or chi-square tests, as appropriate. Rates of change in the CSF biomarkers over time were analyzed with li mixed effects models that included random intercepts and slopes with unstructured covariance. CSF measures were standardized (z-scored) separately for CSF collected at NIH versus JHU using the first available measure at each site, so that model coefficients reflected z-scores while simultaneously accounting for potential differences due to collection site. Time was modeled in the unit of years (since baseline).

The primary analyses evaluated the relationship of demographics and *APOE* ε4 genotype to levels and rates of change in CSF biomarkers. Model predictors included: baseline age (centered), sex, years of education (centered), *APOE* ε4 genotype, time, the interaction (cross-product) of each predictor with time, and $time^2$ for evaluating non-linear (quadratic) trajectories. Models also included a "collection site" indicator, reflecting the location of CSF collection (NIH vs. JHU) to control for potential systematic site differences. To examine the robustness of our primary findings, models using chronological age (in years) as the timescale are also presented (excluding terms for baseline age).

The first set of follow-up models evaluated associations between (1a) baseline tau biomarkers (p-tau_{181} or t-tau) and change in $A\beta_{42}/A\beta_{40}$ (additional model terms: baseline tau and baseline tau x time), and (1b) baseline $A\beta_{42}/A\beta_{40}$ and change in tau (additional model terms: baseline $A\beta_{42}/A\beta_{40}$ and baseline $A\beta_{42}/A\beta_{40}$ x time). The second set of follow-up models evaluated whether accounting for $A\beta_{42}/A\beta_{40}$ positivity affected the relationship between *APOE* ε4 status and biomarker change (additional model terms: $A\beta_{42}/A\beta_{40}$ positivity and $A\beta_{42}/A\beta_{40}$ positivity x time, and the interactions of these terms with *APOE* ε4). $A\beta_{42}/A\beta_{40}$ positivity was calculated as a time-varying variable reflecting dichotomous $A\beta_{42}/A\beta_{40}$ negative versus positive status at each time point using clinically derived cut-points ($A\beta_{42}/A\beta_{40}$ positive = 1 if $A\beta_{42}/A\beta_{40} \leq 0.075$, otherwise 0; see Text S5 in supporting information for the cut-point derivation). The third set of follow-up models evaluated differences in CSF biomarker trajectories by follow-up diagnosis (additional model terms: follow-up diagnosis and follow-up diagnosis x time). The fourth set of follow-up models explored sex differences in CSF biomarker changes by including interactions between sex and baseline age (4a), or sex and *APOE* ε4 genotype (4b), as well as the interactions of these terms with time. Last, we examined whether sex modified the relationship between baseline tau and change in $A\beta_{42}/A\beta_{40}$ (4c), and between baseline $A\beta_{42}/A\beta_{40}$ and change in tau (4d) by including additional terms for the respective baseline biomarkers, interactions with sex, and their interactions with time.

Analyses were run in Stata (v17.0). Estimates and 95% confidence intervals are reported with *p*-values ≤0.05 considered significant.

3 | RESULTS

Participants ($N = 278$; M age = 57.5 years) were cognitively normal at baseline and had 3.7 CSF measures over 10.7 years, on average (86% had ≥2 CSF measures; Table 1). Those who subsequently progressed to MCI or dementia ($n = 94$; 34%) were older, had shorter follow-up, and more abnormal biomarkers (i.e., lower $A\beta_{42}/A\beta_{40}$, higher tau).

3.1 | CSF biomarker changes and impact of demographics, *APOE* ε4 genotype

In the primary analyses (Table 2, Figure 1), with time since baseline as the timescale, there was a significant main effect of *APOE* ε4 genotype for $A\beta_{42}/A\beta_{40}$, indicating lower $A\beta_{42}/A\beta_{40}$ levels among *APOE* ε4 carriers. Additionally, there were significant *APOE* ε4 x time interactions for all CSF biomarkers, indicating greater $A\beta_{42}/A\beta_{40}$ decreases and p-tau_{181} and t-tau increases, among *APOE* ε4 carriers. There were also significant main effects of age (for all biomarkers) and significant age x time interactions (for all biomarkers except p-tau_{181}, $p = 0.093$). Older participants had more abnormal CSF biomarker levels and greater rates of biomarker change. In contrast, CSF biomarker levels and rates of change were unrelated to sex and years of education. Using chronological age as the timescale, the patterns of results were similar, except that the quadratic effect of time (i.e., age^2) was

TABLE 1 Baseline characteristics for participants included in the analyses, for the full sample and stratified by follow-up diagnosis

