The Journal of Prevention of Alzheimer's Disease 12 (2025) 100205

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Utility of plasma GFAP as a secondary endpoint for clinical trials in Alzheimer's disease

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ARTICLE INFO

Keywords:
Plasma GFAP
Biomarker
Clinical trial

ABSTRACT

Background: Clinical trials have recently incorporated plasma glial fibrillary acidic protein (GFAP) as an exploratory endpoint. To include plasma GFAP as a secondary endpoint, it is essential to characterize its longitudinal progression in target populations.

Objective: To evaluate the potential use of plasma GFAP changes as a secondary endpoint in Alzheimer's disease trials.

Methods: We longitudinally evaluated plasma GFAP in individuals with amyloid-beta (Aβ)-PET scans at baseline in three well-characterized cohorts. Cox proportional hazards regression tested the association between changes

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https://doi.org/10.1016/j.tjpad.2025.100205
Received 3 December 2024; Received in revised form 6 May 2025; Accepted 12 May 2025

in plasma GFAP and cognitive function. Analysis of the 95 % confidence interval of annualized change in plasma GFAP provided statistical inference for a significant longitudinal change. Effect size was calculated as the group mean divided by the standard deviation (SD). We estimated the sample size needed to test a 25% drug effect with 80% power on reducing changes in GFAP.

Results: We assessed 487 individuals [176 cognitively unimpaired (CU; 29% Aβ positive) and 311 cognitively impaired (CI; 51% Aβ positive)] with some degree of cerebrovascular disease (Fazekas 1–3), over a mean (SD) follow-up of 1.84 (0.46) years. Changes in plasma GFAP were significantly associated with worsening in Clinical Dementia Rating sum of boxes (CDR-SB) score across the population ($p < 0.0001$). In CU, only Aβ positive individuals showed significant changes in GFAP ($p < 0.001$). On the other hand, both CI Aβ positive and negative individuals showed longitudinal progression in GFAP levels ($p < 0.0001$). The effect size of changes in plasma GFAP was higher in CU Aβ positive (0.44), followed by CI Aβ positive (0.42) and CI Aβ negative (0.38). Clinical trials focusing on CU Aβ positive would require 1320 individuals per study arm, while focusing on CI Aβ positive would require 1440 individuals per study arm.

Conclusion: Plasma GFAP increased in parallel with cognitive decline, making it a candidate for monitoring disease progression in trials aimed at mitigating cognitive deterioration. Although Aβ positivity significantly accelerated GFAP progression, the fact that GFAP was increased in CI Aβ negative with cerebrovascular disease supports its potential use as a secondary endpoint in this population as well.

Introduction

Cerebrospinal fluid (CSF) and positron emission tomography (PET) techniques capable of measuring amyloid-beta (Aβ) and tau have been used as endpoints in numerous clinical trials in Alzheimer's disease (AD) [1]. Blood biomarkers offer an accessible and cost-effective alternative to identify and monitor AD pathology, presenting clear logistical advantages over the established biomarker modalities mentioned above in detecting and monitoring AD pathology [2–4]. Their ease of measurement allows for more frequent assessments compared to neuroimaging or lumbar punctures, making them especially advantageous when considering their incorporation in clinical trials [5–7]. Plasma Aβ42 and Aβ40 ratios and phosphorylated tau (p-tau) at epitopes 181, 217, and 231 (p-tau181, p-tau217, and p-tau231) have been used to identify AD pathological hallmarks and monitor disease modification [8–10]. Recently, plasma glial fibrillary acidic protein (GFAP) has emerged as a biomarker for astrocyte reactivity that seems to be associated with the progression of AD [11,12].

Increasing evidence suggests a significant association of cross-sectional and longitudinal plasma GFAP measurement with Aβ, p-tau, and functional abnormalities [13–16]. Additionally, a recent study investigating the longitudinal associations between plasma GFAP and AD pathology in individuals with Down syndrome revealed that plasma GFAP exhibited a higher diagnostic value in distinguishing symptomatic from asymptomatic groups compared to neurofilament light chain (NfL) or p-tau181 and that longitudinal plasma GFAP is highly correlated with cortical thinning and Aβ pathology [17]. Thus, monitoring plasma GFAP levels over time has the potential to provide insights into the underlying pathological processes associated with AD progression, which reinforces the utility of plasma GFAP as a secondary endpoint in clinical trials. This is particularly important to support the results of primary clinical endpoints that can sometimes be challenging to interpret in relatively short trial periods [18,19].

