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Original Article

Diagnostic and prognostic utility of serum β-synuclein in Alzheimer's disease: a longitudinal cohort study☆

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ABSTRACT

Background: Serum β-synuclein is an emerging blood-based biomarker for synaptic integrity in Alzheimer's disease (AD). However, its comparative performance against the established CSF marker neurogranin and its prognostic utility for longitudinal disease progression remain to be fully characterized.
Method: We analyzed 475 participants from the Alzheimer's Disease Neuroimaging Initiative. We compared serum β-synuclein and CSF neurogranin using receiver operating characteristic analysis and Cox proportional hazards models. We also assessed the cross-sectional associations of both biomarkers with cognitive and neuroimaging markers using linear regression. Linear mixed-effects models were applied to determine if baseline serum β-synuclein levels and longitudinal rate of change predicted disease progression. Finally, the trajectory of serum β-synuclein was modeled across the AD continuum.
Results: Serum β-synuclein distinguished clinical AD dementia from controls with high accuracy (AUC = 0.84). Cross-sectionally, it exhibited robust associations with cognitive deficits and neuroimaging markers, comparable to or exceeding those of CSF neurogranin. Higher baseline serum β-synuclein, but not CSF neurogranin, significantly predicted the risk of conversion to dementia (hazard ratio = 1.83). Longitudinally, both elevated baseline levels and faster rates of increase in serum β-synuclein predicted accelerated cognitive decline and neurodegeneration, independent of baseline amyloid or tau pathology. Trajectory analysis revealed that serum β-synuclein levels accelerated significantly over time specifically in individuals with concurrent amyloid and tau pathology.
Discussion: Serum β-synuclein serves as a robust prognostic biomarker for AD, demonstrating diagnostic accuracy for clinical dementia and superior predictive utility for disease conversion compared to CSF neurogranin. Its ability to track synaptic degeneration independent of core proteinopathies highlights its potential as a dynamic outcome measure for monitoring disease progression in clinical trials.

☆ Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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1. Introduction

The pathological hallmarks of Alzheimer's disease (AD) are the extracellular accumulation of amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein [1]. In 2018, the National Institute on Aging-Alzheimer's Association (NIA-AA) introduced the A/T/N framework, a transformative biological classification system based on biomarkers [2]. This framework marks a paradigm shift from traditional clinical diagnosis of AD by categorizing individuals according to cerebrospinal fluid (CSF) and neuroimaging biomarkers of amyloid (A), tau (T), and neurodegeneration (N). The A/T/N framework has proven particularly valuable for early diagnosis, even at the preclinical stage of AD, and for participant selection in clinical trials of disease-modifying therapies, such as anti-amyloid immunotherapies [3–5]. In recent years, the development of ultrasensitive detection techniques has led to successful identification of powerful blood-based biomarkers (BBMs) for detecting A/T/N pathology, including phosphorylated tau at threonine 217 (p-tau217), the endogenously cleaved, microtubule-binding region containing residue 243 (eMTBR-tau243) and neurofilament light chain (NfL) [6].

However, the original A/T/N framework did not fully capture the multifaceted pathophysiology of AD. The recently updated 2024 Alzheimer's Association criteria address this limitation by incorporating biomarkers of inflammation (I), vascular brain injury (V), and α-synuclein co-pathology (S) alongside the core A, T, and N biomarkers [7,8]. The integration of multiple biomarker modalities holds promise for enhancing diagnostic accuracy, improving disease monitoring, and providing deeper insights into the mechanisms of AD progression. Importantly, this update integrated BBMs into the diagnostic framework, thus paving the way for less invasive and more accessible diagnostic approaches.

Synaptic dysfunction is a critical early event in AD, potentially preceding significant plaque and tangle pathology and correlating more strongly with cognitive decline than either pathology alone [9,10]. Therefore, biomarkers reflecting synaptic function are crucial for early disease detection and progression monitoring. Recent studies have identified several promising synaptic biomarker candidates, including neurogranin, synaptotagmin-1, SNAP-25, GAP-43, synaptic vesicle glycoprotein 2A, α-synuclein and β-synuclein [11,12]. Among these, β-synuclein, a brain-enriched presynaptic protein involved in synaptic vesicle trafficking and neurotransmitter release, demonstrates significant potential as a key biomarker for AD [13]. β-synuclein is detectable in the CSF of individuals with AD and is also significantly increased in their blood, even at the prodromal stage [14–17]. Given that β-synuclein is expressed predominantly in the central nervous system with minimal peripheral expression, its blood levels likely reflect pathological changes occurring within the brain [18,19]. Recent studies have demonstrated that blood β-synuclein levels start to rise 11 years before symptom onset in autosomal dominant AD (ADAD) [20]. In sporadic AD, blood β-synuclein levels were also observed to rise in the preclinical stage [17,21]. However, comprehensive investigation of this novel blood biomarker in AD is still limited, especially in longitudinal cohorts.

In this study, we used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to investigate the diagnostic and prognostic performance of serum β-synuclein in AD. We first compared it with an established synaptic biomarker in CSF, neurogranin, investigating their levels across different diagnostic groups and biological stages. We assessed their accuracy in differentiating AD from cognitively normal (CN) individuals, as well as amyloid-positive (A+) from amyloid-negative (A−) individuals. We further evaluated their prognostic value for predicting conversion to dementia among individuals without dementia at baseline. The associations between serum β-synuclein, CSF neurogranin and other CSF biomarkers, cognitive function and neuroimaging biomarkers were analyzed. We then evaluated whether baseline levels and the longitudinal rate of change in serum β-synuclein predicted subsequent cognitive decline and neurodegenerative changes during the follow-up period. Finally, we characterized the longitudinal trajectory of serum β-synuclein across the AD disease continuum.

2. Methods

2.1. Participants

Data used in this study were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by principal investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Data for the current study were downloaded in May 2025. A total of 475 ADNI participants with available serum β-synuclein assay data were included. Of these, 155 participants also had available CSF neurogranin data and were included in the comparative analyses of these two biomarkers. Additionally, a subset of 241 participants had longitudinal serum β-synuclein measurements and were included in the longitudinal analyses. The flowchart of participant inclusion for each analysis is detailed in Supplementary Fig. S1.

All ADNI participants underwent standardized clinical and neuropsychological assessments, and diagnoses were assigned according to standard research criteria for CN controls, MCI or AD dementia. Detailed diagnostic criteria for ADNI can be found at https://adni.loni.usc.edu/help-faqs/adni-documentation/. Briefly, CN participants had a Mini-Mental State Examination (MMSE) score between 24 and 30; a Clinical Dementia Rating (CDR) score of 0; and absence of depression, MCI, and dementia. MCI participants had a MMSE score between 24 and 30; a subjective memory complaint; objective memory loss as assessed by delayed recall on the Wechsler Memory Scale Logical Memory II; a CDR score of 0.5; preserved activities of daily living; and the absence of dementia. Participants diagnosed with dementia due to AD met the criteria with a MMSE score between 20 and 26 and a CDR score of 0.5 or 1.0, and fulfilled the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD [22].

2.2. Serum β-synuclein assay

All serum β-synuclein data were obtained via the ADNI database. Assays were performed by the laboratory of Oeckl using a validated immunoprecipitation–mass spectrometry method, as previously described [23]. Briefly, 490 μL of serum was mixed with an internal standard solution containing recombinant 15N-β-synuclein (rPeptide, Watkinsville, GA, USA) and subjected to immunoprecipitation using magnetic beads conjugated with anti-β-synuclein antibody (EP1537Y from Abcam, Cambridge, UK). The beads were washed with 50 mM triethylammonium bicarbonate/0.1 % n-Dodecyl-β-D-maltoside using a KingFisher Apex instrument, followed by elution. The precipitated β-synuclein underwent enzymatic digestion with trypsin/LysC (Promega, Walldorf, Germany), and two proteotypic peptides (aa46-58 and aa61-85) were quantified by liquid chromatography-multiple reaction monitoring using an Eksigent MicroLC200, Agilent 1260 pump, and Sciex QTRAP6500 mass spectrometer.

Calibration curves were generated using recombinant human full-length β-synuclein (rPeptide) with concentrations verified by amino acid analysis (Alphalyse A/S, Odense, Denmark). The calibration range was 2 to 30 pg/mL. Samples were analyzed in a total of 14 runs, with serum quality control samples (low, medium, and high concentration) included in each run (intra-assay CV: 0.5 to 11.5 %; inter-assay CV: 8.8 to 11.1 %). Samples were randomized across runs, and analysts were blinded to clinical data.

2.3. CSF neurogranin assay

CSF neurogranin was quantified using electrochemiluminescence immunoassay (Meso Scale Discovery, Gaithersburg, Maryland, USA). The assay employed the monoclonal antibody NG7 as the capture antibody and a polyclonal anti-rabbit NG antibody (ab23570, Upstate) as the detection antibody.

2.4. CSF and PET biomarkers for A/T classification

Core AD biomarkers in CSF (Aβ42, phosphorylated tau at threonine 181 [p-tau181], and total tau [t-tau]) were measured using Roche Elecsys CSF immunoassays on a fully automated Elecsys cobas e601 instrument, following manufacturer's instructions and previously established protocols [24]. Based on CSF Aβ42 and p-tau181 levels, participants were stratified into A−T−, A+T−, A+T+, and A−T+ groups using established cutoff values of 980 pg/mL for Aβ42 and 26.64 pg/mL for p-tau181, in accordance with previously published data and the Roche Elecsys method documentation (UPENNBIOMK_ROCHE_ELECSYS_METHODS_20231109.pdf) [25]. To maximize sample size for stratified analyses, A/T status was inferred for a small subset of participants lacking CSF measurements (11 individuals [9.7 %] in the final longitudinal serum β-synuclein trajectory analysis) using pre-processed [18F]florbetapir and [18F]flortaucipir PET summary data provided by ADNI (ADSP_PHC_PET_Amyloid_Simple_Dec2024.csv and ADSP_PHC_PET_Tau_Simple_Dec2024.csv). For these participants, a retrospective inference approach was applied, leveraging the temporal stability of AD pathologies: a confirmed negative PET scan at a follow-up visit was used to assign a negative A/T status to preceding visits.