	All participants	Remain normal	Progress to MCI/dementia^
N	278	184	94
Age, M (SD) [range]	57.5 (10.29) [20.4–92.5]	55.2 (10.06) [20.4–92.5]	61.9 (9.30) [38.7–84.8]*
Female sex, n (%)	165 (59%)	114 (62%)	51 (54%)
Years of education, M (SD)	17.0 (2.37)	17.2 (2.33)	16.8 (2.43)
*APOE ε*4 carriers, *n* (%)	96 (35%)	61 (33%)	35 (37%)
White race, *n* (%)	271 (98%)	181 (98%)	90 (96%)
Number of CSF measures over time, M (SD) [range]	3.7 (1.9) [1-9]	3.8 (2.0) [1-8]	3.5 (1.79) [1-9]
Years between baseline and last CSF measure, M (SD) [range]	10.7 (7.3) [0-23]	11.4 (7.5) [0-23]	9.2 (6.8) [0-22]*
Years between baseline CSF measure and last (i.e., most recent) diagnosis, M (SD) [range]	13.9 (5.7) [0–23.6]	15.4 (5.3) [0–23.6]	10.8 (5.0) [1–22.8]**
Years between baseline CSF measure and MCI clinical symptom onset, M (SD) [range]	—	—	7.6 (4.5) [0.8–22.4]
CSF $A\beta_{42}/A\beta_{40}$, M (SD)	0.09 (0.02)	0.09 (0.02)	0.08 (0.02)**
CSF p-tau_{181} (pg/ml), M (SD)	34.60 (17.45)	31.30 (13.69)	41.07 (21.77)**
CSF t-tau (pg/ml), M (SD)	259.61 (138.51)	236.05 (111.53)	305.73 (171.52)**
Participants with ≥2 CSF measures over time, n (%)	239 (86%)	158 (86%)	81 (86%)
Number of CSF measures over time for participants with ≥2 CSF measures, M (SD)	4.1 (1.7)	4.2 (1.8)	4.0 (1.6)
Years between baseline and last CSF measure for participants with ≥2 CSF measures, M (SD)	12.4 (6.4)	13.3 (6.3)	10.7 (6.2)*

* $p < 0.05$ and ** $p < 0.001$ for significant differences between remain normal versus progress to MCI/dementia.
^ Of the 94 participants who progressed from normal cognition to MCI/dementia, $n = 86$ and $n = 8$ had a diagnosis of MCI and dementia, respectively, at their last (i.e., most recent) visit.
Abbreviations: A*β*, amyloid beta; *APOE*, apolipoprotein E; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; p-tau, phosphorylated tau; SD, standard deviation; t-tau, total tau.

significant for $A\beta_{42}/A\beta_{40}$ ($p = 0.006$; Table 2). Similar effects were found for the tau/($A\beta_{42}/A\beta_{40}$) ratios (Text S3), and in models excluding extreme participant age groups (i.e., <40 and >85 years; Text S4 in supporting information).

3.2 | Associations between CSF biomarkers

For the models that examined baseline levels of p-tau_{181} or t-tau in relationship to change in $A\beta_{42}/A\beta_{40}$, there were main effects of tau but no tau x time interactions (Table 3). Higher baseline p-tau_{181} and t-tau were each associated with lower $A\beta_{42}/A\beta_{40}$ levels, but not with change in $A\beta_{42}/A\beta_{40}$ over time. In the models that examined baseline $A\beta_{42}/A\beta_{40}$ in relationship to change in tau, both the main effects of $A\beta_{42}/A\beta_{40}$ and the $A\beta_{42}/A\beta_{40}$ x time interaction terms were significant. Lower baseline $A\beta_{42}/A\beta_{40}$ was associated with higher levels of p-tau_{181} and t-tau, and with greater increases in p-tau_{181} and t-tau over time.

3.3 | CSF biomarker changes: impact of *APOE ε*4 when co-varying A*β*42/A*β*40 positivity

With $A\beta_{42}/A\beta_{40}$ as the outcome, there was a main effect of $A\beta_{42}/A\beta_{40}$ positivity and an $A\beta_{42}/A\beta_{40}$ positivity x time interaction (both $P \leq 0.009$; Text S5), indicating lower $A\beta_{42}/A\beta_{40}$ levels and greater $A\beta_{42}/A\beta_{40}$ decreases over time among $A\beta_{42}/A\beta_{40}$-positive individuals. There was a main effect of *APOE ε*4 ($p < 0.001$) but no *APOE ε*4 x time or *APOE ε*4 x $A\beta_{42}/A\beta_{40}$ positivity x time interactions (both

TABLE 2 Results of the longitudinal mixed effects regression models examining CSF biomarker trajectories

