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RESEARCH ARTICLE

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# Prediction of longitudinal synaptic loss in Alzheimer's disease using tau PET and plasma biomarkers

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## Abstract

**INTRODUCTION:** We investigated the associations of longitudinal synaptic loss and cognitive decline with tau burden and plasma biomarkers in Alzheimer's disease (AD).

**METHODS:** Twenty cognitively impaired (CI) individuals and 16 healthy controls (HC) underwent cognitive and plasma biomarker assessments, amyloid positron emission tomography (PET), tau PET, and synaptic density PET; after 1 year, tau and synaptic density PET were repeated. The relationships among tau burden, plasma biomarkers, synaptic density, and cognition were investigated.

**RESULTS:** The CI group had more longitudinal synapse loss and tau deposition than HCs. Longitudinal synaptic loss was positively associated with longitudinal cognitive decline, negatively with longitudinal tau deposition. Plasma glial fibrillary acidic protein (GFAP) mediates the relationship between longitudinal tau deposition and longitudinal synaptic loss. Tau burden, plasma phosphorylated tau181, and GFAP could predict longitudinal synaptic loss and cognitive decline.

Jie Wang and Qi Huang contributed equally to this work.

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**CONCLUSIONS:** The CI group had more longitudinal synapse loss and tau burden increases than HCs. Tau pathology and plasma GFAP could predict longitudinal synapse loss and cognitive decline.

**KEYWORDS**
cognition, longitudinal synapse loss, plasma glial fibrillary acidic protein, plasma phosphorylated tau 181, synaptic density, tau burden

**Highlights**

- Cognitively impaired individuals had more longitudinal synapse loss in the medial temporal lobe, and increased tau burden in the widespread neocortex than healthy controls.
- The longitudinal change of synaptic density was negatively associated with the longitudinal change of tau burden, and positively associated with longitudinal cognitive decline.
- Plasma glial fibrillary acidic protein (GFAP) mediates the relationship between longitudinal tau deposition and longitudinal synaptic loss.
- Tau burden, plasma phosphorylated tau181, and GFAP could predict longitudinal synaptic loss and cognitive decline.

## 1 | BACKGROUND

Alzheimer's disease (AD), the most common cause of dementia in older adults, is a progressive neurodegenerative disease leading to cognitive disabilities and memory loss. The pathological features of AD are the extracellular accumulation of amyloid beta (A$\beta$) peptide in neuritic plaques and the intercellular aggregation of hyperphosphorylated tau protein in neurofibrillary tangles (NFTs),[1] both of which lead to neurodegeneration and synaptic loss, impairing cognition. Previous studies manifested synapse loss was the physical and structural basis of cognitive changes and better correlated with cognitive decline in AD patients.[2,3]

Synaptic vesicle glycoprotein 2A (SV2A) is a protein found in synaptic vesicles across the brain and serves as a biomarker for synaptic density, which can be measured via positron emission tomography (PET) imaging using radioligands like [$^{11}$C]UCB-J and [$^{18}$F]SynVesT-1.[4,5] Previous PET studies have revealed widespread reductions in SV2A binding in the medial temporal lobe and neocortex in early AD and mild cognitive impairment (MCI) patients compared to healthy controls (HCs).[6,7] However, the associations of longitudinal synaptic loss with AD pathology are also unknown. In a small sample follow-up study, the regional synaptic loss was observed to follow tau accumulation in 12 amnestic MCI patients after a delay of 2 years; baseline tau was negatively associated with longitudinal SV2A loss in early Braak regions.[8,9] Importantly, the longitudinal changes in synaptic density in different stages of AD warrant further exploration.

Tau pathology causes dysregulation of the synaptic proteome and leads to functional abnormalities in synaptic transmission. A large body of evidence suggests that tau plays a key role in synaptic impairment.[10] Tau burden was shown to be negatively associated with synaptic density in the medial temporal lobe in PET studies.[11,12] [$^{18}$F]MK6240 is a second-generation tau PET tracer that can quantify tau deposition in the medial temporal lobe region (including the hippocampus) without interference from the choroid plexus, and enables the study of the relationship between tau burden and synaptic density in early disease stages.[13] Additionally, the levels of phosphorylated tau (p-tau)181 in cerebrospinal fluid (CSF) are positively associated with growth-associated protein-43 (GAP43), a presynaptic membrane protein. Neuronal pentraxin 2 (NPTX2), a secreted synaptic protein, is markedly decreased in the *post mortem* brain lysates and CSF of MCI and AD patients, and CSF NPTX2 is positively associated with A$\beta$42 levels and negatively associated with p-tau181 levels.[14]

With the rapid development of plasma biomarkers, it is critical to investigate their associations with longitudinal synaptic loss measured by PET. The single molecule array (Simoa) platform can be used in tests of plasma amyloid and tau pathology and as a biomarker of the astrocytic reactivity of glial fibrillary acidic protein (GFAP) and neuroaxonal damage to neurofilament light chain (NfL).[15–17] Understanding the associations of plasma biomarkers with longitudinal synaptic loss motivates the development of potential methods for evaluating future therapies targeting synapses.

Understanding the dynamic changes in synaptic dysfunction and their relationship with AD imaging and plasma pathologies is urgent. In this study, we aimed (1) to assess the differences in longitudinal changes in tau deposition and synaptic loss between cognitively impaired (CI) and healthy control (HC) groups, (2) to investigate the associations of synaptic loss with plasma biomarkers and tau pathology, and (3) to evaluate the prognostic ability of plasma biomarkers

and tau pathology to predict longitudinal synaptic loss and cognitive decline.

**RESEARCH IN CONTEXT**

1. **Systematic review**: Synapse loss was the physical and structural basis of cognitive changes and better correlated with cognitive decline in Alzheimer's disease patients. With the rapid development of plasma biomarkers, investigating the associations of plasma biomarkers with longitudinal synaptic loss is critical. We searched PubMed, but found no literature reporting the association of longitudinal synaptic loss with plasma biomarkers.
2. **Interpretation**: In this study, we found that cognitively impaired patients exhibited faster longitudinal synaptic loss and more tau deposition than the healthy controls. The longitudinal synaptic loss was negatively associated with longitudinal tau burden increases, and positively associated with longitudinal cognitive decline. Tau pathology (plasma phosphorylated tau 181 and tau burden) and plasma glial fibrillary acidic protein could predict longitudinal synapse loss and cognitive decline.
3. **Future directions**: Future studies will further investigate the temporal relationships among tau pathology, neuroinflammation, and synaptic loss, and how neuroinflammation and tau pathology interact to cause synaptic loss.