2.5. Imaging

Structural T1-weighted MRI data were acquired as part of the ADNI study and processed by the ADSP Phenotype Harmonization Consortium. Two separate processing approaches were used to generate the neuroimaging markers for this analysis. First, cortical thickness was estimated using FreeSurfer (v.6.0) [26], from which a composite cortical thickness measure was calculated as the mean thickness of AD-vulnerable regions, including the bilateral entorhinal, inferior temporal, middle temporal, and fusiform cortices. Second, volumetric measures were derived using the MUlti-atlas region Segmentation utilizing Ensembles (MUSE) software package [27]. From these segmentations, we constructed two AD-associated composite volumes: a medial temporal lobe (MTL) volume, comprising the sum of bilateral hippocampal, entorhinal, parahippocampal, and amygdala volumes; and a broader AD composite volume, which included the MTL regions plus the bilateral precuneus and posterior cingulate volumes. All imaging measures underwent rigorous quality control and were harmonized across different scanner platforms and sites using ComBat-based methods to mitigate site effects [28]. Volumetric measures were additionally adjusted for total intracranial volume.

[18F]-fluorodeoxyglucose (FDG) PET data were obtained from the ADNI "UC Berkeley - FDG analysis" dataset. Detailed methods regarding image processing and analysis are documented in the "UC Berkeley FDG MetaROI methods" file. Briefly, pre-processed PET images were spatially normalized to a standard MNI PET template. The primary outcome measure was a composite standardized uptake value ratio (SUVR), which was calculated from a predefined meta-region of interest (metaROI). This metaROI was derived from a meta-analysis of prior AD literature and encompasses key regions of AD-related hypometabolism, including the bilateral angular gyri, posterior cingulate, and inferior temporal gyri. To generate the SUVR, mean uptake in the metaROI was normalized to the mean uptake of the top 50 % of voxels within a pons/cerebellar vermis reference region.

2.6. Cognitive assessments

Participant cognitive and functional status was evaluated using a battery of established assessments. Global clinical severity was measured using the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB). Overall cognitive decline was assessed with the modified Preclinical Alzheimer's Cognitive Composite (mPACC), which is the sum of standardized scores from the MMSE, ADAS-Cog Delayed Word Recall, Logical Memory Delayed Recall, and Trail Making Test Part B [29]. Disease-specific cognitive performance was evaluated using the Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 (ADAS-Cog 13). Memory function was specifically evaluated using the Alzheimer's Disease Neuroimaging Initiative Memory Composite Score (ADNI MEM), a validated measure derived from multiple memory tests [30].

2.7. Statistics analyses

Baseline demographic, clinical, neuroimaging, and fluid biomarker characteristics were compared across the three diagnostic groups (CN, MCI, and AD). Group differences were assessed using the Chi-squared test for categorical variables (sex and apolipoprotein E [*APOE* ε4] status). For all continuous variables, group comparisons were performed using the non-parametric Kruskal–Wallis test. Log10-transformed serum β-synuclein and CSF neurogranin levels across different diagnostic groups (CN A−, CN A+, MCI A–, MCI A+, AD A–, and AD A+) and biological stages (A−/T−, A+/T−, A+/T+, and A−/T+) were analyzed using general linear models (GLMs), with adjustments for age, sex, education, and *APOE* ε4 status. Post-hoc pairwise comparisons for GLMs were performed on the estimated marginal means with Tukey's adjustment.

The diagnostic performance of serum β-synuclein and CSF neurogranin was assessed using receiver operating characteristic (ROC) curve analysis to differentiate between patients with AD dementia and CN individuals, and separately, to discriminate between A+ and A− individuals. The area under the curve (AUC) and its 95 % confidence interval (CI) were calculated, with CIs estimated via a bootstrap method with 2000 replicates. To further compare their prognostic utility, Cox proportional hazards regression was performed to assess the risk of conversion to AD dementia among non-demented participants (CN and MCI), adjusting for baseline age, sex, education, *APOE* ε4 status, and baseline diagnosis.

Spearman's rank-order correlations were first computed to examine the univariate associations between all biomarkers and outcomes. Further, multiple linear regression adjusting for age, sex, education, and *APOE* ε4 status was used to assess the direct association between serum β-synuclein and CSF neurogranin, and to assess associations of serum β-synuclein and CSF neurogranin with CSF biomarkers, cognitive measures, and imaging markers. For each outcome, a joint model including both serum β-synuclein and CSF neurogranin was fitted to compare their standardized beta coefficients (βstd); differences between βstd were tested using Wald tests with false discovery rate (FDR) correction. Multiple comparison correction was applied to all p values using the FDR method.

Linear mixed-effects models (LMMs) were used to determine if serum β-synuclein predicted the longitudinal progression of cognitive decline and neurodegeneration. First, to assess the effect of baseline β-synuclein levels, models tested the interaction between time and baseline log10-transformed β-synuclein. For participants with longitudinal β-synuclein data, a two-stage approach was used to determine if the rate of β-synuclein change predicted outcome progression: individual slopes of β-synuclein change were derived using LMMs, and the interaction of these slopes with time was then tested in models of cognitive and neuroimaging outcomes. All models were adjusted for baseline age, sex, education, *APOE* ε4 status and baseline clinical diagnosis, and included random intercepts and slopes for time. To assess whether the predictive value of serum β-synuclein was independent of established AD

pathologies, analyses were repeated in participants with available CSF biomarkers, with additional adjustment for baseline CSF Aβ42 or CSF p-tau181 levels, replacing baseline clinical diagnosis in the models. *P* values were corrected for multiple comparisons using the FDR method. Potential moderation by baseline amyloid status, sex and *APOE* ε4 status was explored by adding three-way interaction terms (β-synuclein level/slope × time × moderator) to the models. Finally, a separate LMM examined the trajectory of serum β-synuclein itself as an outcome, comparing rates of change across A/T groups (A−T−, A+T−, and A+T+) via the group × time interaction. This model utilized the same covariate adjustments, included a random intercept for each individual, and was followed by post-hoc Tukey's tests to compare slopes among groups. All statistical analyses were performed using R software (version 4.5.0), and a two-sided p value < 0.05 was considered statistically significant.

3. Results

3.1. Participant characteristics

The baseline characteristics of the 475 participants are summarized in Table 1. The cohort comprised 135 CN individuals, 173 with MCI, and 167 with AD dementia. The proportion of females differed significantly across the CN (48 %), MCI (32 %), and AD (41 %) groups ($p = 0.013$), while there was no significant difference in age among the groups ($p = 0.289$). The frequency of *APOE* ε4 carriers increased significantly from 28.1 % in the CN group to 49.7 % in the MCI group and 64.1 % in the AD group ($p < 0.001$). As expected, significant differences among the CN, MCI, and AD groups were observed across all clinical, neuroimaging, and CSF biomarker measures (all $p < 0.001$).

3.2. Serum β-synuclein and CSF neurogranin levels across the AD continuum

Among the 153 participants with available measurements for both biomarkers, the cohort included CN A− ($n = 31$), CN A+ ($n = 23$), MCI A− ($n = 11$), MCI A+ ($n = 32$), AD A− ($n = 7$), and AD A+ ($n = 49$) groups (Supplementary Table S1). The levels of serum β-synuclein and CSF neurogranin (log10-transformed) across different diagnostic groups and biological stages are shown in Fig. 1. Both biomarkers showed a trend of progressive increase from CN A− to CN A+, MCI A+, and AD A+, but the group differences were more pronounced for serum β-synuclein. After adjusting for age, sex, education, and *APOE* ε4 status, significant differences were observed across diagnostic groups in the levels of serum β-synuclein (partial $\eta^2 = 0.22$, $p < 0.001$) and CSF neurogranin (partial $\eta^2 = 0.009$, $p = 0.020$).

Post-hoc analyses demonstrated that, compared to the CN A− group, serum β-synuclein levels were higher in the MCI A+ (mean difference [MD] = 0.156, 95 % CI: 0.078 to 0.233; $p = 0.001$) and AD A+ groups (MD = 0.202, 95 % CI: 0.130 to 0.275; $p < 0.001$; Fig. 1A). Levels were also higher in the MCI A+ (MD = 0.126, 95 % CI: 0.048 to 0.205; $p = 0.022$) and AD A+ (MD = 0.173, 95 % CI: 0.099 to 0.247; $p < 0.001$) groups compared to the CN A+ group. No statistically significant differences were observed between MCI A− (adjusted mean = 0.972, 95 % CI: 0.884 to 1.061) and MCI A+ (adjusted mean = 1.062, 95 % CI: 1.011 to 1.114), or between AD A− (adjusted mean = 1.028, 95 % CI: 0.918 to 1.138) and AD A+ (adjusted mean = 1.109, 95 % CI: 1.066 to 1.152), likely due to the limited sample sizes in the A− groups.

For CSF neurogranin, levels were higher in the AD A+ (MD = 0.483, 95 % CI: 0.211 to 0.755; $p = 0.008$) and MCI A+ groups (MD = 0.441, 95 % CI: 0.150 to 0.732; $p = 0.037$) compared to the CN A− group (Fig. 1B). Similar to serum β-synuclein, CSF neurogranin levels did not differ significantly between MCI A− (adjusted mean = 2.478, 95 % CI: 2.145 to 2.811) and MCI A+ (adjusted mean = 2.602, 95 % CI: 2.407 to 2.796), or between AD A− (adjusted mean = 2.418, 95 % CI: 2.003 to 2.833) and AD A+ (adjusted mean = 2.644, 95 % CI: 2.482 to 2.805).

When stratified according to the A/T framework (A−/T− $n = 37$, A+/T− $n = 38$, A+/T+ $n = 66$, A−/T+ $n = 12$, Supplementary Table S2), serum β-synuclein levels were significantly higher in the A+/T+ group compared with the A−/T− (MD = 0.185, 95 % CI: 0.121 to 0.249; $p < 0.001$), A+/T− (MD = 0.161, 95 % CI: 0.104 to 0.219; $p < 0.001$), and A−/T+ groups (MD = 0.141, 95 % CI: 0.045 to 0.236; $p = 0.022$; Fig. 1C). CSF neurogranin levels were elevated in the A+/T+ group compared to the A−/T− (MD = 0.700, 95 % CI: 0.488 to 0.912; $p < 0.001$) and A+/T− groups (MD = 0.567, 95 % CI: 0.375 to 0.759; $p < 0.001$; Fig. 1D). Notably, CSF neurogranin levels in the A−/T+ group were also significantly higher than those in the A−/T− (MD = 0.724, 95 % CI: 0.410 to 1.037; $p < 0.001$) and A+/T− groups (MD = 0.591, 95 % CI: 0.268 to 0.915; $p = 0.002$), and did not differ from the A+/T+ group (MD = 0.024, 95 % CI: −0.293 to 0.342; $p = 0.999$).