Timescale: Years from baseline						
	Outcome: $A\beta_{42}/A\beta_{40}$		**Outcome: p-tau$_{181}$**		**Outcome: t-tau**	
Model predictor	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**
Time	0.017 (−0.003, 0.038)	0.100	0.030 (0.009, 0.051)	0.005	0.043 (0.020, 0.065)	< 0.001
Time x time	−0.001 (−0.002, 0.000)	0.093	0.002 (0.001, 0.003)	< 0.001	0.001 (0.000, 0.002)	0.044
Baseline age	−0.033 (−0.043, −0.023)	< 0.001	0.035 (0.024, 0.046)	< 0.001	0.035 (0.024, 0.046)	< 0.001
Baseline age x time	−0.001 (−0.002, −0.000)	0.025	0.001 (-0.000, 0.002)	0.093	0.002 (0.001, 0.003)	0.001
Sex, female	0.005 (−0.205, 0.215)	0.962	0.013 (−0.214, 0.240)	0.910	−0.004 (−0.231, 0.224)	0.973
Sex x time	−0.001 (−0.016, 0.013)	0.841	0.003 (−0.017, 0.023)	0.797	0.009 (−0.008, 0.026)	0.318
Education	0.015 (−0.029, 0.058)	0.511	−0.017 (−0.064, 0.031)	0.487	−0.044 (−0.091, 0.003)	0.068
Education x time	0.002 (−0.001, 0.005)	0.278	−0.001 (−0.005, 0.003)	0.670	0.000 (−0.004, 0.004)	0.998
*APOE ε*4	−0.508 (−0.721, −0.294)	< 0.001	0.106 (−0.126, 0.337)	0.371	0.062 (−0.170, 0.293)	0.602
*APOE ε*4 x time	−0.045 (-0.059, −0.030)	< 0.001	0.044 (0.024, 0.064)	< 0.001	0.039 (0.022, 0.056)	< 0.001
Timescale: Chronological age						
	Outcome: $A\beta_{42}/A\beta_{40}$		**Outcome: p-tau$_{181}$**		**Outcome: t-tau**	
Model predictor	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**
Age	−0.010 (−0.023, 0.003)	0.148	0.034 (0.020, 0.048)	< 0.001	0.033 (0.020, 0.047)	< 0.001
Age x age	−0.001 (−0.001, −0.000)	0.006	0.001 (0.000, 0.001)	< 0.001	0.001 (0.001, 0.001)	< 0.001
Sex, female	0.041 (−0.147, 0.230)	0.667	0.039 (−0.227, 0.305)	0.773	0.074 (−0.164, 0.313)	0.540
Sex x age	−0.003 (−0.016, 0.011)	0.690	0.010 (−0.005, 0.024)	0.195	0.01 (−0.004, 0.023)	0.167
Education	0.003 (−0.036, 0.042)	0.895	−0.001 (−0.056, 0.055)	0.983	−0.020 (−0.070, 0.029)	0.426
Education x age	0.002 (-0.001, 0.005)	0.156	−0.001 (−0.004, 0.002)	0.690	0.000 (−0.003, 0.003)	0.830
*APOE ε*4	−0.688 (−0.879, −0.497)	< 0.001	0.177 (−0.092, 0.446)	0.198	0.119 (−0.122, 0.360)	0.332
*APOE ε*4 x age	−0.044 (-0.058, −0.030)	< 0.001	0.044 (0.029, 0.059)	< 0.001	0.038 (0.024, 0.052)	< 0.001

Note: Different models were estimated for each CSF measure. Models were also adjusted for collection site (National Institutes of Health vs. Johns Hopkins University).
Abbreviations: A*β*, amyloid beta; *APOE*, apolipoprotein E; CI, confidence interval; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; t-tau, total tau.

$p > 0.59$): *APOE ε*4 carriers had lower $A\beta_{42}/A\beta_{40}$ levels but rates of $A\beta_{42}/A\beta_{40}$ change over time did not differ by *APOE ε*4 genetic status after accounting for $A\beta_{42}/A\beta_{40}$ positivity.

For p-tau$_{181}$ and t-tau as outcomes, $A\beta_{42}/A\beta_{40}$ positivity was associated with higher levels of p-tau$_{181}$ and t-tau (both $P \leq 0.003$). There were significant $A\beta_{42}/A\beta_{40}$ positivity x *APOE ε*4 and $A\beta_{42}/A\beta_{40}$ positivity x *APOE ε*4 x time interactions (all $p < 0.02$): relative to *APOE ε*4 non-carriers, *APOE ε*4 carriers had lower tau levels when $A\beta_{42}/A\beta_{40}$ positive, but greater increases in p-tau$_{181}$ and t-tau after reaching $A\beta_{42}/A\beta_{40}$ positivity.