## 2 | METHODS

### 2.1 | Participants

Twenty CI participants, including 10 AD dementia patients and 10 MCI individuals, as well as 16 HCs, were recruited from the memory clinic of Shanghai Jiao Tong University affiliated with Ruijin Hospital and communities in Shanghai. All participants underwent [$^{18}$F]SynVesT-1 PET/MR, [$^{18}$F]Florbetapir, and [$^{18}$F]MK6240 PET/CT (computed tomography) scans, neuropsychological assessments, and blood sample collection at baseline. All the assessments were conducted within 1 month of inclusion. After 1 year all subjects underwent follow-up evaluation; [$^{18}$F]SynVesT-1 PET/MRI (magnetic resonance imaging), [$^{18}$F]MK6240 PET/CT, and neuropsychological assessments were repeated. The inclusion and exclusion criteria were reported in our previous study.[18–20] These study protocols were approved by the institutional review boards of Fudan University Affiliated Huashan Hospital and Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Written informed consent was provided by participants or their family members.

### 2.2 | Neuropsychology

All participants received a comprehensive neuropsychological assessment revised for use in the Chinese population.[21,22] The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment-Basic (MoCA-B) were used to assess global cognition, and six additional neuropsychological tests in three cognitive domains were conducted. Specifically, the Auditory Verbal Learning Test (AVLT), 30 minute long delayed free recall of the AVLT (AVLT-LDR, 12 items), and the AVLT-recognition (24 items) were conducted to assess the memory domain; the animal fluency test (AFT, total score) and Boston Naming Test (BNT, 30 items) were used for the language domain; and the Shape Trails Test (STT), parts A and B (time to completion) were administered to evaluate the executive function domain.[19]

The presence of AD was determined according to the 2018 National Institute on Aging and Alzheimer's Association (NIA-AA) diagnostic criteria, and MCI was diagnosed based on Jak and Bondi's criteria as described in our previous report; notably, amyloid positivity is mandatory for any diagnosis of CI.[23,24] The classification of HC was defined as a lack of cognitive impairment found in any cognitive domain and A$\beta$ negativity.[25,26] Clinical conversion was determined based on neuropsychological assessments at baseline and follow-up.

### 2.3 | Plasma biomarker measurements

The plasma biomarkers were measured using the Quanterix Simoa HD-1 platform.[27] The Neurology 3-Plex A Assay Kit (Lot 502838) was used for the measurement of A$\beta$42 and A$\beta$40, and the Assay Kit V2 (Lot 502923) was used for the measurement of plasma p-tau181 and NfL, as previously reported.[28] The Neurology 4-Plex E Advantage kit (QTX-103670) was used to assess the concentrations of plasma GFAP. The concentrations of the plasma biomarkers are presented in pg/mL.

### 2.4 | PET and MR imaging

[$^{18}$F]SynVesT-1 PET/MR scans were performed on a 3T PET/MR scanner (uPMR 790, United Imaging Healthcare). A 30 minute static PET scan started 60 minutes after intravenous injection of a 185 MBq (± 10%) dose of [$^{18}$F]SynVesT-1, whereas a 3D Dixon sequence was acquired for attenuation correction, and a T1-weighted MR scan was simultaneously performed with previously described parameters.[29,30] [$^{18}$F]Florbetapir and [$^{18}$F]MK6240 PET/CT imaging were performed using PET/CT scanners (Biograph mCT Flow, Siemens) with previously described parameters.[20] Twenty minute scans were conducted 50 minutes after intravenous injection of 370 MBq (± 10%) [$^{18}$F]Florbetapir and 90 minutes after intravenous injection of 185 MBq (± 10%) [$^{18}$F]MK6240.[30,31]

### 2.5 | Data preprocessing

We used SPM12 (Welcome Trust Centre for Neuroimaging; https://www.fil.ion.ucl.ac.uk/spm) for PET image preprocessing following a

previously described procedure. PET data quantification was calculated as the standardized uptake value ratio (SUVR) using the cerebellum, cerebellar gray matter, and inferior cerebellar gray matter as reference regions for [$^{18}$F]SynVesT-1, [$^{18}$F]Florbetapir, and [$^{18}$F]MK6240, respectively. The volume of interest (VOI), defined by the Automated Anatomical Labeling (AAL) atlas, was applied to the PET data,[32,33] which included the frontal, lateral parietal, lateral temporal, medial temporal, occipital, precuneus, and posterior cingulate regions; the insula; and the global cortex (the sum of all 8 VOIs). The positive [$^{18}$F]Florbetapir PET images were defined by visual rating according to the guidelines for interpreting amyloid PET.[30,34,35] Hippocampal volume was calculated by FreeSurfer version 4.3 (https://surfer.nmr.mgh.harvard.edu)[36] and normalized to the intracranial volume to control for cerebral size differences. This hippocampal volume ratio (HPVR) was used for further analysis.

### 2.6 | Multiplex immunofluorescence and immunohistochemical staining and microscopy of *post mortem* human brain tissue

*Post mortem* analyses were performed on brain tissues from an independent sample of six AD patients with a clinical diagnosis confirmed by pathological examination and six controls with no dementia (detailed information in Table S1 in supporting information). Paraffin-embedded human brain sections (4 μm) were deparaffinized in xylene and rehydrated before antigen retrieval in a microwave for 15 minutes. Multiplex immunofluorescence staining was performed with an Alpha Painter X30. The primary and secondary antibodies used are listed in Table S2 in supporting information. The sections were incubated with primary antibodies for 1 hour at 37°C. The AlphaTSA Multiplex IHC Kit (AXT37100031, AlphaX Biotech) was used for visualization. After each staining cycle, heat-induced epitope retrieval was performed to remove all the antibodies, including primary and secondary antibodies. The nuclei were counterstained with 4′,6-diamidino-2-phenylindole (DAPI) for 5 minutes and mounted with a mounting medium. Immunohistochemical staining with anti-4G8 (A$\beta$17-24, 1:4000) and anti-GFAP antibodies (1:50) was performed on adjacent hippocampal sections following a previous protocol;[37] the detailed methods are described in our previous study.[29]

### 2.7 | Statistical analysis

Voxel-wise group comparisons were conducted in SPM12, and analyses of clinical and VOI data were conducted via SPSS. All of the continuous data were found to be normally or approximately normally distributed according to the Kolmogorov–Smirnov test. We calculated the longitudinal change rates ($\Delta$) of the SUVR, HPVR, MMSE, and MoCA-B between baseline and follow-up, $\Delta$ = (follow-up−baseline)/baseline. The group differences in demographics, neuropsychological scores, plasma biomarker levels, and HPVR, SUVR, and $\Delta$SUVR values were compared using the chi-squared test for categorical variables and Student *t* test for continuous variables. Voxel-wise comparisons of the group differences between the CI and HC groups using Student *t* test were performed, with age, sex, and years of education being included as covariates. The differences in the proportion of slices with A$\beta$ (6E10), SV2A, and GFAP staining and the fluorescence intensity of tau in the hippocampal slices were analyzed using the Mann–Whitney *U* test.