Table 1
Demographic and clinical characteristics of participants at baseline.

	N	Cognitively normal (CN)	Mild cognitive impairment (MCI)	Alzheimer's disease dementia (AD)	*p* value
N (% female)	475	135 (48%)	173 (32%)	167 (41%)	0.013
Age (years)	475	75.7 (72.6–78.8)	77.4 (72.5–82.5)	76.9 (71.3–82.0)	0.289
APOE ε4 positive (%)	475	38 (28.1%)	86 (49.7%)	107 (64.1%)	<0.001
Education (years)	475	16.0 (14.0–18.0)	16.0 (13.0–18.0)	16.0 (13.0–18.0)	0.012
CDR-SB	472	0.0 (0.0–0.0)	1.5 (1.0–2.0)	4.5 (3.5–6.0)	<0.001
mPACC	475	0.1 (−1.8–1.6)	−6.5 (−9.8–−3.7)	−14.3 (−17.0–−11.6)	<0.001
ADNI MEM	475	1.0 (0.7–1.5)	0.0 (−0.5–0.5)	−0.9 (−1.4–−0.5)	<0.001
ADAS-Cog 13	464	9.3 (6.0–12.7)	18.3 (12.7–21.7)	28.0 (22.8–34.0)	<0.001
FDG-PET SUVR	226	1.3 (1.2–1.3)	1.2 (1.1–1.2)	1.0 (0.9–1.1)	<0.001
Cortical Thickness (mm)	432	2.8 (2.7–2.9)	2.7 (2.6–2.8)	2.5 (2.3–2.6)	<0.001
AD Composite Volume (mm^3)	459	47159.8 (43406.0–50242.2)	45974.3 (42027.0–49345.1)	41796.2 (38348.4–45906.6)	<0.001
MTL Volume (mm^3)	459	20799.4 (19473.4–22416.4)	19396.8 (17659.2–21211.0)	17253.9 (15582.9–19011.7)	<0.001
Serum β-synuclein (pg/mL)	475	8.2 (6.9–10.5)	10.6 (8.4–13.6)	13.2 (10.6–16.4)	<0.001
CSF Neurogranin (pg/mL)	155	292.5 (143.0–451.9)	463.8 (240.9–613.5)	543.7 (374.6–736.4)	<0.001
CSF t-tau (pg/mL)	209	234.9 (180.6–299.9)	254.8 (204.1–370.5)	329.9 (261.6–396.8)	<0.001
CSF p-tau181 (pg/mL)	209	21.4 (16.3–28.1)	24.8 (17.9–37.6)	32.4 (24.7–42.2)	<0.001
CSF Aβ42 (pg/mL)	209	1087.5 (724.3–1524.8)	687.1 (556.5–1026.4)	543.5 (392.2–685.4)	<0.001

Note: Data are given as median (interquartile ranges) for continuous variables and count (percentage) for categorical variables. Group comparisons were performed using the Kruskal–Wallis test for all continuous variables. The Chi-squared test was used for categorical variables. Abbreviations: ADAS-Cog 13, Alzheimer's Disease Assessment Scale-Cognitive subscale 13; ADNI MEM, Alzheimer's Disease Neuroimaging Initiative Memory Composite Score; Aβ42, amyloid-β 1–42; *APOE*, apolipoprotein E; CDR-SB, Clinical Dementia Rating Sum of Boxes; CSF, cerebrospinal fluid; FDG-PET, [18F]fluorodeoxyglucose positron emission tomography; mPACC, modified Preclinical Alzheimer Cognitive Composite; MTL, medial temporal lobe; p-tau181, phosphorylated tau at threonine 181; t-tau, total tau.

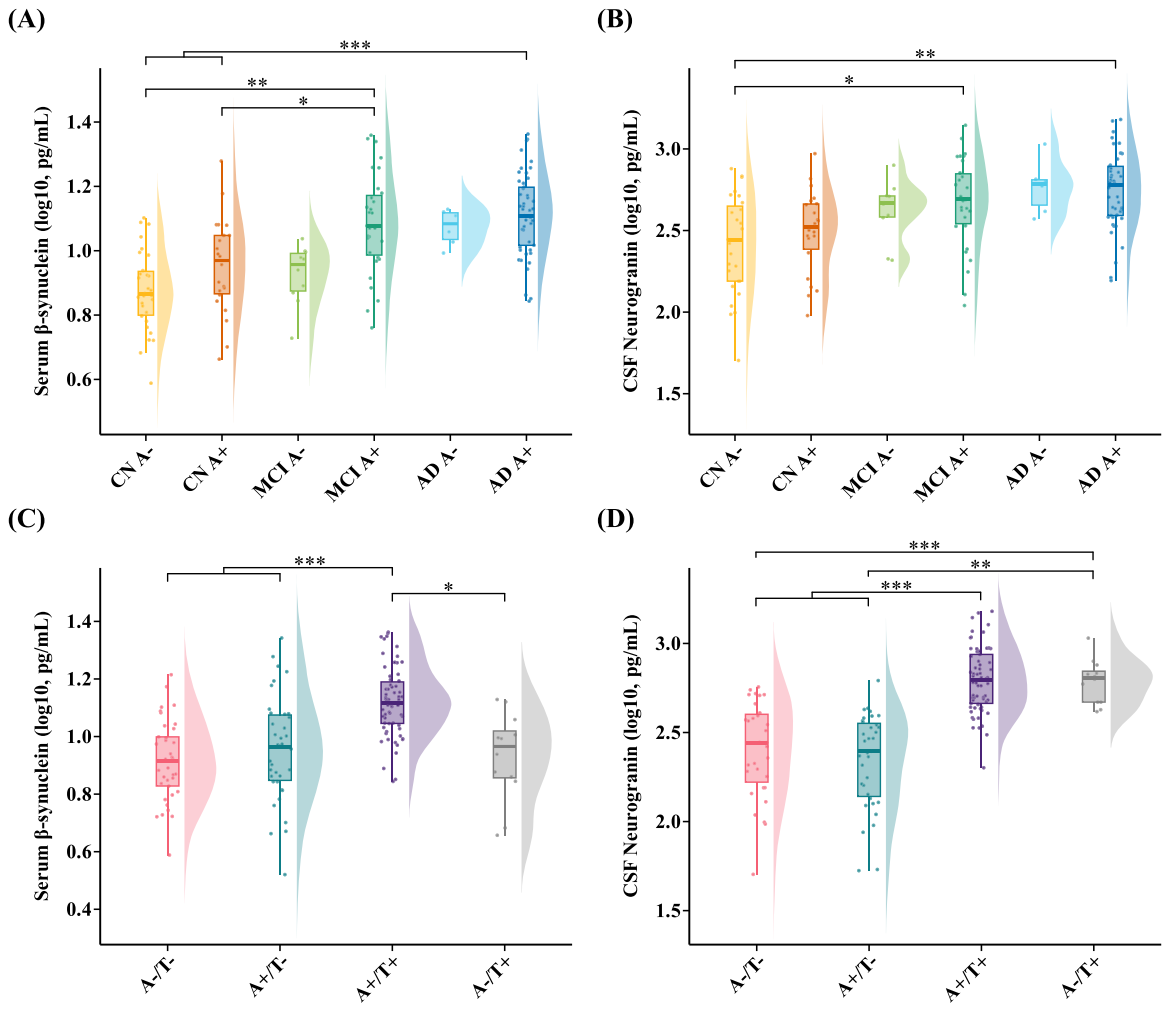

Fig. 1. Serum β-synuclein and CSF neurogranin levels across clinical and biological stages of Alzheimer's disease. The distribution of log10-transformed levels of (A, C) serum β-synuclein and (B, D) CSF neurogranin. Levels are stratified by: (A, B) a combination of clinical diagnosis and amyloid status (CN A−, n = 31; CN A+, n = 23; MCI A−, n = 11; MCI A+, n = 32; AD A−, n = 7; AD A+, n = 49); and (C, D) the A/T biological framework (A−T−, n = 37; A+T−, n = 38; A+T+, n = 66; A−T+, n = 12). Group differences were assessed using general linear models adjusted for age, sex, education, and *APOE* ε4 status, with post-hoc pairwise comparisons performed using Tukey's adjustment. Each plot displays the data distribution as a box plot (left half) and a violin plot (right half), with individual data points shown as dots. Box plots display the median and the interquartile range (IQR), with whiskers extending to the value no further than 1.5 times the IQR. Outliers were retained in the statistical analyses but excluded from visualization. Brackets indicate significant pairwise comparisons: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$. Abbreviations: A−, amyloid-β negative; A+, amyloid-β positive; AD, Alzheimer's disease dementia; CN, cognitively normal; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; T−, tau negative; T+, tau positive.

3.3. Diagnostic and prognostic performance of serum β-synuclein and CSF neurogranin

The diagnostic performance of the biomarkers was assessed using ROC curve analyses (Fig. 2). In discrimination between patients with clinical AD dementia and CN individuals, serum β-synuclein demonstrated good accuracy (AUC = 0.844, 95 % CI: 0.761 to 0.912), approaching the performance of the CSF p-tau181/Aβ42 ratio (AUC = 0.880, 95 % CI: 0.810 to 0.941). In contrast, CSF neurogranin showed lower accuracy (AUC = 0.753, 95 % CI: 0.657 to 0.835). When distinguishing individuals with amyloid pathology (A+) from those without (A−), the performance of both biomarkers was modest, with serum β-synuclein yielding an AUC of 0.752 (95 % CI: 0.672 to 0.826) and CSF neurogranin an AUC of 0.648 (95 % CI: 0.551 to 0.741).