3.4 | CSF biomarker changes and follow-up diagnosis

There were significant main effects of follow-up diagnosis for $A\beta_{42}/A\beta_{40}$, p-tau$_{181}$, and t-tau, indicating more abnormal baseline CSF biomarker levels among those who progressed to MCI/dementia over time. Additionally, there were follow-up diagnosis x time interactions for p-tau$_{181}$ and t-tau, indicating greater increases in tau among participants who progressed to MCI/dementia versus remained normal (Table 4; Figure 2). Further exploratory analyses examining CSF biomarker change before versus after MCI symptom onset indicated greater increases in tau prior to MCI clinical symptom onset, compared to those who remained cognitively normal (Text S6).

3.5 | CSF biomarker changes: interactions among sex and age, *APOE*, and baseline biomarker levels

There were no significant interactions between sex and age or *APOE ε*4 genotype with respect to change in $A\beta_{42}/A\beta_{40}$, p-tau$_{181}$, or t-tau over time (all $p > 0.11$; data not shown).

Sex did not modify the association between baseline p-tau$_{181}$ or t-tau and $A\beta_{42}/A\beta_{40}$ (all $p > 0.06$). However, sex influenced the association between baseline $A\beta_{42}/A\beta_{40}$ and rate of change in p-tau$_{181}$. Significant sex x baseline $A\beta_{42}/A\beta_{40}$ (estimate = 0.295, 95% confidence interval [CI] = [0.090, 0.500], $p = 0.005$) and sex x baseline $A\beta_{42}/A\beta_{40}$ x time (estimate = 0.027, 95% CI = [0.005, 0.050], $p = 0.017$) interactions indicated that the association between baseline $A\beta_{42}/A\beta_{40}$ and both levels and rate of p-tau$_{181}$ change was weaker in females versus males.