At the VOI level, the correlations of synaptic density with tau burden, HPVR, plasma biomarkers, cognitive scores, $\Delta$ synaptic density with $\Delta$ tau burden, $\Delta$ HPVR, and $\Delta$ cognitive scores were investigated via partial correlation analyses with age, sex, and years of education as covariates. We used generalized linear models (GLMs) to determine the associations of baseline global amyloid deposition, tau burden, and HPVR with $\Delta$ synaptic density; baseline synaptic density with $\Delta$ tau burden and $\Delta$ HPVR; and baseline plasma biomarkers with $\Delta$ synaptic density and $\Delta$ cognitive scores.

We also conducted mediation analyses to investigate the relationships among plasma GFAP, tau pathology (tau burden and p-tau 181), $\Delta$ tau burden, $\Delta$ synaptic density, and $\Delta$ cognitive scores while controlling for age, sex, and years of education using PROCESS v4.1 by Andrew F. Hayes. The significance of the mediation was assessed by calculating bias-corrected 95% confidence intervals (c.i.s) by bootstrapping (5000 resamples). For voxel-wise analyses, the significance level was set at $p < 0.05$ with peak-level false discovery rate (FDR) correction, and the cluster-defining voxel threshold was set at the default value of 0.001. Because this was an exploratory study with a small sample size, $p < 0.05$ was considered to indicate a significant correlation (two sided) without correction for multiple comparisons for VOI correlation analyses.

## 3 | RESULTS

### 3.1 | Demographic characteristics and clinical assessments

A total of 36 participants were included in our study. The CI individuals were older than the HC individuals (72.45 ± 7.50 vs. 66.50 ± 8.15, $p = 0.029$) and the CI individuals had more education years than HC individuals (10.20 ± 3.54 vs. 12.88 ± 3.38, $p = 0.028$). The CI group had lower MMSE and MoCA-B scores than the HC group at both baseline and follow-up (Table 1). The CI group exhibited lower $\Delta$MMSE scores (−0.107 ± 0.11 vs. 0.003 ± 0.03, $p = 0.001$) than the HC group. There were no significant differences in the proportion of females or $\Delta$MoCA-B scores between the groups. None of the participants experienced conversion at the 1-year follow-up evaluation, and there were no differences in MMSE or MoCA-B scores between follow-up and baseline in the whole cohort or the CI and HC groups.

### 3.2 | Group differences in synaptic density, AD imaging, and plasma biomarkers

Voxel-wise analysis revealed that the CI group had lower synaptic density in the medial temporal lobe and greater tau burden in the

**TABLE 1** Demographic information and clinical characteristics.

| | CI | HC | *p* value |
|---|---|---|---|
| Number | 20 | 16 | |
| Proportion of females | 60% (12/20) | 67% (11/16) | 0.549 |
| Age | 72.45 ± 7.50 | 66.50 ± 8.15 | **0.029** |
| Education years | 10.20 ± 3.54 | 12.88 ± 3.38 | **0.028** |
| Baseline MMSE | 23.10 ± 3.82 | 28.88 ± 0.81 | **< 0.001** |
| Follow up MMSE | 20.80 ± 5.10 | 28.94 ± 0.92 | **< 0.001** |
| ΔMMSE | −0.107 ± 0.11 | 0.003 ± 0.03 | **0.001** |
| Baseline MoCA-B | 17.60 ± 7.06 | 27.08 ± 1.03 | **< 0.001** |
| Follow up MoCA-B | 16.55 ± 6.46 | 26.69 ± 0.99 | **< 0.001** |
| ΔMoCA-B | −0.048 ± 0.17 | 0.015 ± 0.04 | 0.152 |
| AVLT-LDR | 0.47 ± 0.92 | 4.92 ± 2.66 | **< 0.001** |
| AVLT-Rec | 14.53 ± 2.44 | 21.77 ± 1.78 | **< 0.001** |
| BNT | 17.47 ± 5.38 | 24.15 ± 2.82 | **< 0.001** |
| AFT | 7.80 ± 1.85 | 10.46 ± 2.87 | **0.007** |
| STT-A | 157.30 ± 92.47 | 62.38 ± 15.66 | **0.001** |
| STT-B | 448.15 ± 37.18 | 133.31 ± 49.42 | **0.002** |

*Note*: The bolded *p* values indicate statistical significance ($p < 0.05$).
Abbreviations: AFT, animal fluency test; ALVT-LDR, Auditory Verbal Learning Test long delayed recall; ALVT-Rec, Auditory Verbal Learning Test recognition; BNT, Boston Naming Test; CI, cognitively impaired individuals; HC, healthy control; HPVR, hippocampal volume ratio; MMSE, Mini-Mental State Examination; MoCA-B, Montreal Cognitive Assessment-Basic; STT, Shape Trails Test; Δ = (follow-up—baseline)/baseline.

medial temporal lobe and widespread neocortex than the HC group at both baseline and follow-up, as shown in Figure S1 in supporting information. The CI group had greater amyloid deposition (global [$^{18}$F]Florbetapir SUVR: 1.461 ± 0.197 versus 1.291 ± 0.098, $p = 0.004$) than the HC group at baseline. The CI group had a lower HPVR than the HC group both at baseline (0.0034 ± 0.0002 vs. 0.0043 ± 0.0003, $p < 0.001$) and at follow-up (0.0031 ± 0.0003 vs. 0.0042 ± 0.0003, $p < 0.001$).

VOI analysis revealed that, in the HC group, there were no significant differences in synaptic density or tau burden between baseline and follow-up, as shown in Figure S2A in supporting information. However, in the CI group, synaptic density was significantly lower in the medial temporal lobe ([$^{18}$F]SynVesT-1 SUVR: 0.854 ± 0.059 vs. 0.905 ± 0.056, $p = 0.009$) at follow-up than at baseline. There were no significant differences in tau burden between baseline and follow-up (Figure S2A). However, the CI group had a greater Δ[$^{18}$F]SynVesT-1 SUVR (−0.055 ± 0.041 vs. −0.003 ± 0.050, $p = 0.002$) in the medial temporal lobe than the HC group; the CI group had greater Δ[$^{18}$F]MK6240 SUVR in the widespread neocortex than the HC group, as shown in Figure 1.

The CI group exhibited lower plasma Aβ42/40 levels (0.059 ± 0.020 vs. 0.072 ± 0.020, $p = 0.048$) and higher plasma p-tau181 (4.30 ± 0.944 vs. 1.98 ± 0.574, $p < 0.001$), NfL (20.12 ± 4.765 vs. 13.08 ± 6.207, $p = 0.001$), and GFAP (149.07 ± 40.23 vs. 64.06 ± 23.99, $p < 0.001$) compared to the HC group, as illustrated in Figure S3 in supporting information. We also examined the proportion of hippocampal slices exhibiting Aβ, SV2A, and GFAP staining, along with the fluorescence intensity of tau in these slices. The proportion of 6E10-positive Aβ (64.26 ± 26.46 vs. 22.62 ± 14.13, $p = 0.007$) and GFAP staining (52.46 ± 10.28 vs. 34.69 ± 5.62, $p = 0.004$) was higher in the hippocampi of AD patients than in HC individuals, while the proportion with SV2A staining (21.85 ± 17.98 vs. 55.33 ± 15.61, $p = 0.006$) was lower in the hippocampi of AD patients compared to HC individuals (Figure 2). The average fluorescence intensity for tau (19.71 ± 5.96 vs. 12.67 ± 4.60, $p = 0.045$) was greater in the hippocampus of AD patients than in HC individuals.