Previous studies have tested the performance of plasma p-tau and NfL as endpoints in clinical trials [8,20,21]. To our knowledge, no previous study has investigated the characteristics of plasma GFAP as a secondary endpoint in clinical trials. Here, we tested the hypothesis that plasma GFAP may support the outcome of AD clinical trials focusing on cognitively unimpaired (CU) or cognitively impaired (CI) individuals.

Methods

Participants

We analyzed data obtained from three cohorts which had two measures of plasma GFAP available: Translational Biomarkers in Aging and Dementia (TRIAD) [22], Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu; last accessed March 2025), and Biobank Innovations for Chronic Cerebrovascular Disease with Alzheimer's Disease Study (BICWALZS) [23,24].

The TRIAD cohort included 109 individuals (53 CU Aβ negative, 18 CU Aβ positive, 13 CI Aβ negative, 25 CI Aβ positive) across the AD continuum assessed in a research setting. The ADNI longitudinal cohort included 223 individuals (73 CU Aβ negative, 32 CU Aβ positive, 68 CI Aβ negative, 50 CI Aβ positive) across the AD continuum, assessed in a research setting. We selected individuals who had a follow-up duration $\leq$ 2.5 years to match the TRIAD and BICWALZS cohorts. The BICWALZS cohort included 155 participants of Eastern Asian ethnicity (73 CI Aβ negative, 82 CI Aβ positive). Participants were recruited voluntarily from those who visited neurology or psychiatry memory outpatient clinics. Individuals who had longitudinal measures of plasma GFAP with at least two time points in both cohorts were included. CU individuals were defined as those with global Clinical Dementia Rating (CDR) score equal to 0, whereas CI individuals were defined as those with global CDR score greater than or equal to 0.5, including those with Mild Cognitive Impairment (MCI) and AD dementia with cerebrovascular disease 24–26. All cohort studies were approved by their regional ethical committees – ADNI: the ADNI study was conducted according to Good Clinical Practice guidelines, US 21 CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards, and pursuant to state and federal HIPAA regulations and was approved by the Institutional Review Board of each participating site; TRIAD: reviewed by the McGill University and Douglas Hospital Research Centre Institutional Review Boards; BICWALZS: reviewed by the Institutional Review Board of Ajou University Hospital. All participants provided written informed consent.

Plasma quantification

Plasma samples from the TRIAD cohort were analyzed at the Clinical Neurochemistry Laboratory, University of Gothenburg, Gothenburg, Sweden. In the BICWALZS cohort, plasma samples were analyzed at the University of Pittsburgh, Pittsburgh, USA. In the ADNI cohort, plasma GFAP was measured by the FNIH Biomarker Consortium effort [27]. Plasma GFAP levels were quantified using the Human Neurology 4-Plex E assay (No. 103,670) on the Simoa HD-X platform by Quanterix. Plasma GFAP samples were measured in duplicate in the ADNI cohort [mean: 4.9 % (SD = 0.04)] and in singlicate in the TRIAD and BICWALZS cohorts.

Imaging analysis

In the ADNI cohort, Aβ-PET imaging was performed using [^{18}F]Florbetapir [28,29]. The BICWALZS cohort employed

Table 1
Participants' demographics and key characteristics.

	CU Aβ-PET negative	CU Aβ-PET positive	CI Aβ-PET negative	CI Aβ-PET positive
No.	126	50	154	157
Age at baseline, years (SD)	71.46 (6.07)	74.31 (5.57)	70.12 (7.34)	72.34 (7.76)
Female, No. (%)	71 (56.35%)	32 (64.00%)	88 (57.14%)	98 (62.42%)
Education, years (SD)	16.16 (3.18)	15.31 (3.07)[b]	11.95 (5.69)[a]	11.81 (5.07)[a]
CDR sum of boxes at baseline (SD)	0.07 (0.25)	0.18 (0.43)	1.12 (0.81)[a]	1.95 (1.42)[a,b]
***APOE* ε4, No. (%)**	16 (30.18%)	4 (30.76%)	15 (17.44%)	31 (28.97)
Aβ-PET, Centiloid at baseline	2.91 (9.04)	63.34 (20.94)[a,b]	4.98 (9.47)	69.50 (35.11)[a,b]
Plasma GFAP at baseline (z score, SD)	0.01 (0.94)	1.18 (1.62)[a]	0.23 (1.32)	2.42 (2.15)[a,b]
Follow-up time, years (SD)	1.67 (0.49)	1.68(0.47)[b]	1.97 (0.37)[a]	1.93 (0.43)[a]

Continuous variables are presented as mean (SD). *APOE* ε4 = Apolipoprotein E ε4; GFAP= glial fibrillary acidic protein, CU= cognitively unimpaired, CI= Cognitively impaired, Aβ= Amyloid beta, MCI= Mild cognitive impairment, AD=Alzheimer's disease. [a]Different from CU Aβ PET negative. [b]Different from CI Aβ PET negative.