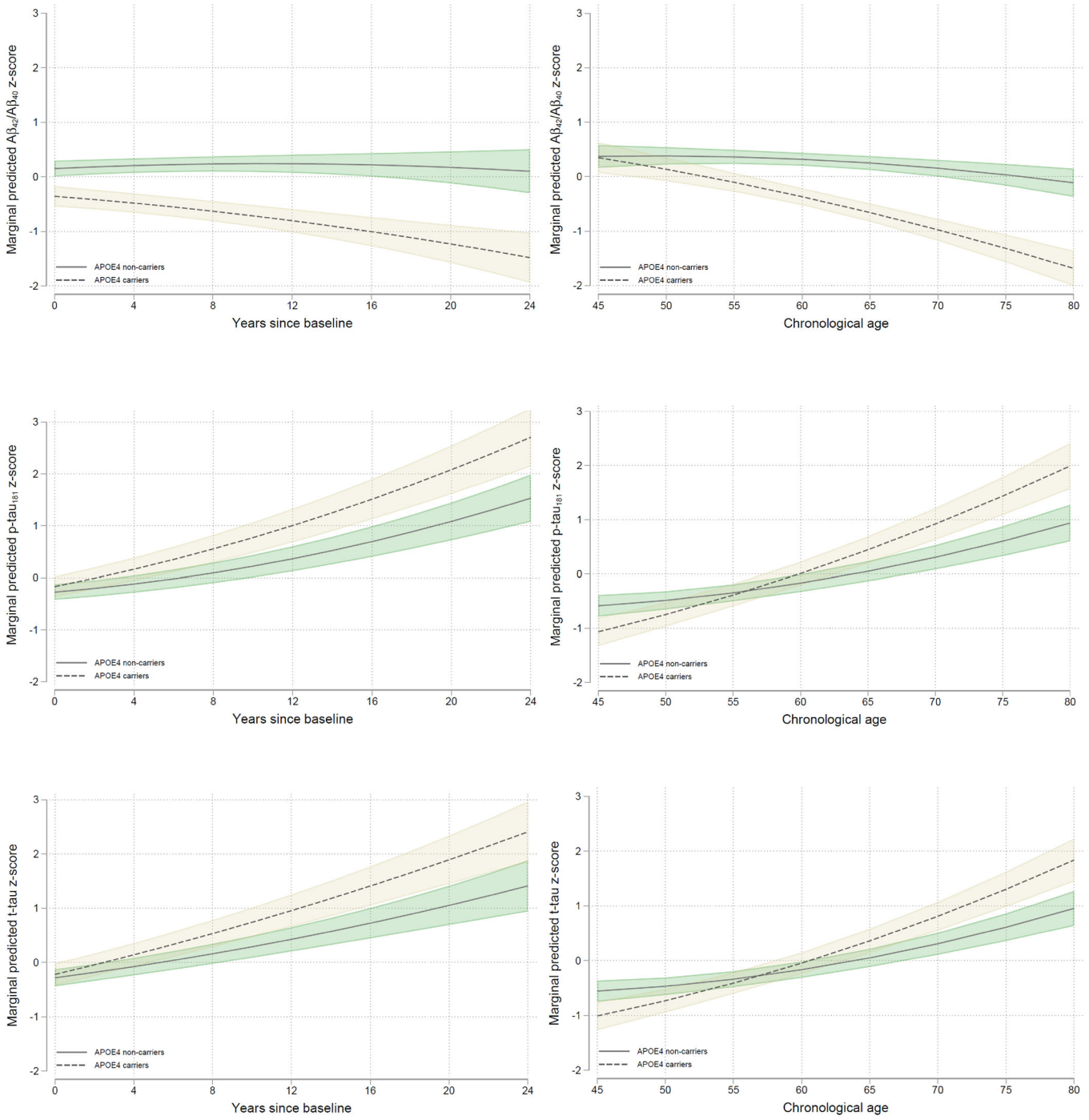

FIGURE 1 Adjusted estimates (95% confidence interval) of longitudinal trajectories of z-scored cerebrospinal fluid (CSF) amyloid beta ($A\beta)_{42}/A\beta_{40}$ (top), phosphorylated tau (p-tau_{181}; middle) and total tau (t-tau; bottom) biomarkers over time by, separately for apolipoprotein E (*APOE*) ε4 carriers (dashed tan lines) and non-carriers (solid green lines). Results are shown using years since baseline (left) and chronological age (right) as the timescale

4 | DISCUSSION

This study examined CSF biomarker trajectories, measured over 10.7 years of follow-up on average, among individuals who were initially cognitively normal and largely middle-aged at baseline. There are several important findings. First, lower CSF $A\beta_{42}/A\beta_{40}$ levels were associated with increases in tau, and accelerations in CSF tau were closely linked to MCI symptom onset. Second, *APOE* ε4 genotype was unrelated to $A\beta_{42}/A\beta_{40}$ rates of change after accounting for $A\beta_{42}/A\beta_{40}$ positivity, but *APOE* ε4 was associated with greater increases in p-tau_{181} and t-tau after reaching $A\beta_{42}/A\beta_{40}$ positivity. Finally, AD biomarker trajectories did not differ by sex or years of education, though there was some evidence that sex may modify the relationship between $A\beta_{42}/A\beta_{40}$ and subsequent change in p-tau_{181}. These

TABLE 3 Results of the longitudinal mixed effects regression models examining the relationship of baseline biomarker levels to CSF biomarker trajectories

	Outcome: $A\beta_{42}/A\beta_{40}$		Outcome: $A\beta_{42}/A\beta_{40}$		Outcome: p-tau_{181}		Outcome: t-tau	
Model predictor	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**	**Estimate (95% CI)**	***p*-value**
Time	0.017 (−0.003, 0.038)	0.098	0.017 (−0.003, 0.038)	0.101	0.034 (0.014, 0.054)	0.001	0.045 (0.023, 0.067)	< 0.001
Time x time	−0.001 (−0.002, 0.000)	0.078	−0.001 (−0.002, 0.000)	0.087	0.002 (0.001, 0.003)	< 0.001	0.001 (0.000,0.002)	0.049
APOE ε4	−0.490 (−0.692, −0.288)	< 0.001	−0.449 (−0.636, −0.261)	< 0.001	−0.086 (−0.298, 0.126)	0.427	−0.073 (−0.298, 0.152)	0.525
APOE ε4 x time	−0.045 (−0.059, −0.030)	< 0.001	−0.043 (−0.058, −0.029)	< 0.001	0.030 (0.011, 0.050)	0.002	0.029 (0.012, 0.046)	0.001
Baseline t-tau	−0.295 (−0.397, −0.193)	< 0.001	–	–	–	–	–	–
Baseline t-tau x time	−0.009 (−0.018, 0.001)	0.066	–	–	–	–	–	–
Baseline p-tau_{181}	–	–	−0.438 (−0.534, −0.343)	< 0.001	–	–	–	–
Baseline p-tau_{181} x time	–	–	−0.006 (−0.016, 0.003)	0.208	–	–	–	–
Baseline $A\beta_{42}/A\beta_{40}$	–	–	–	–	−0.455 (−0.562, −0.348)	< 0.001	−0.320 (−0.434, −0.206)	< 0.001
Baseline $A\beta_{42}/A\beta_{40}$ x time	–	–	–	–	−0.031 (−0.043, −0.020)	< 0.001	−0.022 (−0.033, −0.011)	< 0.001

Note: Different models were estimated for each CSF measure. Models were also adjusted for all variables indicated in Table 2.
Abbreviations: *Aβ*, amyloid beta; *APOE*, apolipoprotein E; CI, confidence interval; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; t-tau, total tau.