## 3.3 | Associations of synaptic density with imaging biomarkers

When analyzing the whole cohort, the regional tau burden was negatively associated with not only corresponding regional synaptic density in the lateral parietal ($r = -0.570$, $p < 0.001$), lateral temporal ($r = -0.685$, $p < 0.001$), medial temporal ($r = -0.575$, $p < 0.001$), posterior cingulate gyrus ($r = -0.718$, $p < 0.001$), occipital ($r = -0.673$, $p < 0.001$), precuneus ($r = -0.507$, $p = 0.002$), insula ($r = -0.462$, $p = 0.005$), and global cortex ($r = -0.545$, $p = 0.001$), but also synaptic density across multiple other brain regions at baseline (Figure S4A in supporting information). We also found that baseline regional tau burden was also negatively associated with follow-up corresponding regional and across multiple other brain regions' synaptic density, as shown in Figure S4B.

In the whole cohort, the longitudinal change rate of synaptic density in the medial temporal lobe was negatively associated with the Δ tau burden in the lateral parietal ($r = -0.499$, $p = 0.002$), frontal ($r = -0.356$, $p = 0.033$), precuneus ($r = -0.379$, $p = 0.023$), occipital lobe ($r = -0.475$ $p = 0.003$), and global cortex ($r = -0.437$, $p = 0.008$), as well as in the posterior cingulate ($r = -0.400$, $p = 0.016$), as shown in Figure 3. However, the rate of change in synaptic density was not significantly associated with ΔHPVR ($r = 0.243$, $p = 0.153$).

Baseline global amyloid deposition could not predict the longitudinal change rate of synaptic density in the medial temporal lobe ($\beta = -0.106$, standard error [SE] = 0.046, $p = 0.052$), and the synaptic density at baseline could not predict the longitudinal change in tau burden and HPVR. However, HPVR could predict the longitudinal change rate of synaptic density in the medial temporal lobe ($\beta = 62.931$, SE = 12.382, $p < 0.001$). The tau burden in the medial temporal lobe, insula, and global cortex could predict the longitudinal rate of change in synaptic density in the medial temporal lobe, as shown in Figure S5 in supporting information.

## 3.4 | Associations of synaptic density with plasma biomarkers

We also investigated the associations of synaptic density with plasma biomarkers and found that baseline plasma Aβ42/40 was not asso-

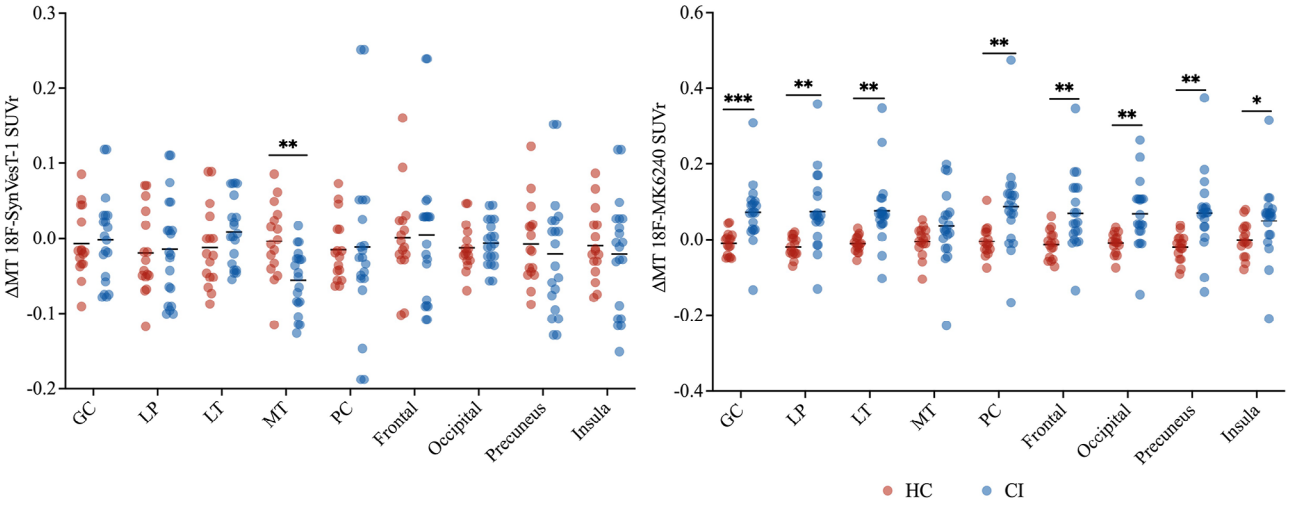


**FIGURE 1** Differences in the longitudinal changes in synaptic density and tau burden between the CI group and the HC group. All $p$ values < 0.05 are marked with *, **, or *** to indicate significant differences between the two groups, with * indicating $p < 0.05$, ** indicating $p < 0.01$, and *** indicating $p < 0.001$. CI, cognitively impaired; GC, global cortex; HC, healthy control; LP, lateral parietal lobe; LT, lateral temporal lobe; MT, medial temporal lobe; PC, posterior cingulate; SUVR, standardized uptake value ratio; $\Delta$ = (follow-up−baseline)/baseline.

ciated with synaptic density in the medial temporal lobe at baseline ($r = 0.219$, $p = 0.200$) or at follow-up ($r = 0.316$, $p = 0.061$). The synaptic density in the medial temporal lobe was negatively associated with plasma p-tau181 ($r = -0.406$, $p = 0.014$; $r = -0.605$, $p < 0.001$), NfL ($r = -0.354$, $p = 0.034$; $r = -0.470$, $p = 0.004$), and GFAP ($r = -0.641$, $p < 0.001$; $r = -0.782$, $p < 0.001$) at baseline and follow-up, as shown in Figure 4.

Plasma Aβ42/40 and NfL levels could not predict the longitudinal change rate of synaptic density in the medial temporal lobe; however, the plasma p-tau181 ($\beta = 0.018$, SE = 0.005, $p = 0.002$) and GFAP ($\beta$ = -0.001, SE = 0.001, $p = 0.003$) levels could predict the longitudinal change rate of synaptic density in the medial temporal lobe, as shown in Figure 4C.

## 3.5 | Associations of global cognition with synaptic density, tau burden, and plasma biomarkers

In the whole cohort, the longitudinal change rate of synaptic density in the medial temporal region was positively associated with the $\Delta$ MMSE score ($r = 0.467$, $p = 0.004$), as shown in Figure 5A. However, the baseline synaptic density could not predict the longitudinal cognition decline (Figure 5B). We also found that baseline tau burden (global cortex: $\beta = -0.123$, SE = 0.024, $p < 0.001$; medial temporal lobe: $\beta = -0.114$, SE = 0.028, $p < 0.001$) could predict the longitudinal rate of change in MMSE scores (Figure 5C).