[^{18}F]Flutemetamol. TRIAD cohort Aβ-PET was quantified using [^{18}F]AZD4694. We applied a previously published method to convert the Aβ-PET standardized uptake value ratio (SUVR) to the Centiloid scale [30]. Aβ-PET positivity was defined as Centiloid value equal or higher to 20, as previously described [31]. The severity of white matter hyperintensities (WMH) was visually graded on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequence using the Fazekas scale as no (0), mild (1), moderate (2), and severe (3) cerebrovascular disease [32].

Statistical methods

The statistical analyses were performed using R statistical software version 4.0.5 (http://www.r-project.org/) and GraphPad Prism version 9.5.0 (https://www.graphpad.com/). For all analyses, plasma GFAP values were z-scored by centering on the mean of CU Aβ negative participants within each cohort. Paired *t*-tests were performed to assess the plasma GFAP differences between baseline and follow-up. The rate of change in biomarkers was calculated between follow-up and baseline as follows: $(\frac{\text{Follow-up-Baseline}}{\Delta\text{time}})$. Cox proportional-hazards analysis was performed to assess whether changes in plasma GFAP levels were predictive of increased odds for increasing CDR sum of boxes score over time. We adjusted the analysis for potential confounding variables (age, sex, and education level, as well as baseline Aβ-PET status). For these analyses, the result was dichotomized into participants who showed an increase versus those who showed a stable CDR sum of boxes score. The effect size was calculated as the mean of change in plasma GFAP in the group divided by the respective standard deviation [33]. We estimated the sample size required for a clinical trial testing a hypothesized 25 % drug effect on longitudinal reduction in plasma GFAP with 80 % of power at a 5 % level using a well-validated formula [34,35].

Results

We studied 487 individuals with longitudinal GFAP [mean age = 71.73 (6.92 SD) years; 289 (59.22%) were female, mean follow-up period 1.84 (0.46 SD), range 0.8–3.75 years]. In the CU group, we had 126 Aβ-PET negative and 50 Aβ PET positive individuals. The CI group had 154 Aβ-PET negative and 157 Aβ-PET positive.

Fazekas ratings of 1–3 were present in 51% of CU Aβ negative, 66% of CU Aβ positive, 95% of CI Aβ negative, and 92% of CI Aβ positive, respectively. The demographics and key characteristics of the population are summarized in Table 1 and **Supplemental Tables 1, 2 and 3**.

Longitudinal changes in plasma GFAP levels

We observed a significant increase in plasma GFAP levels at follow-up compared to baseline in all groups except CU Aβ negative individuals (Fig. 1). In the CU group, the mean difference between baseline and follow-up in plasma GFAP was larger in Aβ positive than in Aβ negative individuals [CU Aβ negative: 0.1 (0.63 SD), $p = 0.09$ and CU Aβ positive: 0.58 (1.03 SD), $p < 0.001$] (Fig. 1A and B). Similarly, in the CI group, the mean difference in plasma GFAP between baseline and follow-up was larger in Aβ positive than Aβ negative individuals [CI Aβ negative: 0.26 (0.67 SD), $p < 0.0001$ and CI Aβ positive: 0.44 (1.19 SD), $p < 0.0001$] (Fig. 1C and D). The annual rate of change of plasma GFAP was significantly different from zero in all groups except CU Aβ negative individuals (Fig. 2). CI Aβ positive individuals showed the highest annualized rate of progression [0.33 (95% confidence interval, 0.16 to 0.45)], followed by CU Aβ positive [0.24 (95% confidence interval, 0.09 to 0.48)] and CI Aβ negative [0.15 (95% confidence interval, 0.09 to 0.26)] (Fig. 2A).

Table 2
Longitudinal change in plasma GFAP is associated with an increased risk of worsening cognition over time.