Prognostic performance was assessed using Cox proportional hazards models to evaluate prediction of conversion from a non-demented state (CN or MCI) to AD dementia. Among 97 participants without dementia at baseline, 30 individuals (CN: 7/54; MCI: 23/43) converted to AD dementia over a mean follow-up of 5.37 years. After adjusting for age, sex, education, *APOE* ε4 status, and baseline cognitive status, higher baseline serum β-synuclein was associated with a significantly increased risk of conversion to AD dementia (hazard ratio [HR] = 1.83 per standard deviation increase, 95 % CI: 1.23 to 2.73; $p = 0.003$; Supplementary Fig. S2). In contrast, baseline CSF neurogranin levels were not significantly associated with conversion risk (HR = 1.67, 95 % CI: 0.81 to 3.46; $p = 0.167$).

3.4. Association of serum β-synuclein, CSF neurogranin and other AD-related markers

Spearman correlation analyses revealed that serum β-synuclein was significantly correlated with all examined CSF, cognitive, and imaging markers (all FDR-adjusted $p < 0.001$; Supplementary Fig. S3). Its associations with cognitive and imaging markers were consistently stronger than those of CSF neurogranin. Notably, serum β-synuclein showed a robust correlation with CSF Aβ42 ($\rho = -0.44$), whereas CSF neurogranin did not, and a stronger correlation with the CSF p-tau181/Aβ42 ratio (ρ = 0.62 vs. 0.55). Conversely, CSF neurogranin exhibited its strongest associations with t-tau ($\rho = 0.86$) and p-tau181 ($\rho = 0.84$).

To evaluate these associations independently of potential

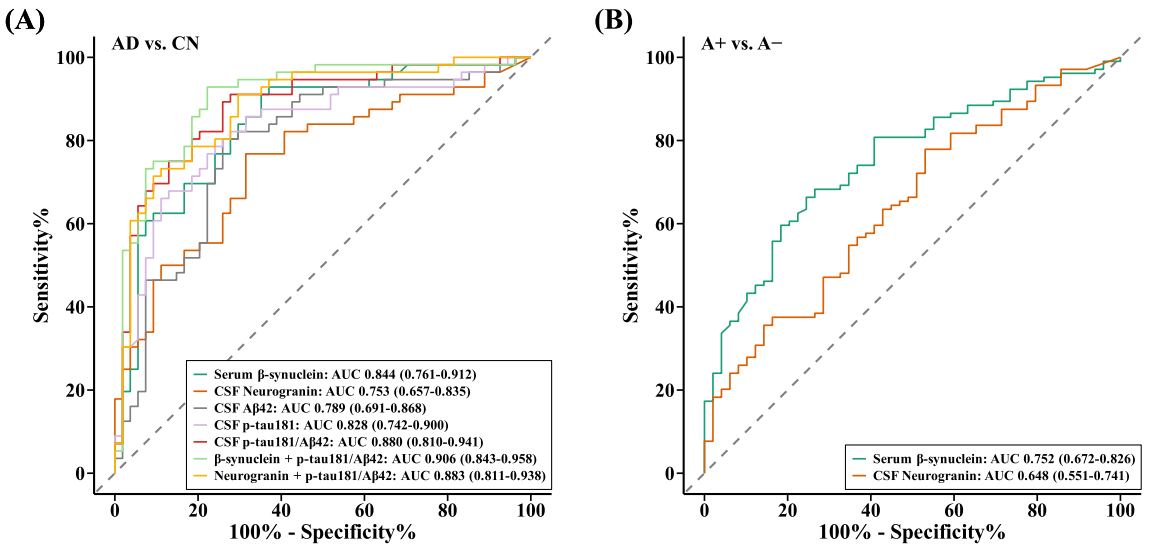

Fig. 2. Diagnostic performance of serum β-synuclein and CSF neurogranin. Receiver operating characteristic curves for: (A) differentiation between patients with AD dementia and CN individuals ($n = 56$ for AD and $n = 54$ for CN); and (B) discrimination between individuals with A+ and A− status ($n = 104$ for A+ and $n = 49$ for A−). AUC values and corresponding 95 % confidence intervals were calculated using a bootstrap method with 2000 replicates. Abbreviations: A−, amyloid-β negative; A+, amyloid-β positive; AD, Alzheimer's disease dementia; AUC, area under the curve; Aβ42, amyloid-β 42; CN, cognitively normal; CSF, cerebrospinal fluid; p-tau181, phosphorylated tau at threonine 181.

confounders, linear regression analyses adjusted for age, sex, years of education, and *APOE* ε4 carrier status were performed (Fig. 3). Serum β-synuclein was positively associated with CSF neurogranin (βstd = 0.33, 95 % CI: 0.17 to 0.49; $p < 0.001$). When examined in relation to other AD biomarkers, the two synaptic markers demonstrated distinct association profiles. Serum β-synuclein was independently associated with lower CSF Aβ42 (βstd = −0.28, 95 % CI: −0.43 to −0.13), while CSF neurogranin showed no such association (Δβstd = −0.39, 95 % CI: −0.65 to −0.14; $p = 0.011$). Both serum β-synuclein and CSF neurogranin were associated with higher p-tau181, t-tau and p-tau181/Aβ42 ratio, with the association between CSF neurogranin and p-tau181 and t-tau was stronger than serum β-synuclein (Δβstd for p-tau181 = −0.66, 95 % CI: −0.82 to −0.50; Δβstd for t-tau = −0.71, 95 % CI: −0.87 to −0.55; both $p < 0.001$). Regarding cognitive decline and neurodegenerative changes, higher levels of both biomarkers were associated with worse outcomes. Although the magnitude of these associations tended to be larger for serum β-synuclein than for CSF neurogranin across most cognitive and imaging measures, differences in standardized effect sizes did not reach statistical significance.

3.5. Baseline serum β-synuclein predicts longitudinal disease progression

The above results demonstrated that serum β-synuclein was a promising biomarker for cognitive decline and neurodegenerative changes, comparable to the established CSF synaptic marker neurogranin. We further used LMMs to investigate whether baseline serum β-synuclein levels predicted the rate of longitudinal progression in clinical and neuroimaging markers for all individuals with available serum β-synuclein data (Fig. 4, Supplementary Fig. S4).

After correction for multiple comparisons, higher baseline β-synuclein was significantly associated with accelerated progression across all tested outcomes. For clinical measures, higher baseline levels predicted a faster decline in measures of early cognitive function (mPACC: βstd = −0.28, 95 % CI: −0.35 to −0.22; $R^2 = 0.36$) and memory (ADNI MEM: βstd = −0.22, 95 % CI: −0.27 to −0.17; $R^2 = 0.45$). Higher baseline levels also predicted more rapid global deterioration as measured by the CDR-SB (βstd = 0.43, 95 % CI: 0.35 to 0.52; $R^2 = 0.30$) and the ADAS-Cog 13 (βstd = 0.35, 95 % CI: 0.28 to 0.42; $R^2 = 0.34$; all $p < 0.001$). For neuroimaging measures, higher baseline β-synuclein was associated with faster neurodegeneration across multiple brain regions. This included accelerated cortical thinning (βstd = −0.23, 95 % CI: −0.28 to −0.18; $R^2 = 0.30$) and accelerated decline in brain glucose metabolism as measured by FDG-PET (βstd = −0.13, 95 % CI: −0.18 to −0.08; $R^2 = 0.38$). Furthermore, higher baseline β-synuclein predicted greater volume loss in the AD composite region (βstd = −0.11, 95 % CI: −0.13 to −0.08; $R^2 = 0.39$), and faster atrophy in the medial temporal lobe (βstd = −0.10, 95 % CI: −0.12 to −0.07; $R^2 = 0.40$; all $p < 0.001$). Importantly, these associations remained statistically significant after additional adjustment for baseline CSF Aβ42 or CSF p-tau181 levels, supporting the independence of serum β-synuclein from established AD pathologies (Supplementary Table S3).

Moderation analyses examining baseline amyloid status revealed significant three-way interactions for CDR-SB ($\beta = 1.68$, $p = 0.034$) and cortical thickness ($\beta = -0.11$, $p = 0.001$; Supplementary Table S4), indicating that the association between higher baseline serum β-synuclein and both global cognitive decline and cortical atrophy was stronger in amyloid-positive individuals. No significant moderation by amyloid status was observed for other cognitive or neuroimaging outcomes. Furthermore, no significant interactions with sex or *APOE* ε4 carrier status were detected for any outcome (all three-way interaction p values > 0.05; Supplementary Table S5), suggesting that the predictive effect of serum β-synuclein was consistent across these subgroups.

3.6. Rate of change in serum β-synuclein predicts longitudinal disease progression

Beyond baseline levels, we investigated whether the longitudinal rate of change of serum β-synuclein also predicted clinical and neuroimaging progression in 241 individuals with longitudinal serum β-synuclein data. After FDR correction for multiple comparisons, steeper increases in serum β-synuclein over time significantly predicted accelerated disease progression across all examined outcomes (Fig. 5, Supplementary Fig. S5). Faster rates of β-synuclein increase were associated with more rapid decline in early cognitive function (mPACC: βstd = −0.30, 95 % CI: −0.38 to −0.22; $R^2 = 0.37$) and accelerated worsening in global clinical severity (CDR-SB: βstd = 0.40, 95 % CI: 0.29 to 0.52; $R^2 = 0.24$). These findings were consistent across other neuropsychological measures, including the ADNI MEM composite score (βstd = −0.23, 95