As shown in Figure 5D, plasma Aβ42/40 levels could not predict the longitudinal rate of change in MMSE scores; however, plasma p-tau181 ($\beta = -0.037$, SE = 0.011, $p = 0.002$), NfL ($\beta = -0.007$, SE = 0.002, $p = 0.004$), and GFAP ($\beta = -0.001$, SE = 0.001, $p = 0.010$) could predict the longitudinal rate of change in MMSE scores.

## 3.6 | The relationships among synaptic density, plasma biomarkers, tau burden, and global cognition

Based on the mediation analysis, we found that plasma GFAP levels mediate the relationship between the $\Delta$ global tau burden and $\Delta$ synaptic density in the medial temporal lobe (indirect effect: $\beta = -0.1124$, 95% c.i.: −0.3623 to −0.0126), as shown in Figure 6. The baseline global cortex and medial temporal lobe tau burden were shown to mediate the relationship between plasma GFAP levels and $\Delta$ MMSE scores (indirect effect: $\beta = -0.0009$, 95% c.i.: −0.0015 to −0.0002; $\beta = -0.0011$, 95% c.i.: −0.0022 to −0.0001), plasma p-tau 181 levels also mediated the relationship between plasma GFAP levels and $\Delta$ MMSE scores (indirect effect: $\beta = -0.0006$, 95% c.i.: −0.0014 to −0.0001).

## 4 | DISCUSSION

In this study, we used [$^{18}$F]SynVesT-1 PET to quantify the longitudinal changes in synaptic density in different stages of AD and investigated the associations of tau pathology (tau burden and plasma p-tau181) and plasma GFAP with longitudinal synaptic loss. Compared to HC individuals, CI patients exhibited a faster longitudinal rate of synaptic loss in the medial temporal lobe. Baseline tau pathology and plasma GFAP were negatively associated with synaptic density at both baseline and follow-up; the longitudinal synaptic loss is positively associated with longitudinal tau burden increase and positively associated with longitudinal cognitive decline. Tau pathology (plasma p-tau181 and tau burden) and plasma GFAP could also predict longitudinal synaptic loss and cognitive decline. These results indicate that longitudinal synaptic loss can be predicted by plasma GFAP and tau pathology and that future development of therapies

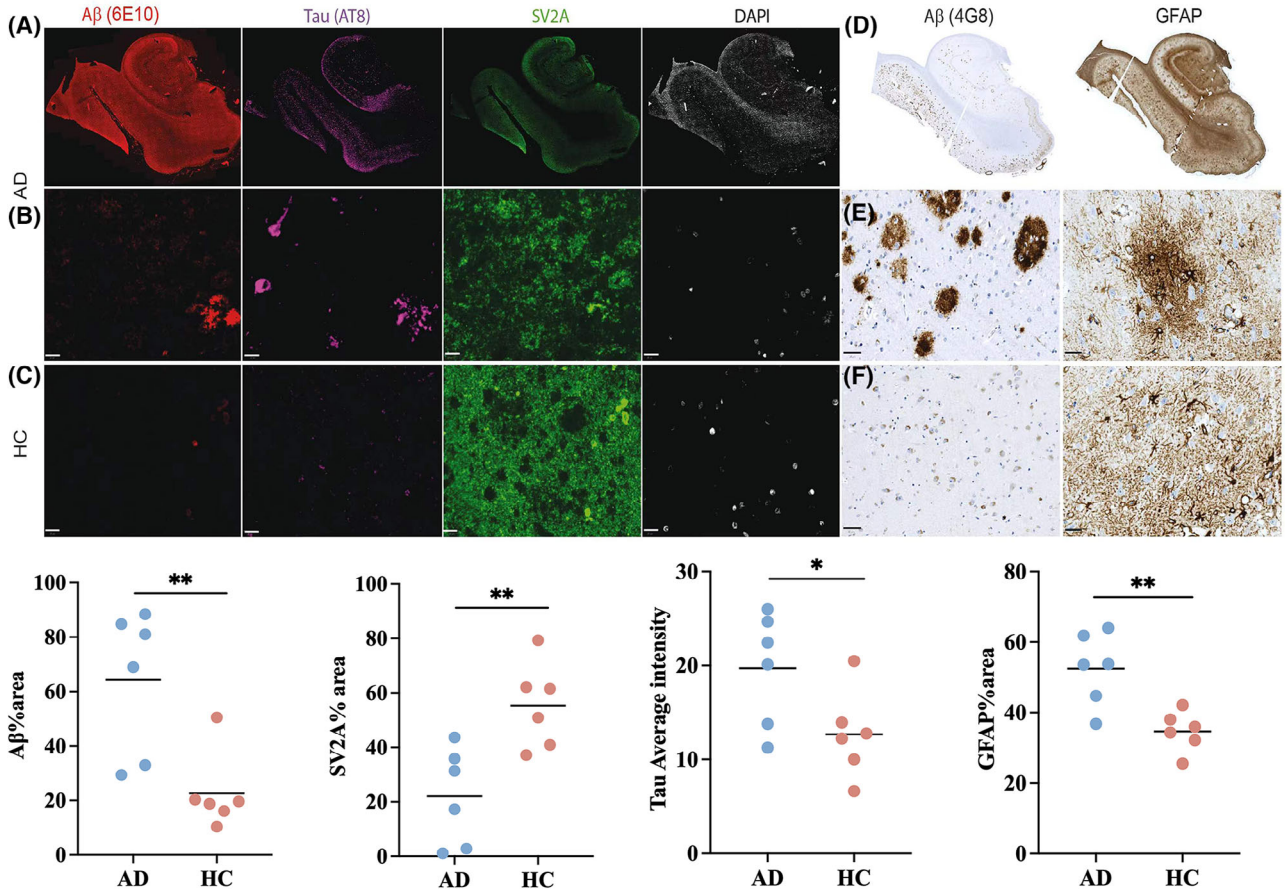


**FIGURE 2** Quantitative analysis of immunofluorescence staining of Aβ, tau, SV2A, and immunochemical staining of Aβ and GFAP in *post mortem* hippocampal slices from AD patients and HCs. A–C, The presence of Aβ plaques (6E10 staining) and tau tangles (AT8 staining), with images showing relatively lower fluorescence intensities of SV2A (green) and GFAP (brown) in the hippocampus of AD patients than in those of HCs. D–F, Representative 4G8 immunochemical staining for diffuse and dense Aβ plaques in hippocampal sections from HCs and AD patients. B, C, E, F, Magnified images of cornu ammonis 4 (CA4). The nucleus was counterstained with DAPI (white). Scale bars = 2000 μm (A, D). Scale bars = 50 μm (B, C, E, F). The proportions of the area with 6E10-positive Aβ and GFAP staining were greater in the hippocampus of AD patients ($n = 6$) than in those of HCs ($n = 6$), whereas the proportion of SV2A staining was lower in the hippocampus of AD patients than in that of HCs. The average fluorescence intensity for tau was greater in the hippocampi of AD patients than in those of HCs. *, **, and *** indicate significant differences between the two groups, with $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively. Aβ, amyloid beta; AD, Alzheimer's disease; DAPI, 4′,6-diamidino-2-phenylindole; GFAP, glial fibrillary acidic protein; HC, healthy control; SV2A, synaptic vesicle glycoprotein 2A.

targeting synapses can be monitored by tau pathology and plasma GFAP.