	HR	95 % confidence interval	P value
Change in GFAP	1.15	1.06–1.23	<0.0001*
Age, years	1.05	0.91–1.21	0.502
Sex	0.81	0.57–1.13	0.29
Education, years	0.94	0.91–0.97	0.004*
Aβ-PET status	1.55	1.14–2.10	0.003*

Cox proportional hazards models demonstrate the effect of longitudinal plasma GFAP in predicting risk for longitudinal cognitive change decline using CDR sum of boxes. Age, sex, education, and Aβ-PET burden were included as covariates in the model. Females were used as the reference group for sex. Abbreviations: GFAP, glial fibrillary acidic protein; HR, hazard ratio; Aβ-PET, amyloid-beta positron emission tomography. Models were corrected by cohort.

We also performed all the above-mentioned analyses within each cohort (**Supplemental Figs. 1–2)**.

We also evaluated longitudinal changes in plasma GFAP by vascular pathology burden among CI Aβ-negative individuals. The annual rate of change was significantly different from zero in individuals with mild vascular pathology [0.19 (95% confidence interval 0.03–0.36)] and for those with moderate to severe pathology [0.39 (95% confidence interval 0.12–0.65)], **Supplemental Fig. 3**.

Association of change in plasma GFAP with worsening cognition

Longitudinal changes in plasma GFAP were significantly associated with an increased risk of worsening cognition over time, using CDR sum of boxes as a proxy of global cognition, in the entire population (HR = 1.15, $p < 0.0001$, Table 2 (**Supplemental Table 4**). The association remained significant when the entire population was stratified in CU and CI groups [CU: HR = 1.77, $p = <0.001$, CI: HR = 1.13, $p < 0.001$,

