Conclusions: Higher plasma GFAP levels differentiated participants with cognitive impairment from those with normal cognition and were associated with worse performance on all neuropsychological tests assessed. GFAP had similar accuracy in detecting those with cognitive impairment compared with p-tau$_{181}$ and NfL, however, a panel of all three biomarkers was optimal. These results support the utility of plasma GFAP in AD detection and suggest the pathological processes it represents might play an integral role in the pathogenesis of AD.

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Keyword 1: dementia - Alzheimer's disease
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5 Antemortem Plasma GFAP Predicts Alzheimer's Disease Neuropathological Changes

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Objective: Blood-based biomarkers offer a more feasible alternative to Alzheimer's disease (AD) detection, management, and study of disease mechanisms than current *in vivo* measures. Given their novelty, these plasma biomarkers must be assessed against post-mortem neuropathological outcomes for validation. Research has shown utility in plasma markers of the proposed AT(N) framework, however recent studies have stressed the importance of expanding this framework to include other pathways. There is promising data supporting the usefulness of plasma glial fibrillary acidic protein (GFAP) in AD, but GFAP-to-autopsy studies are limited. Here, we tested the association between plasma GFAP and AD-related neuropathological outcomes in participants from the Boston University (BU) Alzheimer's Disease Research Center (ADRC).
Participants and Methods: This sample included 45 participants from the BU ADRC who had a plasma sample within 5 years of death and donated their brain for neuropathological examination. Most recent plasma samples were analyzed using the Simoa platform. Neuropathological examinations followed the National Alzheimer's Coordinating Center procedures and diagnostic criteria. The NIA-Reagan Institute criteria were used for the neuropathological diagnosis of AD. Measures of GFAP were log-transformed. Binary logistic regression analyses tested the association between GFAP and autopsy-confirmed AD status, as well as with semi-quantitative ratings of regional atrophy (none/mild versus moderate/severe) using binary logistic regression. Ordinal logistic regression analyses tested the association between plasma GFAP and Braak stage and CERAD neuritic plaque score. Area under the curve (AUC) statistics from receiver operating characteristics (ROC) using predicted probabilities from binary logistic regression examined the ability of plasma GFAP to discriminate autopsy-confirmed AD status. All analyses controlled for sex, age at death, years between last blood draw and death, and *APOE e4* status.
Results: Of the 45 brain donors, 29 (64.4%) had autopsy-confirmed AD. The mean (SD) age of the sample at the time of blood draw was 80.76 (8.58) and there were 2.80 (1.16) years between the last blood draw and death. The sample included 20 (44.4%) females, 41 (91.1%) were White, and 20 (44.4%) were *APOE e4* carriers. Higher GFAP concentrations were associated with increased odds for having autopsy-confirmed AD (OR=14.12, 95% CI [2.00, 99.88], p=0.008). ROC analysis showed plasma GFAP accurately discriminated those with and without autopsy-confirmed AD on its own (AUC=0.75) and strengthened as the above covariates were added to the model (AUC=0.81). Increases in GFAP levels corresponded to increases in Braak stage (OR=2.39, 95% CI [0.71-4.07], p=0.005), but not CERAD ratings (OR=1.24, 95% CI [0.004, 2.49], p=0.051). Higher GFAP levels were associated with greater temporal lobe atrophy (OR=10.27, 95% CI [1.53 ,69.15],

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p=0.017), but this was not observed with any other regions.
Conclusions: The current results show that antemortem plasma GFAP is associated with non-specific AD neuropathological changes at autopsy. Plasma GFAP could be a useful and practical biomarker for assisting in the detection of AD-related changes, as well as for study of disease mechanisms.

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6 Examining Interactions Between Longitudinal, Intraindividual Fluctuations in Cognition and Alzheimer's Disease Biomarkers to Predict Eventual Disease Progression

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Objective: The purpose of the present study was to study the clinical significance of fluctuations in cognitive impairment status in longitudinal studies of normal aging and dementia. Several prior studies have shown fluctuations in cognition in longitudinal studies is associated with greater risk of conversion to dementia. The present study defines "reverters" as participants who revert between cognitive normality and abnormality according to the Clinical Dementia Rating (CDR™). A defining feature of the CDR at the Knight Alzheimer's Disease Research Center (Knight ADRC) at Washington University in St. Louis is that the CDR is calculated by clinicians blinded to cognitive data and any prior assessments so that conclusions are drawn free of circularity and examiner bias. We hypothesized reverters, when compared to cognitively normal participants who remain unimpaired, would have worse cognition, abnormal biomarkers, and would eventually progress to a stable diagnosis of cognitive impairment.
Participants and Methods: From ongoing studies of aging and dementia at the Knight ADRC, we selected cognitively normal participants with at least three follow-up visits. Participants fell into three categories: stable cognitively normal ("stable CN"), converters to stable dementia ("converters"), and reverters. Cognitive scores at each visit were z-scored for comparison between groups. A subset of participants had fluid biomarker data available including cerebrospinal fluid (CSF) amyloid and phosphorylated-tau species, and plasma neurofilament light chain (NfL). Mixed effect models evaluated group relationships between biomarker status, *APOE* ε4 status, and CDR progression.
Results: 930 participants were included in the study with an average of 5 years of follow-up (Table 1). 661 participants remained cognitively normal throughout their participation while 142 progressed to stable dementia and 127 participants had at least one instance of reversion. Compared to stable CN, reverters had more abnormal biomarkers at baseline, were more likely to carry an *APOE* ε4 allele, and had better cognitive performance at baseline (Table 2, Figure 1). Compared to converters, reverters had less abnormal biomarkers at baseline, were less likely to carry an *APOE* ε4 allele, and had overall better cognitive performance at baseline. In longitudinal analyses, cognitive trajectories of reverters exhibited a larger magnitude of decline compared to stable CNs but the magnitude of decline was not as steep as converters.
Conclusions: Our results confirm prior studies that showed reversion in cognitive status, when compared to stable cognitive normality, is associated with worse overall genetic, biomarker and cognitive outcomes. Longitudinal analyses demonstrated reverters show significantly more decline than stable participants and a higher likelihood of eventual conversion to a stable dementia diagnosis. Reverters' cognitive trajectories appear to occupy a transitional phase in disease progression between that of cognitive stability and more rapid and consistent progression to stable dementia. Identifying participants in the preclinical phase of AD who are most likely to convert to symptomatic AD is critical for secondary prevention clinical trials. Our results suggest that examining intraindividual variability in cognitive impairment using unbiased, longitudinal CDR scores may be

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