Compared to the HC group, the CI group had a lower synaptic density in the medial temporal lobe and greater tau burden in the medial temporal lobe and widespread neocortex; these findings are consistent with the previous study.[38] Within a 1-year interval, synaptic loss in the CI group decreased significantly at follow-up compared to baseline, whereas no difference was observed in the HC group. This finding was also consistent with that of a previous report showing that amnestic MCI individuals also displayed significant synaptic loss and tau deposition within a follow-up of 2 years. However, more interestingly, we detected a higher rate of synaptic loss in CI patients than in HC individuals. Immunohistochemical analyses similarly revealed that AD patients had lower synaptic density and greater tau burden and GFAP levels in the hippocampus than HC participants and confirmed that [$^{18}$F]MK6240 can quantify the tau burden in the hippocampus. These findings indicate that synaptic loss is a key feature in AD, and as levels of AD biomarkers increase, synaptic loss also increases in AD.

Here, we found that the regional tau burden at baseline was negatively associated with the corresponding regional and across multiple other regions' synaptic density at both baseline and follow-up, which is consistent with the findings of our previous study.[8] The longitudinal change in synaptic density in the medial temporal lobe was negatively associated with the longitudinal change in tau burden in the widespread neocortex, while for synaptic density in other brain regions there are some positive correlations. This may be because significant longitudinal changes in synaptic density were mainly limited to the medial temporal lobe, whereas tau accumulation extended to widespread neocortex. Positive correlations may reflect early tau deposition, when synaptic loss has not yet occurred, and compensatory increases in synaptic density may arise. Indeed, the baseline tau burden could predict longitudinal synaptic loss in the medial tem-

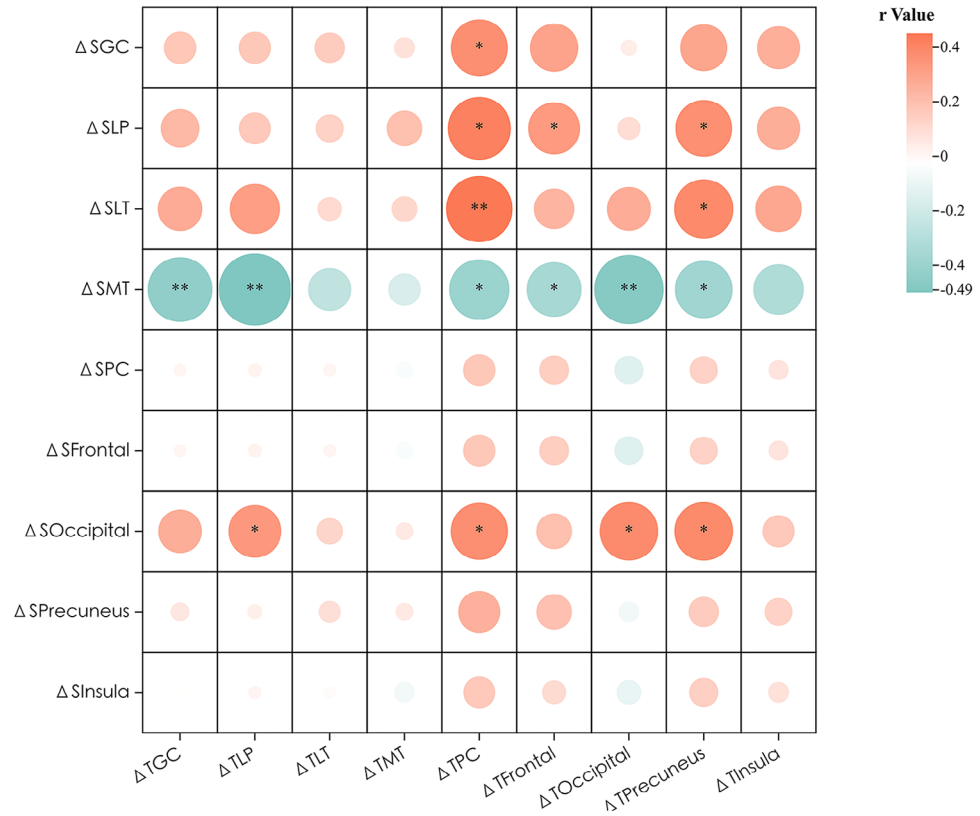


**FIGURE 3** Associations of $\Delta$ synaptic density with $\Delta$ tau burden in the whole cohort. The statistical model is a partial correlation model with age, education years, and sex as covariates; all $p$ values < 0.05 are marked with *. GC, global cortex; LP, lateral parietal lobe; LT, lateral temporal lobe; MT, medial temporal lobe; PC, posterior cingulate; SUVR, standardized uptake value ratio; $\Delta$ = (follow-up – baseline)/baseline; $\Delta$S, $\Delta$[$^{18}$F]SynVesT-1 SUVR; $\Delta$T, $\Delta$ [$^{18}$F]MK6240 SUVR.