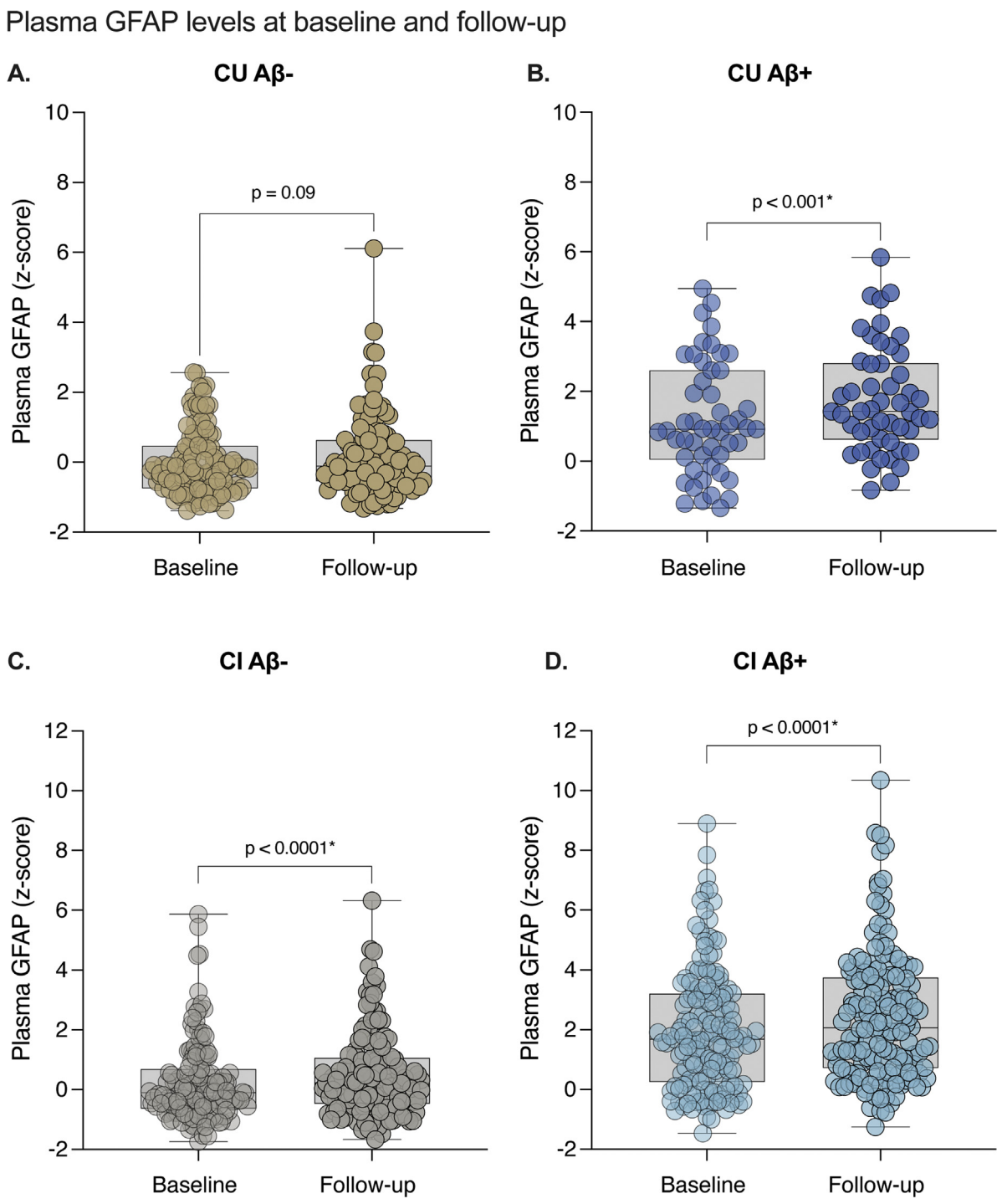

Fig. 1. Comparison of plasma GFAP levels between baseline and follow-up in individuals stratified by Aβ status. Box and whisker plots show differences between baseline and follow-up visits. **A.** CU Aβ negative: mean follow-up 1.67 years, SD = 0.49; **B.** CU Aβ positive: mean follow-up 1.68 years, SD = 0.47; **C.** CI Aβ negative: mean follow-up 1.97 years, SD = 0.37; **D.** CI Aβ positive: mean follow-up 1.93 years, SD = 0.43. Higher values at follow-up indicate increased plasma GFAP levels compared to baseline.

Table 3]. Similarly, within the ADNI, TRIAD and BICWALZS cohorts, changes in plasma GFAP were associated with an increased risk of worsening cognition (**Supplemental Table 5**).

Effect size and sample size estimation for using plasma GFAP as a secondary trial endpoint

In the CU group, the effect size was numerically higher in Aβ positive (0.44) than in CU Aβ negative individuals (0.16) (Fig. 2B). In the CI group, we observed a similar magnitude of effect size in Aβ positive (0.42) and Aβ negative individuals (0.38) (Fig. 2B). Next, we estimated the sample size needed for clinical trials evaluating the effect of a hypothetical drug intervention in reducing the progression of plasma GFAP. Although CU Aβ negative individuals did not show a statistically significant increase in GFAP levels, we could estimate that a trial in this population would require 9320 individuals per study arm. The same trial in CU Aβ positive individuals would require 1320 per study arm, which represents a decrease of 85% in the sample size in comparison to

