

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

















The Journal of Prevention of Alzheimer's Disease

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

Original Article



Multimodal biomarker characterization of amnestic objective subtle cognitive decline in aging and preclinical Alzheimer's disease

David López-Martos^{a,b,*} , Raffaele Cacciaglia^{a,b,c} , Marc Suárez-Calvet^{a,b,c,d} , Gemma Salvadó^{a,e} , Mahnaz Shekari^{a,b}, Armand González-Escalante^{a,b}, Marta Milà-Alomà^{a,f,g} , Anna Brugulat-Serrat^{a,b,c,h} , Carolina Minguillon^{a,b,c} , Matteo Toniettoⁱ , Edilio Borroniⁱ , Gregory Kleinⁱ , Clara Quijano-Rubio^j , Gwendlyn Kollmorgen^k , Henrik Zetterberg^{l,m,n,o,p,q,r} , Kaj Blennow^{l,m}, Juan Domingo Gispert^{a,b,c,s} , Oriol Grau-Rivera^{a,b,c,d,*} , Gonzalo Sánchez-Benavides^{a,b,c,*} , for the ALFA study¹

^a Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain^b Hospital del Mar Research Institute, Barcelona, Spain^c Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable, Instituto de Salud Carlos III, Madrid, Spain^d Servei de Neurologia, Hospital del Mar, Barcelona, Spain^e Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Lund, Sweden^f Department of Veterans Affairs Medical Center, Northern California Institute for Research and Education (NCIRE), San Francisco, CA, USA^g Department of Radiology, University of California, San Francisco, San Francisco, CA, USA^h Global Brain Health Institute, San Francisco, CA, USAⁱ Pharma Research and Early Development, F Hoffmann-La Roche Ltd., Basel, Switzerland^j Roche Diagnostics International Ltd, Rotkreuz, Switzerland^k Roche Diagnostics GmbH, Penzberg, Germany^l Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, University of Gothenburg, Mölndal, Sweden^m Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Swedenⁿ Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK^o UK Dementia Research Institute at UCL, London, UK^p Hong Kong Center for Neurodegenerative Diseases, Clear Water Bay, Hong Kong, China^q Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA^r Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA^s Centro de Investigación Biomédica en Red Bioingeniería, Biomateriales y Nanomedicina, Instituto de Salud Carlos III, Madrid, Spain

ARTICLE INFO

Keywords:

Alzheimer's disease
 Amnestic objective subtle cognitive decline (obj-SCD)
 Episodic memory
 Multimodal biomarkers

ABSTRACT

Background: The objective of this study was to provide a multimodal biomarker characterization of amnestic objective subtle cognitive decline (obj-SCD) in aging and preclinical Alzheimer's disease (AD).

Methods: Prospective observational study; data from the Alzheimer's and Families+ (ALFAs+) cohort, including cognitively unimpaired (CU) individuals with available baseline CSF biomarkers (normal or AD *continuum* profiles) and longitudinal neuropsychological assessment (2 time points, 3-year follow-up). Amnestic obj-SCD was defined using robust longitudinal neuropsychological references with multivariate base rate thresholds of significant decline (Free and Cued Selective Reminding Test, Memory Binding Test, Wechsler Memory Scale IV: Logical Memory). Study outcomes included plasma p-tau217, NfL, and GFAP; CSF p-tau181/Aβ42, NfL, and GFAP; Aβ and tau PET; and MRI Grey Matter volume (GMv). The associations of amnestic obj-SCD with fluid (plasma and CSF) and neuroimaging biomarkers (PET and GMv) were evaluated using mixed-effects and voxel-wise linear regression models, respectively.

* Corresponding authors at: Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation. Wellington 30, 08005, Barcelona, Spain.

E-mail addresses: dlopez@barcelonabeta.org (D. López-Martos), ograu@barcelonabeta.org (O. Grau-Rivera), gsanchezb@barcelonabeta.org (G. Sánchez-Benavides).

¹ The complete list of collaborators of the ALFA study can be found in the acknowledgments section.

<https://doi.org/10.1016/j.tjpad.2026.100612>

Received 10 February 2026; Received in revised form 14 April 2026; Accepted 18 May 2026

Available online 8 June 2026

2274-5807/© 2026 The Author(s). Published by Elsevier Masson SAS on behalf of SERDI Publisher. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Results: 350 CU individuals were included (mean age 61 years; 60% female; mean education 14 years; 35% CSF A β -positive). Amnesic obj-SCD was identified in 10% of the sample, associated with greater AD pathology (higher plasma p-tau217, CSF p-tau181/A β 42, global A β PET, medial temporal tau PET), neurodegeneration (higher plasma and CSF NfL, reduced GMv in cingulate cortex, longitudinal GMv reductions in hippocampus) and inflammation (higher plasma and CSF GFAP, longitudinal GMv increases in neocortical brain regions).