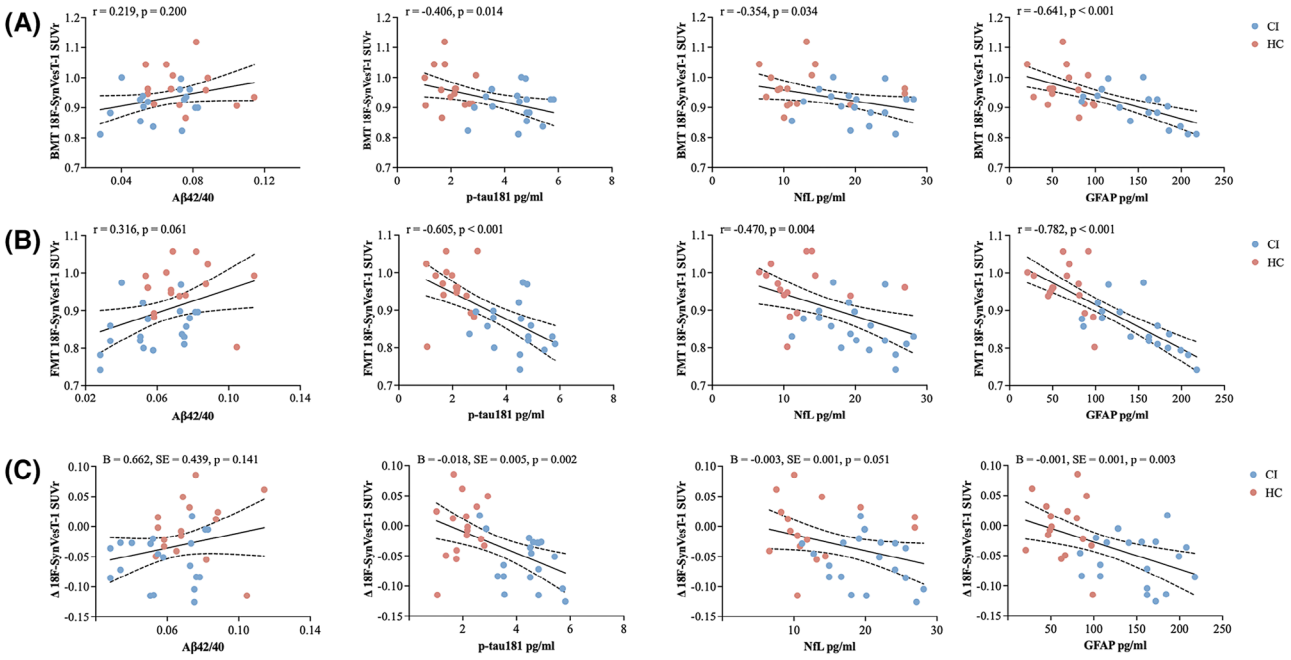


**FIGURE 4** Associations of plasma biomarkers with synaptic density in the medial temporal lobe with in the whole cohort. A) Baseline synaptic density, (B) follow-up synaptic density, (C) the longitudinal change of synaptic density. A$\beta$, amyloid beta; B, baseline; F, follow-up; GFAP, glial fibrillary acidic protein; MT, medial temporal lobe; NfL, neurofilament light chain; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio; $\Delta$ = (follow-up–baseline)/baseline.

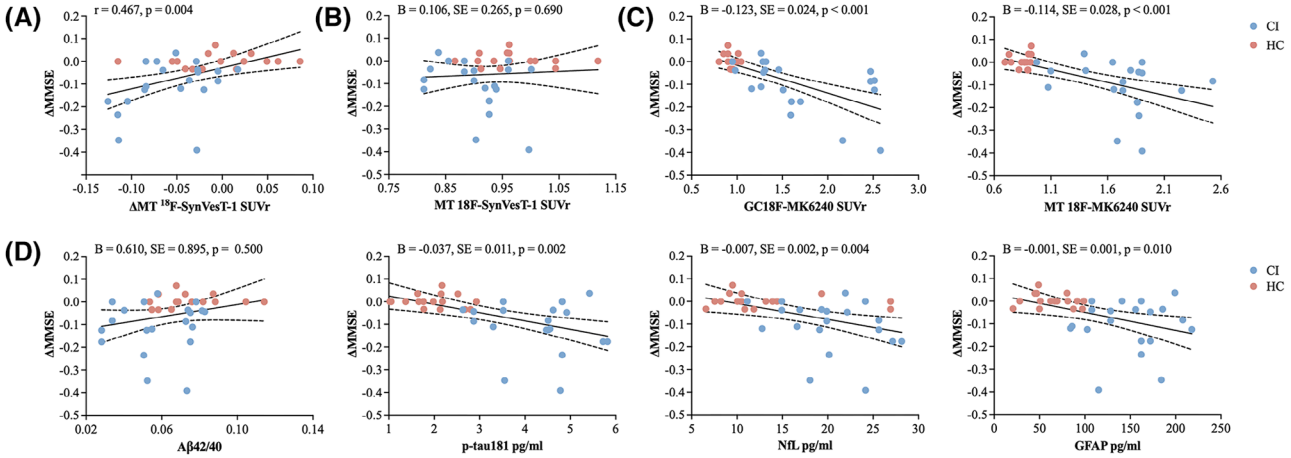


**FIGURE 5** Associations of global cognition with synaptic density, tau burden, and plasma biomarkers. A, Association of the $\Delta$ [$^{18}$F]SynVesT-1 SUVR in the medial temporal lobe with $\Delta$ MMSE. The statistical model is a partial correlation model with age, education years, and sex as covariates. The dashed lines represent the 95% confidence intervals of the best-fit lines. B–D, Association of baseline tau burden and plasma biomarkers with the $\Delta$MMSE scores. The statistical model is a general linear model with age, education years, and sex as covariates. The dashed lines represent the 95% confidence intervals of the best-fit lines. A$\beta$, amyloid beta; GC, global cortex; GFAP, glial fibrillary acidic protein; MMSE, Mini-Mental State Examination; MT, medial temporal lobe; NfL, neurofilament light chain; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio; $\Delta$ = (follow-up−baseline)/baseline.