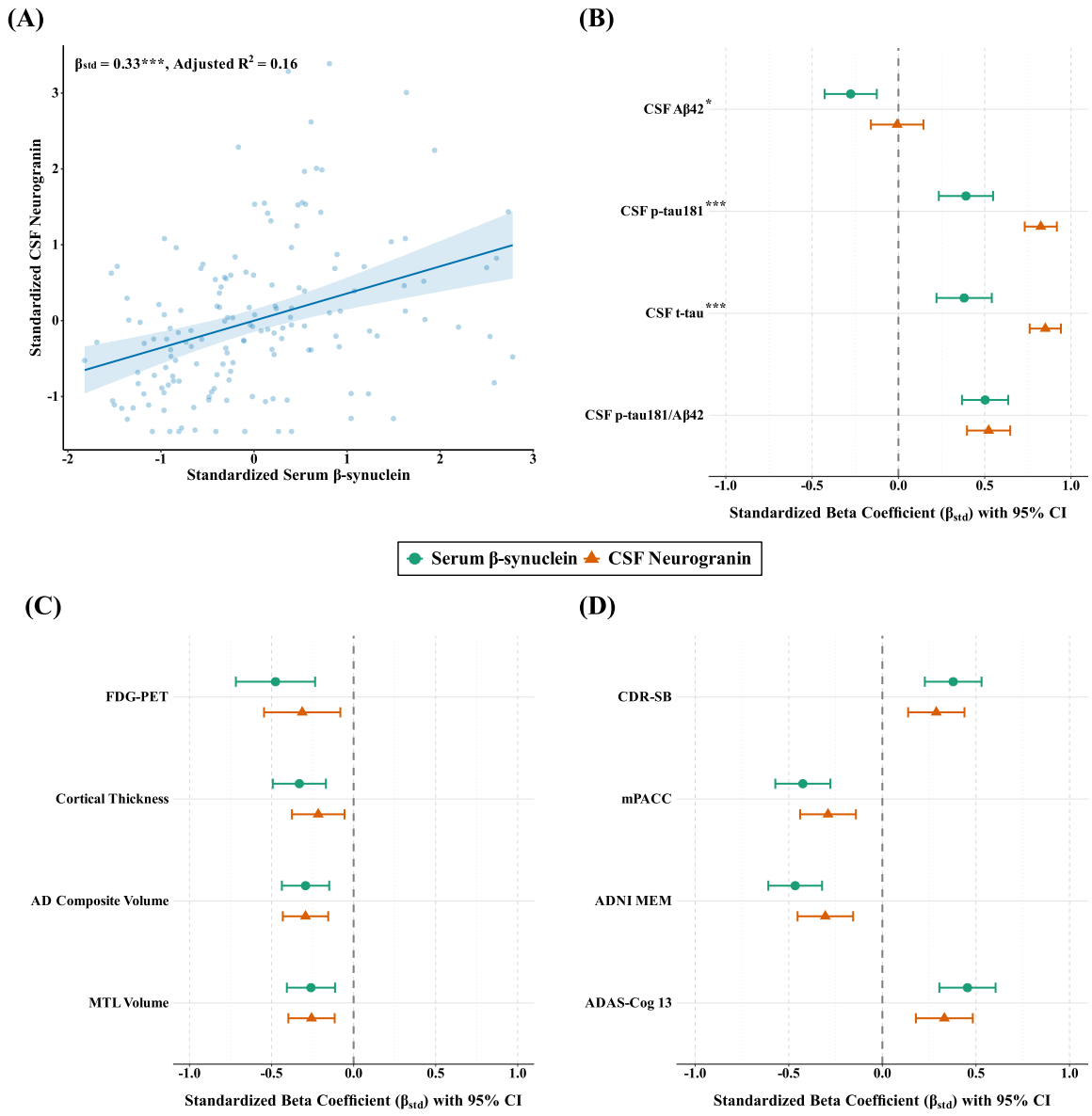

Fig. 3. Independent associations of serum β-synuclein and CSF neurogranin with AD-related markers. (A) Scatter plot showing the independent association between serum β-synuclein and CSF neurogranin after standardization. The line represents the linear regression fit, and the shaded area indicates the 95 % confidence interval. The model was adjusted for age, sex, education, and *APOE* ε4 status. (B-D) Forest plots showing standardized beta coefficients (βstd) from a series of multiple linear regression models, stratified by marker category: (B) CSF biomarkers; (C) cognitive scores; and (D) imaging measures. Each model assessed the independent association between a predictor (serum β-synuclein or CSF neurogranin) and a specific outcome marker, after adjusting for the same covariates. Points represent the standardized β coefficient and error bars indicate the 95 % confidence intervals. Asterisks next to the outcome labels indicate a statistically significant difference between βstd for serum β-synuclein and CSF neurogranin for the same outcome, tested using a Wald test (***$p < 0.001$, **$p < 0.01$, *$p < 0.05$). All p values were corrected for multiple comparisons using the false discovery rate method. Abbreviations: AD Composite Volume, Alzheimer's Disease composite region volume; ADAS-Cog 13, Alzheimer's Disease Assessment Scale-Cognitive subscale 13; ADNI MEM, Alzheimer's Disease Neuroimaging Initiative Memory Composite Score; Aβ42, amyloid-β 42; CDR-SB, Clinical Dementia Rating Sum of Boxes; CSF, cerebrospinal fluid; FDG-PET, [18F]fluorodeoxyglucose positron emission tomography; mPACC, modified Preclinical Alzheimer's Cognitive Composite; MTL, medial temporal lobe; p-tau181, phosphorylated tau at threonine 181; t-tau, total tau.

% CI: −0.28 to −0.17; $R^2 = 0.45$) and the ADAS-Cog 13 (βstd = 0.34, 95 % CI: 0.25 to 0.42; $R^2 = 0.31$; all $p < 0.001$). For neuroimaging outcomes, faster rates of β-synuclein increase predicted faster neurodegeneration, including more rapid cortical thinning (βstd = −0.27, 95 % CI: −0.33 to −0.20; $R^2 = 0.31$), accelerated decline in brain glucose metabolism (βstd = −0.16, 95 % CI: −0.23 to −0.09; $R^2 = 0.40$), and faster atrophy in both the AD composite region (βstd = −0.12, 95 % CI: −0.16 to −0.09; $R^2 = 0.41$) and the medial temporal lobe (βstd = −0.11, 95 % CI: −0.14 to −0.08; $R^2 = 0.37$; all $p < 0.001$). Importantly, the predictive associations between longitudinal serum β-synuclein change and all clinical and neuroimaging outcomes remained statistically significant after additional adjustment for baseline CSF Aβ42 or CSF p-tau181 levels (Supplementary Table S6).

Moderation analyses examining baseline amyloid status identified a significant three-way interaction only for cortical thickness (β = −0.08, $p < 0.001$; Supplementary Table S7), indicating that faster increases in serum β-synuclein were more strongly associated with accelerated cortical atrophy in amyloid-positive individuals. No significant moderation by amyloid status was observed for other cognitive or neuroimaging outcomes. Moreover, no significant interactions with sex or *APOE* ε4 carrier status were detected for any outcome (all three-way interaction p values > 0.05; Supplementary Table S8), suggesting that

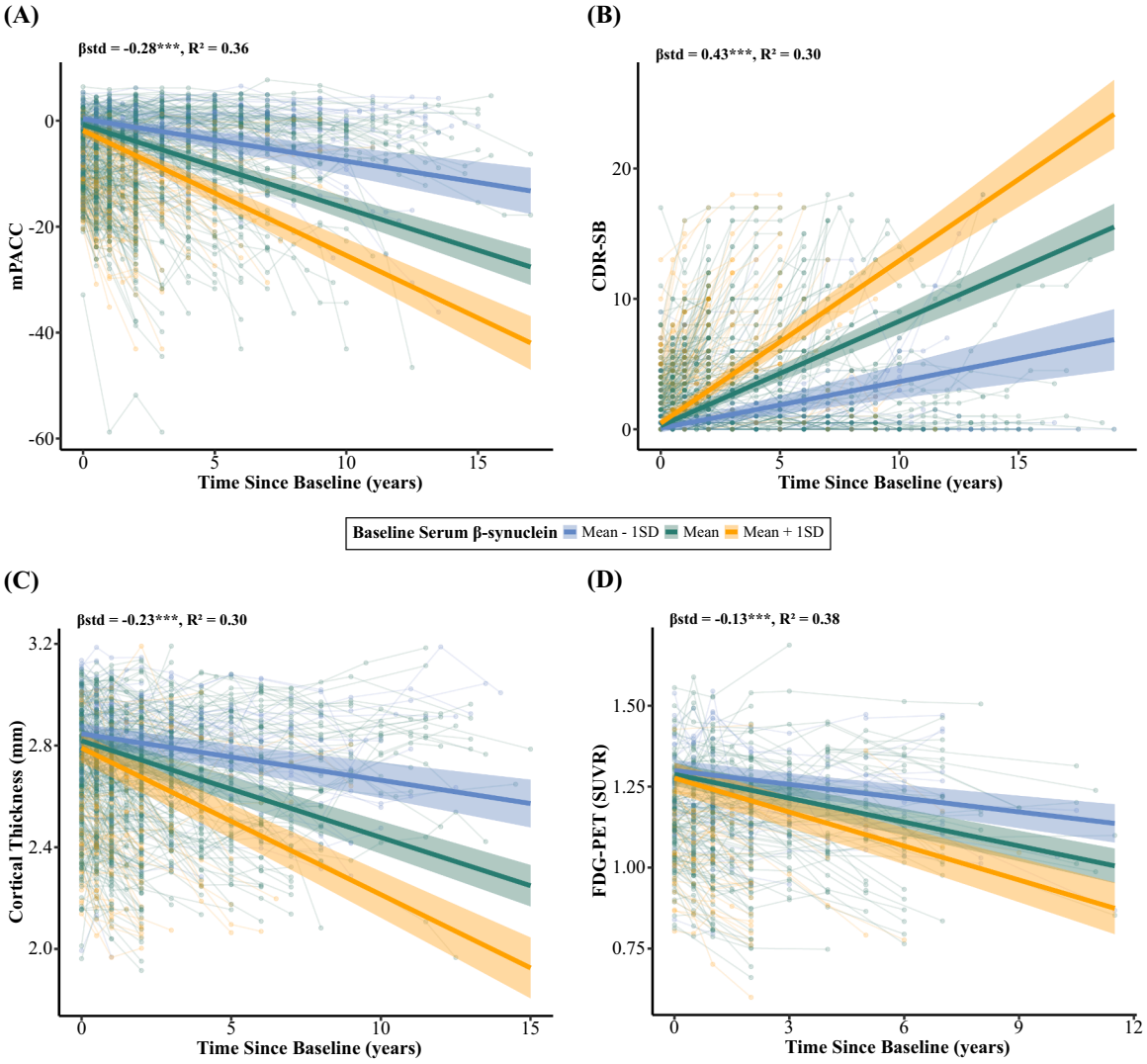

Fig. 4. Association between baseline serum β-synuclein levels and longitudinal progression of cognitive and neuroimaging markers. Longitudinal trajectories of (A) mPACC ($n = 412$), (B) CDR-SB ($n = 417$), (C) Cortical Thickness ($n = 378$), and (D) FDG-PET ($n = 228$), stratified by baseline serum β-synuclein level. The three main trend lines represent the estimated marginal trajectories from linear mixed-effects models for participants with low (Mean - 1SD), mean, and high (Mean + 1SD) baseline levels of log10-transformed serum β-synuclein. Shaded areas represent the 95 % confidence intervals. Thin lines represent individual participant trajectories. All models tested the interaction between baseline β-synuclein level and time, adjusting for baseline age, sex, education, *APOE* ε4 status, and baseline clinical diagnosis, and included random intercepts and slopes for time for each participant. The standardized beta coefficient (βstd) for the interaction term and the marginal R-squared (R^2) for the fixed effects are displayed in each panel. *** indicates an FDR-adjusted $p < 0.001$ for the interaction term. Abbreviations: CDR-SB, Clinical Dementia Rating Sum of Boxes; FDG-PET, [18F]fluorodeoxyglucose positron emission tomography; mPACC, modified Preclinical Alzheimer's Cognitive Composite; SD, standard deviation.

the predictive value of longitudinal serum β-synuclein change was consistent across these subgroups.