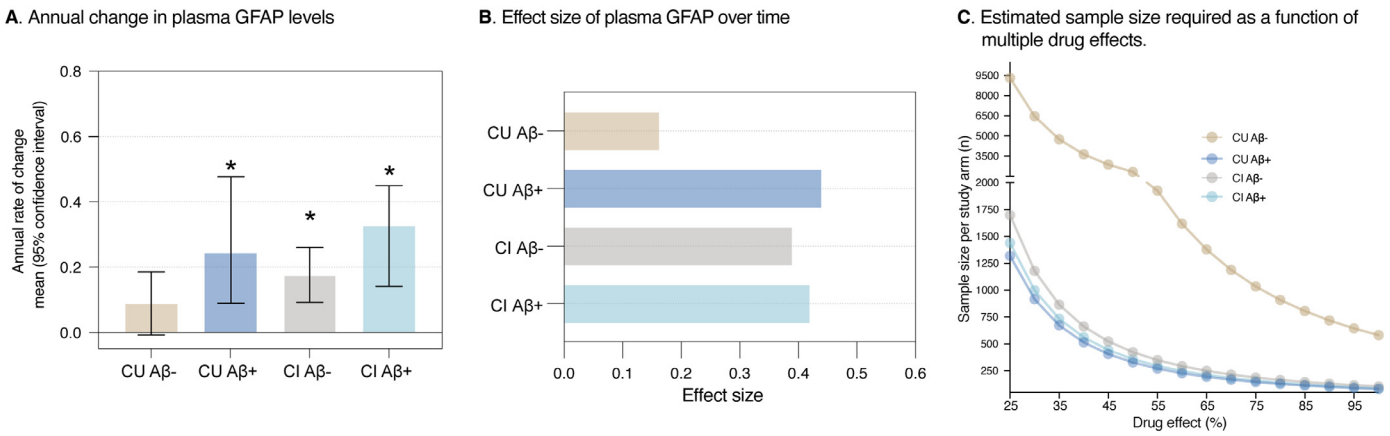

Fig. 2. Plasma GFAP annual rate of change, effect size, and trial sample size estimates as a function of multiple estimated drug effects. A. The vertical bars show the mean rate of changes with their respective 95 % confidence intervals in cognitively unimpaired (CU) and cognitively impaired (CI) individuals stratified by Aβ status. **B**. The horizontal bars represent the effect size in each group. **C**. The dots in the curves represent the sample size per study arm as a function of multiple hypothesized drug effects (x-axis), for a clinical trial targeting a reduction in change in plasma biomarkers with 80 % power and 0.05 alpha. (*) Indicates that the 95% confidence interval does not cross zero, meaning the longitudinal change is significantly different from zero.

Table 3
Longitudinal change in plasma GFAP, associates with an increased risk of progression to worsening cognition across the AD continuum.

	HR	95 % confidence interval	P value
A. Cognitively unimpaired (CU)			
Change in GFAP	1.77	1.04–3.04	0.03*
Age, years	0.82	0.52–1.23	0.392
Sex	1.83	0.81–4.01	0.141
Education, years	0.86	0.73–1.00	0.05
Aβ-PET status	1.54	0.64–3.76	0.319
B. Cognitively impaired (CI)			
Change GFAP	1.13	1.05–1.22	0.001*
Age, years	1.14	0.97–1.34	0.103
Sex	0.63	0.43–92	0.01*
Education, years	0.93	0.89–0.98	<0.01*
Aβ-PET status	1.51	1.07–2.12	0.01*

Cox proportional hazards models demonstrate the effect of longitudinal plasma GFAP in predicting risk for subsequent cognitive change measured using CDR sum of boxes in **A.** Cognitively unimpaired (CU) and **B.** Cognitively impaired (CI) individuals. Age, sex, education, and Aβ-PET burden are included as covariates in the model. Females were used as the reference group for the sex as a covariate. Abbreviations: GFAP, glial fibrillary acidic protein; HR, hazard ratio; Aβ-PET, amyloid-beta positron emission tomography. Models were corrected by cohort.

CU Aβ negative (Fig. 2C, **Supplemental Table 6)**. A trial in the CI Aβ negative group would require 1698 individuals per study arm, whereas the same trial in the CI Aβ positive group would require 1440 individuals per study arm, which represents a decrease in the sample size of 15% (Fig. 2C). The progressive decrease in the required sample size per study arm with the progressive increase in drug effects is displayed in Fig. 2C.

Discussion

In this study, we evaluated the characteristics of longitudinal changes in plasma GFAP across three cohorts to understand how these may inform studies that use plasma GFAP as a secondary outcome of clinical trials. We found that changes in GFAP were associated with an increased risk of worsening cognition. Aβ positive individuals showed the highest progression rate and effect sizes for changes in plasma GFAP over approximately 2 years. Furthermore, a significant change in plasma GFAP in CI Aβ negative individuals supports the potential utility of this biomarker as an endpoint in clinical trials focusing on this population.

Longitudinal changes in plasma GFAP were associated with an increased risk of cognitive decline in our population. This finding supports recent literature that shows that changes in GFAP predict memory decline [13]. Furthermore, earlier investigations have demonstrated an association between plasma GFAP levels and cognitive decline across various racial and ethnic groups [36,37]. We can hypothesize that, taken together, observational studies support the possibility that changes in plasma GFAP have the potential to predict cognitive deterioration in clinical trials. Therefore, trials could potentially leverage changes in plasma GFAP to help monitor treatment response [38]. This could be especially valuable in detecting pathophysiological changes that may not be apparent through clinical testing. Specifically, our results suggest that tracking plasma GFAP changes, particularly in CU Aβ positive, may serve as an early indicator of disease progression before the onset of clinical symptoms, allowing monitoring of at-risk individuals.

Our results demonstrate a marked increase in plasma GFAP levels in individuals following the AD continuum. These findings are in line with previous studies showing a greater increase in plasma GFAP in Aβ positive compared to Aβ negative individuals [39], as well as that plasma GFAP levels are highly correlated with Aβ biomarkers [40,41]. Recently, the TRAILBLAZER-ALZ and Clarity trials leveraged GFAP as an exploratory endpoint and found a significant decrease in plasma GFAP in their treatment groups [42,43], supporting it as a useful secondary endpoint for anti-Aβ trials. Here, we showed that the CU Aβ positive group presented significant longitudinal changes in plasma GFAP levels. This is in line with recent literature suggesting that plasma GFAP abnormalities play a key role in AD-related progression in CU populations by accelerating cognitive decline [44–46] and tau pathology [12,47,48]. Finally, our findings underscore the potential of using changes in plasma GFAP as a secondary endpoint in AD clinical trial.