Discussion: These findings highlight the need for standardized clinical staging criteria to enhance early detection and risk stratification in aging and preclinical AD.

1. Background

Alzheimer's disease (AD) encompasses a preclinical stage preceding mild cognitive impairment (MCI) and dementia, defined by underlying neuropathological changes without clinical impairment [1]. In 2011, the National Institute on Aging and the Alzheimer's Association (NIA-AA) defined subtle cognitive decline as a transitional stage between normal cognition and MCI, characterized by low cognitive performance not meeting clinical threshold [2]. The 2018 NIA-AA guidelines [3] and 2024 Alzheimer's Association revised criteria [4] further conceptualized this stage as transitional decline (Stage 2), between the asymptomatic period (Stage 1) and cognitive impairment (Stage 3). Diagnostic guidelines specify that transitional cognitive decline should be documented by subtle, subclinical changes (1–3 years), based on objective neuropsychological testing and/or subjective reports of decline.

The literature suggests that the most clinically relevant manifestation of clinical Stage 2 may be objective episodic memory decline, reflecting a subclinical amnesic syndrome in preclinical AD [5,6]. In contrast, subjective cognitive decline (SCD) may not capture this transitional stage, as it may be reduced or already absent in MCI patients with impaired cognitive awareness (i.e., anosognosia) [7], limiting its predictive value across the preclinical stage of AD, where distinct metacognitive profiles and trajectories, ranging from increased to decreased cognitive awareness, have been identified [8]. Although the Alzheimer's Association [4] and the International Working Group [9] provided relevant conceptual frameworks, practical clinical staging guidelines remain lacking [10,11]. The absence of common standards for defining transitional decline presents a major challenge for early detection and risk stratification.

Clinical research increasingly supports the conceptualization of objectively defined subtle cognitive decline (obj-SCD), reflecting growing interest in this field (see Thomas & Edmonds, 2025, for a systematic review) [12]. These investigations proposed discrete categorizations of obj-SCD consistent with clinical Stage 2, however methodologies varied widely: ranging from single tests to composite scores, distinct cut-offs, cross-sectional *versus* longitudinal designs, and spanning from clinically based to data-driven approaches. Particularly, longitudinal studies are still few and optimal methods for its definition remain uncertain. While prospective studies show that AD pathophysiology tracks cognitive decline in cognitively unimpaired (CU) individuals [13,14], establishing standards for distinguishing normal cognitive trajectories from variability associated with underlying neuropathological progression remains challenging [15].

Robust neuropsychological references that account for longitudinal clinical progression and/or AD biomarkers provide higher thresholds for defining normal cognition [16–19]. Established methods for measuring neuropsychological change, such as the Reliable Change Index (RCI) and Standardized Regression-Based (SRB) models, account for test-retest correlation, practice effects, and sociodemographic adjustments shaping intra-individual normative trajectories [20,21]. Previously, we combined these methods to develop robust AD biomarker-based longitudinal neuropsychological references, demonstrating greater sensitivity in detecting significant cognitive decline, particularly in episodic memory [22]. The integration of robust longitudinal references with multivariate base rate thresholds, identifying significant deviation from

the normative frequency of low performance across multiple neuropsychological measures [23,24], provides a standardized framework for clinical staging of obj-SCD.

Building on this framework, this study aimed to provide a comprehensive multimodal biomarker characterization of amnesic obj-SCD, evaluating associations with core AD biomarkers (A β and tau) and biomarkers of non-specific processes involved in AD pathophysiology (inflammation and neurodegeneration), ranging from fluid (plasma and cerebrospinal fluid [CSF]) to neuroimaging measurements (positron emission tomography [PET] and Magnetic Resonance Imaging [MRI] Grey Matter Volume [GMv]).