3.7. Longitudinal trajectories of serum β-synuclein across AD disease continuum

The longitudinal trajectory of serum β-synuclein as a function of age is shown in Supplementary Fig. S6. When stratified by the A/T framework (Fig. 6), distinct longitudinal patterns emerged. Serum β-synuclein levels increased significantly over time in the A+T− group (annual increase = 0.45 pg/mL, 95 % CI: 0.03 to 0.86; $p = 0.034$) and accelerated further in the A+T+ group (annual increase = 0.86 pg/mL, 95 % CI: 0.40 to 1.31; $p < 0.001$). Conversely, the A−T− group remained stable over time ($p = 0.30$). Direct comparison confirmed that the rate of accumulation in the A+T+ group was significantly steeper than that in the A−T− group (difference in slopes = 0.69 pg/mL/year, $p = 0.042$).

4. Discussion

This study provides a comprehensive cross-sectional and longitudinal investigation of serum β-synuclein's potential as a blood-based biomarker for AD. Our findings indicate that serum β-synuclein's levels progressively increase across the AD continuum, demonstrating high diagnostic accuracy in distinguishing clinically diagnosed AD from CN individuals. Longitudinally, elevated baseline levels significantly predicted the risk of conversion to dementia. Notably, this study provides a direct comparison between serum β-synuclein and the established postsynaptic marker CSF neurogranin. While both markers reflected synaptic dysfunction, serum β-synuclein demonstrated superior prognostic utility for clinical progression. Furthermore, both baseline levels and change rates of serum β-synuclein were strong predictors of cognitive decline and neurodegeneration, independent of baseline amyloid or tau pathology. These findings support the potential utility of serum β-synuclein for both the diagnosis and prognosis of AD.

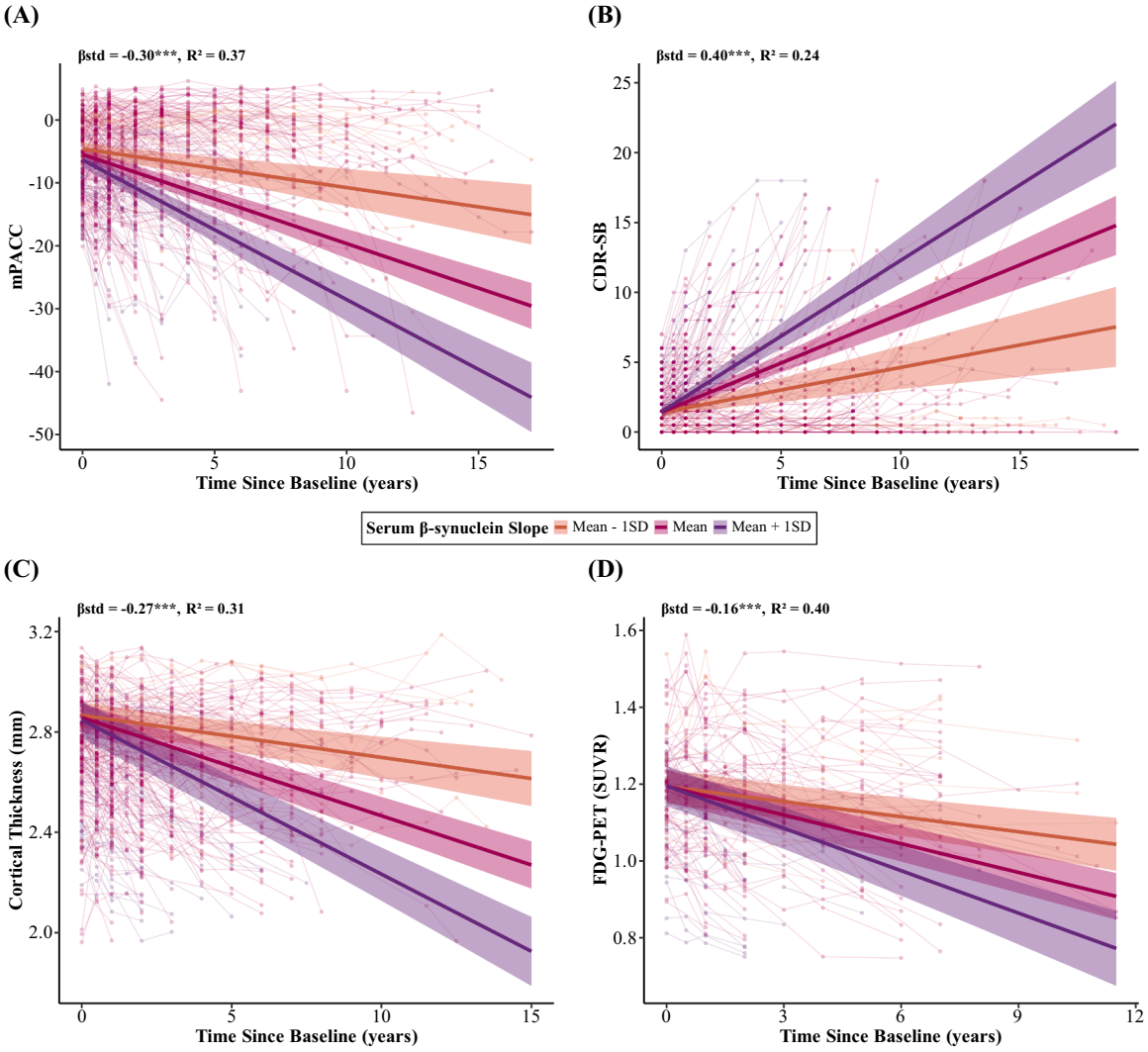

Fig. 5. Association between rate of change in serum β-synuclein and longitudinal progression of cognitive and neuroimaging markers. Longitudinal trajectories of (A) mPACC ($n = 241$), (B) CDR-SB ($n = 240$), (C) Cortical Thickness ($n = 221$), and (D) FDG-PET ($n = 136$), stratified by individual β-synuclein slope levels. Individual slopes of β-synuclein change were derived for each participant using linear mixed-effects models in a two-stage analytical approach. The three main trend lines represent the estimated marginal trajectories from linear mixed-effects models for participants with low (Mean - 1SD), mean, and high (Mean + 1SD) individual β-synuclein slopes. Shaded areas represent the 95 % confidence intervals. Thin lines represent individual participant trajectories. All models tested the interaction between individual β-synuclein slopes and time, adjusting for baseline age, sex, education, *APOE* ε4 status, and clinical diagnosis, and included random intercepts and slopes for time for each participant. The standardized beta coefficient (βstd) for the interaction term and the marginal R-squared (R^2) for the fixed effects are displayed in each panel. *** indicates an FDR-adjusted $p < 0.001$ for the interaction term. Abbreviations: CDR-SB, Clinical Dementia Rating Sum of Boxes; FDG-PET, [18F]fluorodeoxyglucose positron emission tomography; mPACC, modified Preclinical Alzheimer's Cognitive Composite; SD, standard deviation.

CSF neurogranin was selected for comparison as it is a well-validated, AD-specific biomarker that reflects the integrity of the post-synaptic compartment [31–33]. Our finding that CSF neurogranin correlates strongly with CSF tau, but not with Aβ42, aligns with previous reports [34,35], supporting the view that neurogranin release is a downstream event reflecting tau-associated dendritic damage. However, this strong collinearity suggests that neurogranin levels may largely mirror tau pathology, potentially limiting its ability to provide independent prognostic information. In contrast, serum β-synuclein exhibited a distinct profile modulated by both amyloid and tau pathologies. While its initial elevation is linked to amyloid pathology, our data show its trajectory accelerates dramatically only in the presence of co-existing tau pathology. This pattern supports a model of synergistic injury: Aβ accumulation may initiate a low-level, chronic presynaptic stress, whereas the subsequent onset of tau pathology likely precipitates widespread synaptic dysfunction [36–39]. Consequently, the steep rise in serum β-synuclein observed in the A+T+ stage likely captures this compounded synaptic toxicity.

Comparisons between CSF and serum biomarkers require caution due to the physiological distinctness of central and peripheral compartments. While CSF biomarkers offer a proximal readout of cerebral pathophysiology, serum levels represent a distal signal influenced by blood-brain barrier (BBB) permeability and systemic dilution [40,41]. Conventionally, CSF markers are expected to correlate more closely with central pathology. Contrary to this expectation, however, our analyses revealed that serum β-synuclein was a superior predictor of conversion to AD dementia compared to CSF neurogranin. Furthermore, serum β-synuclein showed comparable or stronger associations with cognitive and neuroimaging outcomes. This apparent paradox may be attributable to the high CNS-specificity of β-synuclein [42], or the possibility that peripheral levels capture an integrated signal reflecting both synaptic density and BBB integrity. Additionally, previous analysis showed that presynaptic markers are affected earlier and more severely than post-synaptic markers in AD [43]; thus, as a presynaptic marker, β-synuclein

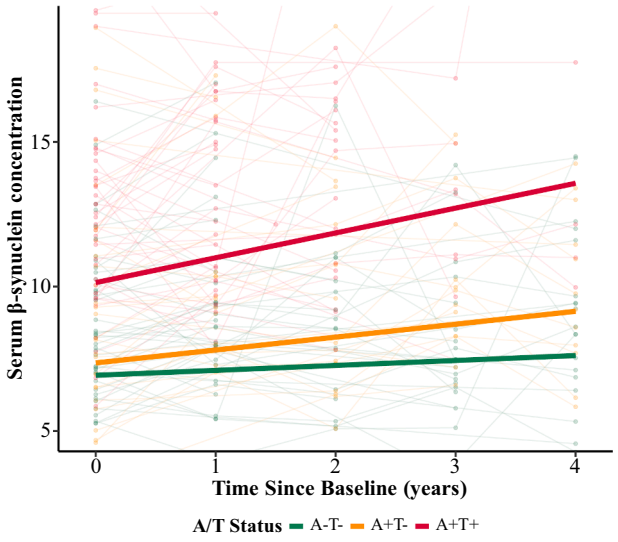

Fig. 6. Longitudinal trajectories of serum β-synuclein across A/T pathological groups. The plot shows longitudinal serum β-synuclein levels in individuals stratified by their baseline A/T status (A−T−, $n = 42$; A+T−, $n = 28$; A+T+, $n = 43$). The solid lines represent the estimated marginal trajectories from a linear mixed-effects model that was adjusted for baseline age, sex, education, *APOE* ε4 status, and clinical diagnosis. Individual data points are shown for each participant at each visit. Abbreviations: A−, amyloid-β negative; A+, amyloid-β positive; T−, tau negative; T+, tau positive.

may provide greater sensitivity to early disease progression than the postsynaptic marker neurogranin.