We found that plasma GFAP showed a significant increase over time in CI Aβ negative individuals. Notably, all our CI Aβ negative individuals in the BICWALZS and TRIAD cohorts presented some degree of cerebrovascular pathology. Therefore, it could be argued that the aforementioned findings are supported by studies showing elevated GFAP levels in CI Aβ negative individuals with high WMH load [49] and an association between plasma GFAP and WMH burden [50,51]. The link between plasma GFAP and vascular lesions is compelling, as GFAP is thought to represent astrocyte reactivity often associated with different types of brain lesions, such as those caused by vascular pathology [52]. As a re-

sult, there is a rationale supporting the idea that both the accumulation of AD pathology and vascular injury can lead to the leakage or release of GFAP from astrocytes [53]. These results support GFAP as a potential biomarker of tissue response in the presence or absence of Aβ pathology for clinical trials. This suggests that although single anti-Aβ therapies decrease GFAP levels, this biomarker may be especially important in the context of combined therapies that may target more than one pathway associated with its increase. The effect of the combined therapies would potentially show a greater decrease in GFAP levels than the effect of single therapies.

One of the strengths of this study lies in the use of data from cohorts in North America and Asia, increasing the generalizability of our results to more ethnically diverse populations, which is a pressing issue in AD clinical trials. The association of changes in GFAP with changes in cognition in both the CU and CI groups further supports the idea that changes in GFAP can be used as an outcome related to cognitive benefit. Certain limitations should be considered when interpreting our results. Some of the analyses had a relatively small sample size when the entire population was stratified by cognitive status and Aβ-PET positivity. In the BICWALZS cohort, tau-PET imaging data were unavailable, precluding the adjustment of the Cox-hazard analysis for tau-PET. Furthermore, using only two time points to study longitudinal changes in plasma GFAP may limit our understanding of its trajectory during disease progression. Therefore, additional and longer follow-up timepoints could yield more comprehensive insights into plasma GFAP dynamics in the population. While plasma GFAP changes are strongly associated with AD pathology, they are also elevated in other neurodegenerative disorders [54]. Thus, AD clinical trials should evaluate changes in plasma GFAP as a secondary endpoint in alongside with disease-specific biomarkers to enhance the interpretability of their results. Changes in plasma GFAP had the largest effect size for clinical trials in CU Aβ positive individuals compared to other studies groups. However, when compared to studies using other AD-specific plasma biomarkers, such as p-tau181 [21] and p-tau217 [55], plasma GFAP demonstrated a more modest effect size. Lastly, more data are needed to understand the association between changes in GFAP biofluid levels following drug exposure and actual brain tissue changes in astrocyte reactivity.

To conclude, changes in GFAP have the potential to be used as a secondary endpoint in clinical trials across the spectrum of AD, from CU to individuals with dementia, as well as in individuals with cognitive impairment due to other age-related conditions such as cerebrovascular disease. Finally, the data displayed here could serve as a blueprint to support sample size estimation for clinical trials using GFAP as a secondary endpoint.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Henrik Zetterberg reports a relationship with Abbvie, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, reMYND, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave that includes: consulting or advisory. Henrik Zetterberg reports a relationship with Cellectricon, Fujirebio, Alzecure, Biogen, and Roche that includes: speaking and lecture fees. Henrik Zetterberg reports a relationship with Brain Biomarker Solutions in Gothenburg AB (BBS) that includes: equity or stocks. Kaj Blennow reports a relationship with Abcam, Axon, Biogen, Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers that includes:. Kaj Blennow reports a relationship with Brain Biomarker Solutions in Gothenburg AB (BBS) that includes: equity or stocks. Serge Gauthier reports a relationship with Cerveau Therapeutics that includes: consulting or advisory. Eduardo R Zimmer reports a relationship with Nintx, Novo Nordisk, Masima that includes: consulting or advisory. Eduardo R Zimmer reports a relationship with Masima that includes: equity or stocks. Thomas K. Karikari reports a relationship with for Quanterix Corp., SpearBio Inc., Neurogen Biomarking LLC that includes: consulting or advisory. Thomas K. Karikari reports a relationship with Neurogen Biomarking LLC. that includes: equity or stocks. Thomas K. Karikari has received honoraria for grant review from the Quebec Consortium for Drug Discovery, Canada, all outside of the submitted work. TKK has received blood biomarker data on defined research cohorts from Janssen and Alamar Biosciences for independent analysis and publication, with no financial incentive and/or research funding attached. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