2. Methods

2.1. Study participants

This study was conducted within the Alzheimer's and Families+ (ALFA+) cohort, a longitudinal extension of the ALFA parent cohort at the BarcelonaBeta Brain Research Center, Barcelona, Spain [25]. The ALFA cohort recruited CU individuals aged 45–74 years, free from major medical, psychiatric, or neurological conditions. The ALFA+ cohort represents a selected subset of ALFA participants enriched for AD risk factors, including parental history of AD and carriage of the apolipoprotein E (*APOE*) ϵ 4 allele. Eligibility criteria for ALFA+ included prior participation in ALFA and willingness to participate in clinical and neuropsychological assessment, blood and CSF collection, as well as MRI and PET imaging. Participants with cognitive impairment, systemic illnesses, or monogenic AD mutation were excluded. Full details are provided in the Supplementary Material.

In this study, we included CU participants from ALFA+ with available baseline CSF biomarker determination and longitudinal neuropsychological evaluations (two visits over a 3-year follow-up). Individuals with normal CSF biomarker profiles or within the AD *continuum* were retained, whereas individuals with suspected non-AD pathology were excluded, according to the AT(N) classification system (see Multimodal Biomarker Panel and Classification System). Selection criteria were consistent with previous work in the ALFA+ cohort, as previously described [22].

2.2. Standard protocol approvals, registrations, and patient consents

The ALFA+ study (ALFA-FPM-0311) was approved by the Independent Ethics Committee of Parc de Salut Mar, Barcelona, and is registered on ClinicalTrials.gov (NCT02485730). All participants provided written informed consent, as approved by the Ethics Committee. The study was performed in accordance with the principles of the Declaration of Helsinki.

2.3. Biomarker measurements

2.3.1. Plasma and cerebrospinal fluid (CSF)

Participants underwent longitudinal fasting blood and CSF collection [26,27]. Plasma biomarkers included p-tau217, NfL, and GFAP, while CSF biomarkers included A β 42/40, p-tau181, t-tau, p-tau181/A β 42, NfL, and GFAP. All biomarkers except plasma p-tau217 were analyzed at the Clinical Neurochemistry Laboratory, University of Gothenburg,

Sweden. Plasma p-tau217 was measured by Eli Lilly using an in-house Meso Scale Discovery (MSD) assay [28]. CSF A β 42/40, NfL, and GFAP, as well as plasma NfL and GFAP, were quantified with the NeuroToolKit, a panel of prototype electrochemiluminescence Elecsys® immunoassays on fully automated Cobas® e 411 or e 601 modules (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). CSF p-tau181 and t-tau were measured with Elecsys Phospho-Tau (181P) and Total-Tau electrochemiluminescence immunoassays on Cobas e 601 module, and CSF p-tau181/A β 42 with the same Elecsys platform.

2.3.2. Positron emission tomography (PET)

Participants underwent longitudinal A β PET, with a subset also completing tau PET at follow-up. Scans were acquired on a Siemens Biograph mCT scanner with cranial CT for attenuation correction. A β PET (~185 MBq [¹⁸F]flutemetamol) was acquired 90–110 min post-injection, and tau PET (368.75 MBq [¹⁸F]RO948) 70–90 min post-injection (20 min, 4 × 5 min frames for both A β and tau PET). Images were reconstructed using ordered subset expectation maximization with time-of-flight and point spread function modeling (A β : 8 iterations, 21 subsets, 3 mm; tau: 4 iterations, 21 subsets, 4 mm), co-registered to T1-weighted MRI, and spatially normalized to MNI space via DARTEL. Standardized Uptake Value Ratios (SUVRs) were defined using the whole cerebellum as the reference for A β PET and inferior cerebellum for tau PET. Longitudinal A β PET changes were computed voxel-wise. All images were smoothed with an 8-mm FWHM Gaussian kernel. Additionally, A β PET Centiloid units were quantified using validated methods [29].

2.3.3. Magnetic resonance imaging (MRI)

Participants underwent longitudinal MRI scans on a 3T Philips Ingenia CX scanner using T1-weighted 3D-turbo field echo sequences (0.75 mm³ isotropic voxel; FOV 240×240×180 mm³; flip angle 8°; TR 9.9 ms; TE 4.6 ms; TI 900 ms). Grey matter (GM) segmentation was performed using SPM12 and mapped to common space, with a template generated from these segmentations warped to MNI space via DARTEL. Native GM images were modulated by Jacobian determinants to preserve local GM volume (GMv). Longitudinal GMv changes were computed using SPM's pairwise longitudinal registration in native space, and resulting Jacobians were normalized to MNI space using DARTEL. All images were smoothed with an 8-mm FWHM Gaussian kernel. Total intracranial volume (TIV) was computed as the sum of GM, white matter (WM), and CSF volumes.