Our findings indicate that serum β-synuclein has limited sensitivity for detecting early amyloid pathology. Specifically, we observed no significant difference in its levels between CN individuals with and without amyloid pathology. This contrasts with some prior reports suggesting elevated serum β-synuclein in preclinical AD [16,17]; this discrepancy may be attributable to cohort differences or the limited sample size of preclinical cases in the present analysis. The biomarker's modest performance in early detection was reinforced by ROC analysis, which yielded an AUC of 0.75 for discriminating between amyloid-positive and amyloid-negative individuals. This cross-sectional pattern was mirrored by the longitudinal trajectory, where a significant acceleration in the rate of change was evident only after the establishment of tau pathology (the A+T+ stage). In contrast to its limitations in early screening, serum β-synuclein demonstrated robust utility as a marker of disease severity and prognosis. Cross-sectionally, it accurately identified established clinical disease, differentiating patients with AD dementia from controls with an AUC of 0.84—performance comparable to the CSF p-tau181/Aβ42 ratio. These levels tracked closely with disease severity, showing strong associations with cognitive deficits, brain atrophy, and hypometabolism, consistent with previous findings [17,44]. However, while prior cross-sectional studies could not capture temporal dynamics, our longitudinal design addresses this limitation. We provide novel evidence that both elevated baseline levels and, crucially, a rapid longitudinal rate of increase in serum β-synuclein are strong, independent predictors of future cognitive decline and neurodegeneration. Importantly, these associations persisted after adjusting for baseline CSF Aβ42 or p-tau181, suggesting that serum β-synuclein captures dimensions of progressive synaptic failure independent of core AD proteinopathy. These results underscore the value of serial monitoring of serum β-synuclein to identify patients at high risk of rapid progression.

Synaptic pathology is a convergent feature across the spectrum of neurodegenerative diseases, including AD, Parkinson's disease, Lewy body dementia, frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS) [45–47]. In AD, synaptic dysfunction is recognized not merely as a downstream consequence but as a key driver of cognitive impairment that correlates closely with clinical status [48–50]. While fluid biomarkers for core pathologies (e.g., plasma p-tau217 for amyloid/tau) and general neuroaxonal injury (e.g., NfL) are well-established, there remains a critical need for accessible markers capable of specifically monitoring synaptic integrity. Current evidence supports serum β-synuclein as a valuable marker for this purpose, distinguishing AD-related synaptic degeneration from other proteinopathies. Unlike NfL, which is non-specifically elevated across diverse neurodegenerative disorders [51], serum β-synuclein levels remain largely stable in patients with pure FTD or ALS, typically rising only when concurrent AD pathology is present [21,44]. Although our data in sporadic AD suggest elevations become most prominent with established pathology, studies in autosomal dominant AD have detected elevated serum β-synuclein up to 11 years prior to symptom onset, significantly preceding the rise of NfL [20]. Furthermore, serum β-synuclein provides complementary value to plasma p-tau isoforms by directly indexing synaptic structure, a measure more tightly linked to cognitive performance and cortical atrophy than amyloid or tau load alone [14,21]. Consequently, serum β-synuclein holds substantial promise for clinical trials, both for stratifying preclinical individuals at high risk of rapid decline and as a surrogate endpoint to verify synaptic preservation in response to disease-modifying therapies.

This study has several limitations. First, direct comparison between serum β-synuclein and CSF neurogranin was restricted to a sub-cohort with available data for both biomarkers, which limited statistical power for some stratified analyses. Validation through larger, independent cohorts is essential to confirm these findings. Second, our findings are derived from the ADNI cohort, which primarily consists of White and highly educated individuals. Therefore, validating these results in diverse, multi-ethnic, and community-based populations is a crucial step to ensure generalizability. Third, our A/T classification relied on CSF biomarkers. While CSF classification is well-validated, the inclusion of PET imaging would have provided complementary information regarding the spatial distribution of pathology. Fourth, we did not include a direct comparison with other emerging plasma biomarkers, such as the plasma Aβ42/40 ratio or p-tau217. Future head-to-head studies are crucial to definitively position serum β-synuclein within the rapidly evolving panel of blood-based AD biomarkers. Fifth, the lack of non-AD neurodegenerative control groups in this cohort precludes assessment of the biomarker's specificity in a differential diagnostic context. Finally, the longitudinal trajectories were estimated from a cohort comprising individuals at varying disease stages at baseline. To fully characterize the temporal dynamics and natural history of serum β-synuclein, prospective studies tracking individuals from a cognitively

unimpaired state to overt dementia are necessary.

In conclusion, our study supports serum β-synuclein as a robust, dynamic blood-based biomarker of disease progression in AD. Its capacity to predict cognitive decline and neurodegeneration, independent of core amyloid and tau pathologies, highlights its utility as a scalable tool for monitoring disease severity and, potentially, as a surrogate endpoint for synaptic preservation in clinical trials.

Ethics approval and consent to participate

The ADNI study was conducted in accordance with the Declaration of Helsinki, ethical approval in ADNI was given by the local ethical committees of all involved sites. Informed written consent was obtained from all participants at each site.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used Gemini in order to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Data sharing

Data used in this study were obtained from the ADNI database (adni.loni.usc.edu). The data are publicly available to qualified researchers upon application.

CRediT authorship contribution statement

Siqi Xie: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Yumei Liang:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Ting Yang:** Writing – review & editing, Data curation. **Dandan Sheng:** Writing – review & editing, Data curation. **Lan Ding:** Writing – review & editing, Data curation. **Jianping Jia:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100514.

References

[1] Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. Nat Rev Dis Primer 2021;7:33. https://doi.org/10.1038/s41572-021-00269-y.
[2] Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535–62. https://doi.org/10.1016/j.jalz.2018.02.018.
[3] Yu J, Li J, Suckling J, Feng L, Pan A, Wang Y, et al. Frequency and longitudinal clinical outcomes of Alzheimer's AT(N) biomarker profiles: a longitudinal study. Alzheimers Dement 2019;15:1208–17. https://doi.org/10.1016/j.jalz.2019.05.006.
[4] Pascoal TA, Leuzy A, Therriault J, Chamoun M, Lussier F, Tissot C, et al. Discriminative accuracy of the A/T/N scheme to identify cognitive impairment due to Alzheimer's disease. Alzheimers Dement Diagn Assess Amp Dis Monit 2023;15:e12390. https://doi.org/10.1002/dad2.12390.
[5] Canu E, Rugarli G, Coraglia F, Basaia S, Cecchetti G, Calloni SF, et al. Real-word application of the AT(N) classification and disease-modifying treatment eligibility in a hospital-based cohort. J Neurol 2024;271:2716–29. https://doi.org/10.1007/s00415-024-12221-7.
[6] Hunter TR, Santos LE, Tovar-Moll F, De Felice FG. Alzheimer's disease biomarkers and their current use in clinical research and practice. Mol Psychiatry 2025;30:272–84. https://doi.org/10.1038/s41380-024-02709-z.
[7] Jack CR, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement 2024;20:5143–69. https://doi.org/10.1002/alz.13859.
[8] Jack CR, Andrews SJ, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for the diagnosis and staging of Alzheimer's disease. Nat Med 2024;30:2121–4. https://doi.org/10.1038/s41591-024-02988-7.
[9] Chen Y, Fu AKY, Ip NY. Synaptic dysfunction in Alzheimer's disease: mechanisms and therapeutic strategies. Pharmacol Ther 2019;195:186–98. https://doi.org/10.1016/j.pharmthera.2018.11.006.
[10] Tzioras M, McGeachan RI, Durrant CS. Spires-Jones TL. Synaptic degeneration in Alzheimer disease. Nat Rev Neurol 2023;19:19–38. https://doi.org/10.1038/s41582-022-00749-z.
[11] Colom-Cadena M, Spires-Jones T, Zetterberg H, Blennow K, Caggiano A, DeKosky ST, et al. The clinical promise of biomarkers of synapse damage or loss in Alzheimer's disease. Alzheimers Res Ther 2020;12:21. https://doi.org/10.1186/s13195-020-00588-4.
[12] Mecca AP, Chen M, O'Dell RS, Naganawa M, Toyonaga T, Godek TA, et al. In vivo measurement of widespread synaptic loss in Alzheimer's disease with SV2A PET. Alzheimers Dement 2020;16:974–82. https://doi.org/10.1002/alz.12097.
[13] Mohaupt P, Pons M-L, Vialaret J, Delaby C, Hirtz C, Lehmann S. β-synuclein as a candidate blood biomarker for synaptic degeneration in Alzheimer's disease. Alzheimers Res Ther 2022;14:179. https://doi.org/10.1186/s13195-022-01125-1.
[14] Halbgebauer S, Oeckl P, Steinacker P, Yilmazer-Hanke D, Anderl-Straub S, von Arnim C, et al. Beta-synuclein in cerebrospinal fluid as an early diagnostic marker of Alzheimer's disease. J Neurol Neurosurg Psychiatry 2021;92:349–56. https://doi.org/10.1136/jnnp-2020-324306.
[15] Barba L, Abu Rumeileh S, Bellomo G, Paolini Paoletti F, Halbgebauer S, Oeckl P, et al. Cerebrospinal fluid β-synuclein as a synaptic biomarker for preclinical Alzheimer's disease. J Neurol Neurosurg Psychiatry 2023;94:83–6. https://doi.org/10.1136/jnnp-2022-329124.