FIGURE 2 Adjusted estimates (95% confidence interval) of longitudinal trajectories of z-scored cerebrospinal fluid (CSF) amyloid beta $(A\beta)_{42}/A\beta_{40}$ (top), phosphorylated tau (p-tau_{181}; middle) and total tau (t-tau; bottom) biomarkers over time, separately for those who remained normal (solid green lines) versus progressed to mild cognitive impairment dementia (dashed tan lines). Results are modeled using years since baseline as the timescale

findings are consistent with hypothetical AD biomarker models,[2] proposing accelerated biomarker changes during preclinical AD, with these changes occurring over long periods of time beginning as early as midlife.

Compared to those who remained normal, those who progressed to MCI/dementia had greater rates of change in p-tau_{181} and t-tau (and

TABLE 4 Results of the longitudinal mixed effects regression models examining CSF biomarker trajectories by follow-up diagnosis (remain normal vs. progress to MCI/dementia)

	Outcome: $A\beta_{42}/A\beta_{40}$		Outcome: p-tau_{181}		Outcome: t-tau	
Model predictor	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value	Estimate (95% CI)	*p*-value
Time	0.018 (−0.004, 0.040)	0.101	0.015 (−0.007, 0.038)	0.176	0.034 (0.010, 0.057)	0.005
Time x time	−0.001 (−0.002, 0.000)	0.092	0.002 (0.001, 0.003)	< 0.001	0.001 (0.000, 0.002)	0.037
APOE ε4	−0.492 (−0.701, −0.284)	< 0.001	0.094 (−0.134, 0.322)	0.420	0.051 (−0.177, 0.280)	0.659
APOE ε4 x time	−0.045 (−0.059, −0.030)	< 0.001	0.042 (0.022, 0.062)	< 0.001	0.037 (0.020, 0.054)	< 0.001
Follow-up diagnosis (progressed vs. remained normal)	−0.415 (−0.637, −0.193)	< 0.001	0.365 (0.122, 0.607)	0.003	0.318 (0.074, 0.561)	0.011
Follow-up diagnosis x time	−0.001 (−0.017, 0.015)	0.883	0.038 (0.016, 0.060)	0.001	0.023 (0.004, 0.042)	0.019

Note: Different models were estimated for each CSF measure. Models were also adjusted for all variables indicated in Table 2.
Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; CI, confidence interval; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; p-tau, phosphorylated tau; t-tau, total tau.

tau/[$A\beta_{42}/A\beta_{40}$] ratios; see also Moghekar et al.[14]), with exploratory analyses suggesting changes in tau occurred prior to MCI clinical symptom onset. This suggests accelerations in tau are more closely linked to MCI symptom onset than changes in amyloid. This is in line with recent findings from our group,[11] which reported that baseline levels of CSF tau were associated with proximal progression to MCI clinical symptoms (within 7 years, with 7 years being the mean time from baseline to MCI clinical symptom onset), whereas baseline $A\beta_{42}/A\beta_{40}$ was associated with more distal progression (>7 years). It is also consistent with findings showing strong relationships between tau and cognition among cognitively normal individuals, particularly in the presence of amyloid,[8,15,24–27] and with short-term longitudinal CSF findings in autosomal dominant AD (ADAD), suggesting increases in CSF tau are most evident prior to an individual's expected age of symptom onset.[28]

In contrast, the rate of change in CSF $A\beta_{42}/A\beta_{40}$ did not differ between those who remained normal versus progressed to MCI/dementia. Given there were baseline differences between these groups, it is likely that the greatest $A\beta_{42}/A\beta_{40}$ change occurred prior to the observation period (particularly for individuals who progressed to MCI more proximally to baseline), which in turn initiated increases in tau prior to symptom onset. For example, it has been suggested that CSF $A\beta_{42}$ plateaus at least 9 years before dementia onset,[29] with studies in ADAD reporting similar CSF $A\beta_{42}$ plateaus relative to the estimated age of symptom onset.[30] Additionally, it may be that some participants who have remained cognitively normal to date are undergoing amyloidosis associated with preclinical AD, reducing our ability to detect diagnostic group differences. Our findings differ from Roe et al.,[31] which reported that participants who progressed to MCI/dementia had greater declines in CSF $A\beta_{42}$ compared to those who remained cognitively normal, but no difference in p-tau_{181} and t-tau rates of change. Reasons for these different findings might be related to the measure of Aβ used ($A\beta_{42}/A\beta_{40}$ vs. $A\beta_{42}$), cohort characteristics (e.g., AD family history; baseline age), or mean number of biomarker assessments (3.7 vs. 1.8). Of note, our results (and Roe et al.[31]) indicate that CSF AD biomarker changes occur very early in the disease process. This aligns with autopsy findings that have identified neurofibrillary tangles and neuritic plaques in middle-aged and younger individuals.[5,13]