2.4. Multimodal biomarker panel and classification system

According to previous work in the ALFA+ cohort, the AT(N) classification system was used to define biomarker profiles in consistency with the 2018 NIA-AA research framework [3]. CSF biomarker classification was determined using previously validated cut-offs in the ALFA+ cohort: A β -positivity (A+) was defined by A β 42/40 ratio < 0.071, tau-positivity (T₁+) by p-tau181 > 24 pg/mL, and neurodegeneration-positivity ([N]+) by t-tau > 300 pg/mL [26]. Following 2024 Alzheimer's Association revised criteria [4], this study focused on core AD biomarkers and biomarkers of non-specific processes involved in AD pathophysiology, including plasma, CSF, PET, and MRI biomarker measurements. Full details are provided in the Supplementary Material (Supplementary Tables 1 and 2).

2.5. Neuropsychological measurements

2.5.1. Tests and questionnaires

Free and Cued Selective Reminding Test (FCSRT): The Spanish FCSRT was used to assess episodic memory employing a controlled learning procedure [30]. Participants learned 16 semantically unrelated words paired with cues and completed three recall trials, each preceded by a 20-second subtraction task. Trials included free recall followed by cued

recall for unrecalled items, with selective reminding applied only in the first two trials. Delayed free and cued recall was assessed after 25–35 min. Variables of interest included total free immediate recall (0–48), total immediate recall (0–48), total free delayed recall (0–16), and total delayed recall (0–16).

Memory Binding Test (MBT): The Spanish MBT was used to assess episodic memory employing an associative learning procedure [31]. Participants learned two lists of 16 semantically paired words under controlled conditions, followed by recall of each list by semantic category and free recall of all 32 items. Delayed recall (free and facilitated) was tested after 30 min. Variables of interest included total immediate paired recall (0–32), total immediate free recall (0–32), total delayed paired recall (0–32), and total delayed free recall (0–32).

Wechsler Memory Scale-IV (WMS-IV) Logical Memory (LM) Subtest: The Spanish WMS-IV LM subtest was used to assess narrative episodic memory [32]. Participants immediately recalled two orally presented stories (B and C), recalled them after 20–30 min, and then completed a recognition task. Variables of interest included immediate recall (0–50), delayed recall (0–50), and recognition (0–30).

Clinical Dementia Rating (CDR): The Spanish CDR was used to screen global cognition and daily functioning across six domains, yielding a global score from 0 (no impairment) to 3 (severe dementia) [33].

Mini Mental State Examination (MMSE): The Spanish MMSE was used to screen global cognition, assessing orientation, registration, attention, recall, language, and constructive praxis (0–30) [34].

Subjective Cognitive Decline Questionnaire (SCD-Q): The Spanish SCD-Q was used to assess SCD, completed by both participant and study partner, independently [35]. The questionnaire contains three initial yes/no items and 24 questions on everyday cognitive difficulties. Categorically defined SCD status was determined according to the first item (“Do you perceive memory or cognitive difficulties?” for participants; “Do you perceive he/she has cognitive or memory difficulties?” for study partners). Total scores quantified SCD (0–24).

2.5.2. Clinical staging

Criteria for clinical staging were defined *a priori*. In line with current diagnostic frameworks, the designation of CU refers to the absence of cognitive impairment and does not preclude subtle cognitive decline [4]. Accordingly, obj-SCD is therefore defined within the CU range, capturing a transitional stage not meeting the threshold of MCI.

Amnesic, objective subtle cognitive decline (obj-SCD): Amnesic obj-SCD was defined using a longitudinal, multi-criteria psychometric approach selected to enhance diagnostic sensitivity and specificity, based on robust longitudinal neuropsychological references integrated with multivariate base-rate thresholds of significant cognitive decline. Participants were required to meet the following criteria: significant cognitive decline across multiple episodic memory measures (FCSRT, MBT, and WMS-IV LM variables previously defined), operationalized as AD biomarker-based complex SRB change < -1.645 SD per variable (which corresponds approximately to the 5th percentile under the assumptions of normal distribution). Complex SRB change indices were computed using robust longitudinal neuropsychological references, previously developed and validated in an independent study of the ALFA+ cohort, which were referenced to the A β -negative group (baseline CSF A-T₁-[N]⁻; n = 228) and adjusted for age, sex, and education, with a prespecified cut-off of change ≤ 5th percentile per variable to define statistically significant longitudinal decline [22]. Building on these robust normative framework, a multivariate base-rate threshold was applied to determine the presence of amnesic obj-SCD. To identify significant deviation across the multiple episodic memory variables, previously validated permutation-derived thresholds were used [36], enhancing specificity of classification: participants with ≥10 available variables (range 10 to 11) were required to show decline on ≥3, and those with <10 available variables (range 4 to 9) were required to show decline on ≥2. This framework explicitly accounts for the non-independence among variables and the non-linear relationship

between the expected frequency of low scores and battery length, providing empirically validated thresholds with clinical significance. All participants had complete longitudinal data available for the 4 main measures of the FCSRT; full details on classification criteria, including correlation among the SRB change indices and descriptive information of multivariate base rate thresholds are provided in Supplementary Figure 1 and Supplementary Table 3, respectively.