[16] Oeckl P, Bluma M, Bucci M, Halbgebauer S, Chiotis K, Sandebring-Matton A, et al. Blood β-synuclein is related to amyloid PET positivity in memory clinic patients. Alzheimers Dement 2023;19:4896–907. https://doi.org/10.1002/alz.13046.
[17] Oeckl P, Janelidze S, Halbgebauer S, Stomrud E, Palmqvist S, Otto M, et al. Higher plasma β-synuclein indicates early synaptic degeneration in Alzheimer's disease. Alzheimers Dement 2023;19:5095–102. https://doi.org/10.1002/alz.13103.
[18] Beyer K, Munoz-Marmol AM, Sanz C, Marginet-Flinch R, Ferrer I, Ariza A. New brain-specific beta-synuclein isoforms show expression ratio changes in Lewy body diseases. Neurogenetics 2012;13:61–72. https://doi.org/10.1007/s10048-011-0311-8.
[19] Tanji K, Mori F, Nakajo S, Imaizumi T, Yoshida H, Hirabayashi T, et al. Expression of β-synuclein in normal human astrocytes. Neuroreport 2001;12:2845–8. https://doi.org/10.1097/00001756-200109170-00018.
[20] Oeckl P, Mayer B, Bateman RJ, Day GS, Fox NC, Huey ED, et al. Early increase of the synaptic blood marker β-synuclein in asymptomatic autosomal dominant Alzheimer's disease. Alzheimers Dement 2025;21:e70146. https://doi.org/10.1002/alz.70146.
[21] Barba L, Bellomo G, Alcolea D, Wojdala AL, Gaetani L, Fortea J, et al. Serum level changes of the synaptic marker beta-synuclein in Alzheimer's disease continuum and other dementias. J Neurol Neurosurg Psychiatry 2025. https://doi.org/10.1136/jnnp-2025-336189. jnnp-2025-336189.
[22] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease. Neurology 1984;34:939. https://doi.org/10.1212/WNL.34.7.939. –939.
[23] Oeckl P, Halbgebauer S, Anderl-Straub S, von Arnim CAF, Diehl-Schmid J, Froelich L, et al. Targeted mass spectrometry suggests beta-synuclein as synaptic blood marker in Alzheimer's disease. J Proteome Res 2020;19:1310–8. https://doi.org/10.1021/acs.jproteome.9b00824.
[24] Bittner T, Zetterberg H, Teunissen CE, Ostlund RE, Militello M, Andreasson U, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. Alzheimers Dement J Alzheimers Assoc 2016;12:517–26. https://doi.org/10.1016/j.jalz.2015.09.009.
[25] Meyer P-F, Pichet Binette A, Gonneaud J, Breitner JCS, Villeneuve S. Characterization of Alzheimer disease biomarker discrepancies using cerebrospinal fluid phosphorylated tau and AV1451 positron emission tomography. JAMA Neurol 2020;77:508. https://doi.org/10.1001/jamaneurol.2019.4749.
[26] Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci 2000;97:11050–5. https://doi.org/10.1073/pnas.200033797.
[27] Doshi J, Erus G, Ou Y, Resnick SM, Gur RC, Gur RE, et al. MUSE: multi-atlas region segmentation utilizing ensembles of registration algorithms and parameters, and locally optimal atlas selection. NeuroImage 2016;127:186–95. https://doi.org/10.1016/j.neuroimage.2015.11.073.
[28] Beer JC, Tustison NJ, Cook PA, Davatzikos C, Sheline YI, Shinohara RT, et al. Longitudinal ComBat: a method for harmonizing longitudinal multi-scanner imaging data. NeuroImage 2020;220:117129. https://doi.org/10.1016/j.neuroimage.2020.117129.
[29] Donohue MC, Sperling RA, Salmon DP, Rentz DM, Raman R, Thomas RG, et al. The preclinical Alzheimer cognitive composite. JAMA Neurol 2014;71:961. https://doi.org/10.1001/jamaneurol.2014.803.
[30] Crane PK, Carle A, Gibbons LE, Insel P, Mackin RS, Gross A, et al. Development and assessment of a composite score for memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Brain Imaging Behav 2012;6:502–16. https://doi.org/10.1007/s11682-012-9186-z.
[31] Wellington H, Paterson RW, Portelius E, Törnqvist U, Magdalinou N, Fox NC, et al. Increased CSF neurogranin concentration is specific to Alzheimer disease. Neurology 2016;86:829–35. https://doi.org/10.1212/WNL.0000000000002423.
[32] Kester MI, Teunissen CE, Crimmins DL, Herries EM, JackH Ladenson, Scheltens P, et al. Neurogranin as a cerebrospinal fluid biomarker for synaptic loss in symptomatic Alzheimer disease. JAMA Neurol 2015;72:1275. https://doi.org/10.1001/jamaneurol.2015.1867.
[33] Portelius E, Zetterberg H, Skillbäck T, Törnqvist U, Andreasson U, Trojanowski JQ, et al. Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease. Brain 2015;138:3373–85. https://doi.org/10.1093/brain/awv267.
[34] Casaletto KB, Elahi FM, Bettcher BM, Neuhaus J, Bendlin BB, Asthana S, et al. Neurogranin, a synaptic protein, is associated with memory independent of Alzheimer biomarkers. Neurology 2017;89:1782–8. https://doi.org/10.1212/WNL.0000000000004569.
[35] Mattsson N, Insel PS, Palmqvist S, Portelius E, Zetterberg H, Weiner M, et al. Cerebrospinal fluid tau, neurogranin, and neurofilament light in Alzheimer's disease. EMBO Mol Med 2016;8:1184–96. https://doi.org/10.15252/emmm.201606540.
[36] Zhou L, McInnes J, Wierda K, Holt M, Herrmann AG, Jackson RJ, et al. Tau association with synaptic vesicles causes presynaptic dysfunction. Nat Commun 2017:8. https://doi.org/10.1038/ncomms15295.
[37] Moreno H, Morfini G, Buitrago L, Ujlaki G, Choi S, Yu E, et al. Tau pathology-mediated presynaptic dysfunction. Neuroscience 2016;325:30–8. https://doi.org/10.1016/j.neuroscience.2016.03.044.
[38] Arbel-Ornath M, Hudry E, Boivin JR, Hashimoto T, Takeda S, Kuchibhotla KV, et al. Soluble oligomeric amyloid-β induces calcium dyshomeostasis that precedes synapse loss in the living mouse brain. Mol Neurodegener 2017;12:27. https://doi.org/10.1186/s13024-017-0169-9.
[39] Busche MA, Chen X, Henning HA, Reichwald J, Staufenbiel M, Sakmann B, et al. Critical role of soluble amyloid-β for early hippocampal hyperactivity in a mouse model of Alzheimer's disease. Proc Natl Acad Sci 2012;109:8740–5. https://doi.org/10.1073/pnas.1206171109.
[40] Galasko D, Golde TE. Biomarkers for Alzheimer's disease in plasma, serum and blood - conceptual and practical problems. Alzheimers Res Ther 2013;5:10. https://doi.org/10.1186/alzrt164.
[41] Blennow K, Zetterberg H. The past and the future of Alzheimer's disease CSF biomarkers—a journey toward validated biochemical tests covering the whole spectrum of molecular events. Front Neurosci 2015;9. https://doi.org/10.3389/fnins.2015.00345.
[42] Barba L, Paolini Paoletti F, Bellomo G, Gaetani L, Halbgebauer S, Oeckl P, et al. Alpha and beta synucleins: from pathophysiology to clinical application as biomarkers. Mov Disord 2022;37:669–83. https://doi.org/10.1002/mds.28941.
[43] de Wilde MC, Overk CR, Sijben JW, Masliah E. Meta-analysis of synaptic pathology in Alzheimer's disease reveals selective molecular vesicular machinery vulnerability. Alzheimers Dement 2016;12:633–44. https://doi.org/10.1016/j.jalz.2015.12.005.
[44] Oeckl P, Anderl-Straub S, Danek A, Diehl-Schmid J, Fassbender K, Fliessbach K, et al. Relationship of serum beta-synuclein with blood biomarkers and brain atrophy. Alzheimers Dement 2023;19:1358–71. https://doi.org/10.1002/alz.12790.
[45] Marttinen M, Kurkinen KM, Soininen H, Haapasalo A, Hiltunen M. Synaptic dysfunction and septin protein family members in neurodegenerative diseases. Mol Neurodegener 2015;10. https://doi.org/10.1186/s13024-015-0013-z.
[46] Dejanovic B, Sheng M, Hanson JE. Targeting synapse function and loss for treatment of neurodegenerative diseases. Nat Rev Drug Discov 2024;23:23–42. https://doi.org/10.1038/s41573-023-00823-1.
[47] Wilson DM, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I. Hallmarks of neurodegenerative diseases. Cell 2023;186:693–714. https://doi.org/10.1016/j.cell.2022.12.032.
[48] Anschuetz A, Schwab K, Harrington CR, Wischik CM, Riedel G. A meta-analysis on presynaptic changes in Alzheimer's disease. J Alzheimers Dis 2024;97:145–62. https://doi.org/10.3233/JAD-231034.
[49] Jackson J, Jambrina E, Li J, Marston H, Menzies F, Phillips K, et al. Targeting the synapse in Alzheimer's disease. Front Neurosci 2019;13. https://doi.org/10.3389/fnins.2019.00735.
[50] Meftah S, Gan J. Alzheimer's disease as a synaptopathy: evidence for dysfunction of synapses during disease progression. Front Synaptic Neurosci 2023;15. https://doi.org/10.3389/fnsyn.2023.1129036.
[51] Halbgebauer S, Abu-Rumeileh S, Oeckl P, Steinacker P, Roselli F, Wiesner D, et al. Blood β-synuclein and neurofilament light chain during the course of prion disease. Neurology 2022;98:e1434–45. https://doi.org/10.1212/WNL.0000000000200002.