We also found that lower baseline $A\beta_{42}/A\beta_{40}$ was associated with longitudinal increases in p-tau_{181} and t-tau, but baseline tau was not associated with change in $A\beta_{42}/A\beta_{40}$. Although prior studies among cognitively normal individuals have reported associations between amyloid measures and longitudinal increases in tau, these studies were conducted in older (*M* age >70 years) cohorts with shorter follow-up.[6,8,24,25,32] Together, these findings support the view that early amyloid changes may initiate or accelerate tau accumulation and neuronal injury,[2,33] providing an important therapeutic window for slowing AD pathogenesis prior to symptom onset.

Notably, *APOE* ε4 carriers had lower levels of $A\beta_{42}/A\beta_{40}$ (but not tau), but no differences in $A\beta_{42}/A\beta_{40}$ declines after accounting for *APOE* ε4-related differences in $A\beta_{42}/A\beta_{40}$ positivity over time. These findings are in accordance with the known role for *APOE* ε4 in amyloid aggregation and clearance, and consistent with an earlier age of amyloid and AD dementia onset among *APOE* ε4 carriers.[3,34,35] Interestingly, prior studies on the relationship of *APOE* ε4 to amyloid change have been mixed. Some studies among cognitively normal individuals have reported increased rates of amyloid accumulation among *APOE* ε4 carriers,[36–38] whereas others have reported faster changes only among *APOE* ε4 carriers with low amyloid burden (Burnham et al.[4] and Lim and Mormino; [39] see also Schindler et al.[40]), or no difference in amyloid accumulation by *APOE* ε4 genotype.[4,41,42] Our findings suggest that observed differences in $A\beta_{42}/A\beta_{40}$ trajectories between *APOE* ε4 carriers and non-carriers reflect higher rates and earlier ages of amyloid positivity among *APOE* ε4 carriers (resulting in a more advanced preclinical disease stage).

APOE ε4 genotype was associated with greater rates of change in CSF p-tau_{181} and t-tau after reaching $A\beta_{42}/A\beta_{40}$ positivity. We hypothesize much of this effect is driven by associations between *APOE* ε4 and $A\beta_{42}/A\beta_{40}$: because *APOE* ε4 carriers are more likely to develop amyloid positivity at earlier ages,[3] they may also be more likely to show

amyloid-related increases in tau during the observation period. Consistent with this, a prior study estimated that the effect of *APOE* ε4 genotype on neurofibrillary tangle pathology is mainly mediated by amyloid pathology.[43] However, *APOE* ε4 genotype was associated with changes in p-tau$_{181}$ and t-tau independent of baseline Aβ_{42}/Aβ_{40} levels (Table 3), which may suggest some amyloid-independent effects of *APOE* ε4 on tau accumulation.[44,45] Few comparable studies have evaluated the relationship of *APOE* ε4 to longitudinal changes in tau. Consistent with our results, one study reported a trend toward greater CSF p-tau$_{181}$ and t-tau accumulation among older cognitively normal *APOE* ε4 carriers with lower baseline Aβ_{42}.[6] Our results also appear consistent with a prior study showing that rates of change in p-tau$_{181}$ and t-tau over ~7 years of follow-up occurred earlier in cognitively normal, middle-aged *APOE* ε4 carriers compared to non-carriers.[38] In contrast, other studies of older cognitively normal individuals, or with shorter biomarker follow-up, have found no direct association between *APOE* ε4 genotype and tau biomarker change (CSF:[6,31,46]; PET:[8]). Inconsistencies may be due to differences in length of biomarker follow-up and participant age, as biomarker studies capture only a snapshot of neurobiological changes that occur over decades.

Our results also suggest that there are no sex-related differences in CSF AD biomarker trajectories; however, there was some evidence of weaker coupling between Aβ_{42}/Aβ_{40} and change in p-tau$_{181}$ among females compared to males. This is consistent with recent findings from our group, whereby Aβ_{42}/Aβ_{40} and p-tau$_{181}$ had weaker associations with risk of MCI symptom onset in females than males at younger baseline ages, but the differences between sexes diminished with increasing baseline age.[11] However, sex differences in amyloid biomarkers are controversial,[47] and the lack of relationship between sex and tau differs from recent findings in various diagnostic groups, which have reported higher tau levels[7,9,48] (but see[49]) and greater short-term tau accumulation[6,8] in *APOE* ε4-carrying or amyloid-positive females. Reasons for these mixed findings are not clear, warranting additional studies.