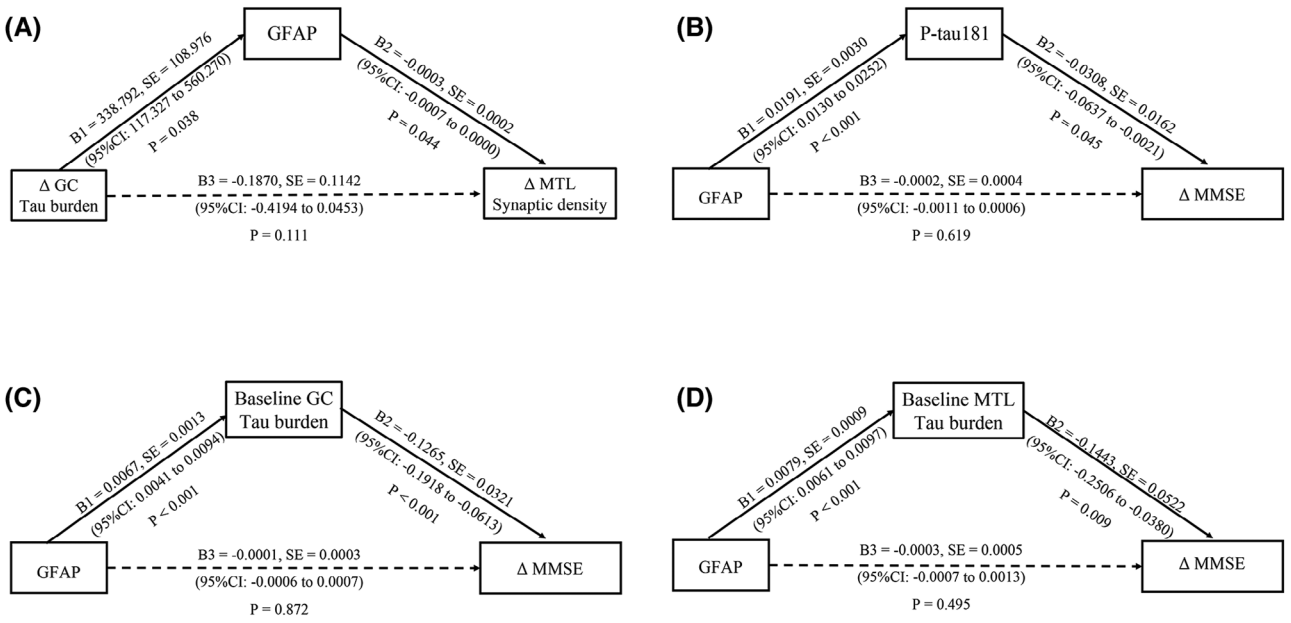


**FIGURE 6** Relationships among tau burden, GFAP, synaptic density, and cognition in the whole cohort. A, Plasma GFAP mediates the relationship between longitudinal global tau burden and longitudinal synapse loss in the medial temporal lobe. B, Baseline global tau burden mediates the relationship between baseline plasma GFAP and longitudinal cognition decline. C, Baseline tau burden in the medial temporal lobe mediates the relationship between baseline plasma GFAP and longitudinal cognition decline. The solid and dashed lines indicate the significant and non-significant pathways, respectively. CI, confidence interval; GC, global cortex; GFAP, glial fibrillary acidic protein; MMSE, Mini-Mental State Examination; MTL, medial temporal lobe; p-tau, phosphorylated tau; SE, standard error.

poral lobe, whereas the baseline synaptic density could not predict the longitudinal change in tau burden. This finding is also consistent with *post mortem* human brain studies that revealed lower levels of synaptic protein expression in NFT-containing neurons than in neurons without NFTs and showed that the number of synapses decreases gradually with increasing Braak stage and is negatively correlated with the number of NFTs.[39,40] Preclinical research has shown that tau accumulation precedes synaptic loss and that the spread of soluble tau protein to connected brain regions occurs trans-synaptically; pathogenic tau binds to synaptic vesicles via its N-terminal domain and interferes with

presynaptic functions, including synaptic vesicle mobility and release rates, lowering neurotransmission and ultimately leading to synaptic loss.[7,41,42] There is one other study investigating the relationship between longitudinal synaptic loss and tau burden in amnestic mild cognitive impairment.[9] In this study, they also reported baseline tau was negatively associated with longitudinal SV2A loss in early Braak regions and with SV2A at follow-up across regions. A key strength of our study is the separate analyses conducted for HC and AD groups, which helps to investigate the differences in longitudinal SV2A loss and tau deposition in different AD stages. Another point is that we also explored the relationship between plasma biomarkers and longitudinal SV2A loss.

To identify cost-effective biomarkers to predict longitudinal synaptic loss, we further investigated the associations between synaptic loss and plasma biomarkers. We found that baseline plasma p-tau181 and GFAP levels could predict longitudinal changes in synaptic density in the medial temporal lobe. Previous studies have shown that synaptic biomarkers, such as neurogranin (Ng) and synaptosomal associated protein-25 (SNAP25), are negatively associated with p-tau181 and GFAP levels in the CSF.[17,43,44] Plasma GFAP is a biomarker for neuroinflammation; notably, preclinical studies have shown that microglia and astrocytes drive synaptic degeneration in animal models of aging and AD via the ingestion of tagged synapses, contributing to cognitive decline.[45,46] These activated cells lose homeostatic functions, reduce their secretion of neurotrophic factors, and produce increased amounts of proinflammatory cytokines and chemokines, which could directly eliminate synaptic structures, leading to synapse loss but also leading to neuronal dysfunction and damage.[47] Our results also verified that plasma p-tau181 and GFAP are promising potential markers of longitudinal synaptic loss.

Mediation analysis revealed that plasma GFAP mediates the relationship between longitudinal tau burden and longitudinal synaptic loss. The accumulation of tau burden can trigger the activation of glial cells, subsequently initiating neuroinflammatory responses. Persistent abnormal activation of glial cells and the release of pro-inflammatory factors further drive the pathological progression of tau. The proportion of activated glial cells in the brain is closely associated with tau pathology in AD. The interaction between glial cell activation and tau burden acts synergistically to exacerbate AD pathology.[48,49] The role of glial cells in synapse degeneration in AD is that synapses are opsonized and removed via phagocytic mechanisms, potentially as a result of RNA and protein changes that occur at the synapse in response to A$\beta$ and tau pathology.[50] The upregulation of proinflammatory markers by glial cells during AD has been consistently reported in both humans and mice, suggesting that the accumulation of AD-associated pathologies to some extent drives detrimental changes in microglia and astrocytes, which in turn exacerbate synaptic degeneration.[51] These findings may further show that neuroinflammation plays an important role in the synaptic loss caused by tau pathology in AD. Although emerging evidence suggests that inflammation has a causal role in AD, the detection of inflammatory markers has not yet been established as a method for monitoring patients with AD, despite its potential value.[52] Our findings show that plasma GFAP has great potential as a specific marker of inflammation and that plasma GFAP is a prognostic marker of longitudinal synapse loss and a mediator of the effects of tau pathology on SV2A PET burden. In light of the invasiveness of lumbar punctures for CSF and the high cost of PET imaging, plasma GFAP could become a widely available screening tool to reflect changes in synaptic density in AD patients.

Synapse loss has been referred to as the major pathological correlate of cognitive impairment in AD.[53] In our study, we found that longitudinal synapse loss in the medial temporal lobe was positively associated with longitudinal cognitive decline. These findings are consistent with the hypothesis that synaptic density and cognitive impairment occur in close temporal proximity. We also found that baseline plasma GFAP and tau pathology could predict longitudinal changes in MMSE scores and that tau pathology (tau burden and p-tau181) mediates the relationship between plasma GFAP and longitudinal cognitive decline, further suggesting that neuroinflammation and tau pathology are closely associated and may contribute jointly to disease progression, thus triggering a cascade of pathological events that ultimately results in cognitive decline through synaptic loss.

This study has several limitations. First, the sample size was relatively small, and the follow-up time was short; we must be cautious in drawing far-reaching conclusions from these preliminary findings. Second, the CI participants included both AD and MCI patients, but we did not analyze the subgroups. Third, plasma GFAP only indirectly reflects neuroinflammation in the brain, and subsequent studies should obtain data on CSF GFAP levels to more directly quantify changes in neuroinflammation.

In this study, we found that CI patients had more severe longitudinal synapse loss and tau deposition at the 1-year follow-up than HC individuals. The longitudinal synaptic loss is positively associated with longitudinal tau burden increase and positively associated with longitudinal cognitive decline. Tau pathology and plasma GFAP were negatively associated with synaptic density at both baseline and follow-up and could predict longitudinal synapse loss and cognitive decline. Our results confirmed that plasma p-tau181 and GFAP could predict longitudinal synaptic loss, thus suggesting their potential usefulness as promising markers for monitoring longitudinal synaptic loss and for the development of treatments targeting synapses in the future.

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## CONFLICT OF INTEREST STATEMENT

The authors report that they have no conflicts or competing interests.

Author disclosures are available in the supporting information.

## CONSENT STATEMENT

This manuscript has been seen and approved by all authors. All authors declare no conflicts of interest that may directly or indirectly influence the content of the manuscript submitted.

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## SUPPORTING INFORMATION

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

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