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Acknowledgements

We thank the TRIAD and BICWALZS studies personnel for their effort and participants for their time, data and specimens. TRIAD cohort was supported by grants MOP-11–51–31 and RFN 152985, 159815, 162303 from the Canadian Institutes of Health Research (CIHR); MOP-11–51–31 from the Canadian Consortium of Neurodegeneration and Aging (CCNA); the Weston Brain Institute; and grants NIRG-12–92–92090 and NIRP-12–259245 from the Alzheimer Association. The BICWALZS study utilized biospecimens and data from the Biobank Innovations for Chronic Cerebrovascular Disease With Alzheimer's disease Study (BICWALZS), funded by the Korea Disease Control and Prevention Agency for the Korea Biobank Project (#4845–303). This work was supported by the National Research Foundation of Korea (NRF), funded by the Ministry of Science and ICT (NRF-2019R1A5A2026045), and also by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HR21C1003). Dr Pascoal is supported by the NIA (grant Nos. R01AG075336 and R01AG073267). Dr. Rosa-Neto is funded by Fonds de Recherche du Québec–Santé (Chercheur Boursier, PR-N

and 2020-VICO-279314) and CIHR-CCNA. Dr Abbas is supported by the Alzheimer's Association (grant No. AACSFD-23–1151197). Dr Ferreira is supported by the Alzheimer's Association (AARFD-22–923814). Dr Bellaver is supported by the Alzheimer's Association (AARFD-22–974627) and the National Institute of Aging (5 P01 AG025204–17). Dr Povala is supported by the Alzheimer's Association (24AARFD-1243899). Dr Bauer-Negrini is supported by the Alzheimer's Association (AARFD-23–1150249). Dr Blennow is supported by the Swedish Research Council (2017–00915), the Alzheimer Drug Discovery Foundation (RDAPB-201809–2016615), the Swedish Alzheimer Foundation (AF-742881), Hjärnfonden (FO2017–0243), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (ALFGBG-715986), the European Union Joint Program for Neurodegenerative Disorders (JPND2019–466–236), the NIH (1R01AG068398–01), and the Alzheimer's Association 2021 Zenith Award (ZEN-21–848495). Dr Zimmer receives financial support from CNPq [312410/20182; 435642/2018–9; 312306/2021–0; 409066/2022–2], ARD/FAPERGS [21/2551–0000673–0], AA [AARGD-21–850670], CNPQ/FAPERGS/PRONEX [16/2551–0000475–7], the Brazilian National Institute of Science and Technology in Excitotoxicity and Neuroprotection [465671/2014–4], Instituto Serrapilheira [Serra-1912–31365], and National Academy of Neuropsychology [ALZ-NAN-22–928381]. Dr Karikari receives financial support from Swedish Research Council (Vetenskåpradet; #2021–03244), Alzheimer's Association (#AARF21–850325), Swedish Alzheimer Foundation (Alzheimerfonden), Aina (Ann) Wallströms and Mary-Ann Sjöbloms stiftelsen, Emil och Wera Cornells stiftelsen. Dr Zetterberg is a Wallenberg Scholar supported by grants from the Swedish Research Council (Nos. 2022–01018 and 2019–02397), the European Union's Horizon Europe research and innovation programme under grant agreement No. 101053962, Swedish State Support for Clinical Research (No. ALFGBG-71320), the Alzheimer Drug Discovery Foundation, USA (No. 201809–2016862), the AD Strategic Fund and the Alzheimer's Association (No. ADSF-21–831376-C, No. ADSF-21–831381-C, and No. ADSF-21–831377-C), the Bluefield Project, the Olav Thon Foundation, the Erling- Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (No. FO2022–0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 860197, the European Union Joint Programme–Neurodegenerative Disease Research (JPND2021- 00694), the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre, and the UK Dementia Research Institute at University College London (UKDRI-1003).

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) NIH Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). The ADNI is funded by the National Institute on Aging (NIH), the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.;Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated companyGenentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100205.

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