Finally, the CSF biomarkers were unrelated to years of education. Although additional studies with other measures of intellectual/cognitive experiences are needed, this suggests education-related differences in MCI/AD dementia risk are not due to differences in the accumulation of AD pathology (as measured by these biomarkers) during the *earliest* disease phases, in line with a recent review reporting limited evidence of a relationship between AD biomarkers and intellectual experiences.[50]

This study has limitations. First, generalizability is limited because this volunteer sample was predominantly White, highly educated, and enriched for a family history of AD dementia. Although the mean baseline age was 57.5 years, the age range was large (20–93 years). Second, despite the moderate sample size, we may have been underpowered to detect three-way interactions. Third, while we took several approaches to adjust for pre-analytic factors related to Aβ_{42} (see Sections 2.3 and 2.5), these may have been insufficient and resulted in an underestimation of Aβ_{42}/Aβ_{40} effects. Fourth, despite the long duration of follow-up, CSF collection among those who progressed to MCI/dementia was more limited, particularly *after* MCI symptom onset, impacting our ability to examine biomarker changes during the earliest symptomatic disease phases. We were also unable to examine whether biomarker trajectories differed for those who progressed to MCI versus dementia, or separately for *APOE* ε2/ε4, *APOE* ε3/ε4, and *APOE* ε4/ε4, although these are important questions for future work.

To our knowledge, no prior study among initially cognitively normal, primarily middle-aged individuals has described CSF AD biomarker changes over this duration of follow-up. These findings advance our understanding of early AD-related biomarker changes by further highlighting the important role of amyloid in the acceleration of tau, as well as the importance of studying longitudinal AD biomarker changes during middle age.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health (grant numbers U19-AG033655, P30-AG066507). The authors are grateful to the members of the BIOCARD Scientific Advisory Board who provide continued oversight and guidance regarding the conduct of the study including: Drs David Holtzman, William Jagust, David Knopman, Walter Kukull, and Kevin Grimm, and Drs John Hsiao and Laurie Ryan, who provide oversight on behalf of the National Institute on Aging. The authors thank the members of the BIOCARD Resource Allocation Committee who provide ongoing guidance regarding the use of the biospecimens collected as part of the study, including: Drs Constantine Lyketsos, Carlos Pardo, Gerard Schellenberg, Leslie Shaw, Madhav Thambisetty, and John Trojanowski. The authors acknowledge the contributions of the Geriatric Psychiatry Branch of the intramural program of NIMH, who initiated the study (Principal investigator: Dr. Trey Sunderland). The authors are indebted to Dr. Karen Putnam, who provided documentation of the Geriatric Psychiatry Branch study procedures and the data files received from NIMH.

The BIOCARD Study consists of 7 Cores and 2 Projects with the following members: (1) the Administrative Core (Marilyn Albert, Rostislav Brichko); (2) the Clinical Core (Marilyn Albert, Anja Soldan, Corinne Pettigrew, Greg Pontone, Leonie Farrington, Jules Gilles, Nicole Johnson, Maura Grega, Gay Rudow, Scott Rudow); (3) the Imaging Core (Michael Miller, Susumu Mori, Tilak Ratnanather, Andrea Faria, Anthony Kolasny, Kenichi Oishi, Laurent Younes, Hanzhang Lu); (4) the Biospecimen Core (Abhay Moghekar, Jacqueline Darrow, Alexandria Lewis); (5) the Informatics Core (Ann Ervin, David Shade, Jennifer Jones, Hamadou Coulibaly, Kathy Moser); (6) the Biostatistics Core (Mei-Cheng Wang, Yuxin [Daisy] Zhu, Jiangxia Wang); (7) the Neuropathology Core (Juan Troncoso, Javier Redding, Roberta Knox); (8) Project 1 (Paul Worley, Jeremy Walston), and (9) Project 2 (Mei-Cheng Wang, Sufei Sun).

CONFLICTS OF INTEREST

CP, AS, JW, and MCW have no disclosures. Dr. Greenberg is Editor-in-Chief of the other open access journal of the Alzheimer's Association: *Alzheimer's & Dementia—Translational Research and Clinical Interventions*. Dr. Albert is an advisor to Eli Lilly. Dr. Moghekar receives research support to JHU (but no direct or indirect salary support) from Fujirebio Diagnostics to analyze CSF preanalytics.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pettigrew C, Soldan A, Wang J, et al. Longitudinal CSF Alzheimer's disease biomarker changes from middle age to late adulthood. *Alzheimer's Dement*. 2022;14:e12374. https://doi.org/10.1002/dad2.12374