Amnestic, mild cognitive impairment (MCI): Amnestic MCI was defined using a cross-sectional multi-criteria psychometric approach, applied at both baseline and follow-up, selected to enhance diagnostic specificity while maintaining consistency with standard clinical practice. Participants were required to meet the following criteria: CDR global score > 0; MMSE score < 27, and the conservative application of the neuropsychological criteria for aMCI, operationalized as performance < 1.65 SD below the conventional normative mean on at least 2 of 4 main measures from the FCSRT.

2.6. Statistical analysis

2.6.1. Characteristics of the participants

Baseline characteristics of the full sample of participants were summarized and characteristics of the two groups of interest (stable and amnestic obj-SCD) were compared using univariate ANOVAs for continuous variables and Chi-square tests for categorical variables. Nominal *p*-values < 0.05 were considered statistically significant.

2.6.2. Robust normative longitudinal neuropsychological change

Neuropsychological variables used for clinical staging were summarized descriptively and compared between groups (stable and amnestic obj-SCD) using *t*-tests, with effect sizes quantified by Cohen's *d*. Further details on cognitive outcomes across domains are presented in Supplementary Table 4. All statistical analyses were conducted in R (version 4.2.1) within RStudio (version 2022.07.1). Nominal *p*-values < 0.05 were considered statistically significant.

2.6.3. Fluid biomarkers

Associations of amnestic obj-SCD with plasma and CSF biomarkers were evaluated using linear mixed-effects (LME) regression models

(lme4; R 4.2.1, RStudio 2022.07.1). Log10-transformed biomarkers were modeled as outcomes in separate models, with group (0: Stable, 1: Amnestic obj-SCD) as the main predictor, adjusting for age, sex, *APOE-ε4*, and time. Models included two time points, a group × time interaction, and a participant-level random intercept. Time visit was coded categorically, with age modeled as time-varying to account for exact follow-up intervals. Results are reported as standardized β coefficients with 95% confidence intervals, *p*-values, marginal and conditional R², and AIC. Nominal *p*-values < 0.05 were considered significant. Full details are provided in Supplementary Table 5.

2.6.4. Neuroimaging biomarkers

Associations of amnestic obj-SCD with PET and GMv biomarkers were assessed using voxel-wise fixed-effects regression models (SPM12; MATLAB 2022b). Neuroimaging data were modeled as outcomes in separate models, with group (0: Stable, 1: Amnestic obj-SCD) as the main predictor, adjusting for age, sex, *APOE-ε4*, TIV (GMv only), and follow-up interval in years (longitudinal models only). Models applied an explicit GM mask, further excluding the cerebellum. Results are reported at cluster and peak levels, including cluster size (*k*), *p*-values and *T*-values, peak MNI coordinates (*x*, *y*, *z*), and anatomical labels. Nominal *p*-values < 0.005 with cluster extent > 100 voxels were considered significant. Full details are provided in Supplementary Table 6.

2.6.5. Exploratory analysis

Exploratory analyses, restricted to the subset of participants with amnestic obj-SCD, evaluated associations of log10-transformed fluid biomarkers with observed longitudinal changes in GMv using fixed-effects linear regression models (RStudio). Longitudinal GMv changes were extracted at the cluster level from ROIs defined *post-hoc* by previous group-level contrasts (MarsBaR 0.45; MATLAB 2022b). Mean GMv change values normalized for TIV, were modeled as outcomes, adjusting for age, sex, and follow-up interval in years. Results are reported in line with previous models. Nominal *p*-values < 0.05 were considered significant. Full details are provided in Supplementary Table 7.

Table 1

Baseline characteristics of the participants.

Characteristics	Full Sample, n = 350 (100%)	Stable, n = 315 (90%)	Amnestic obj-SCD, n = 35 (10%)	<i>p</i> -value
<i>Demographic</i>				
Age, mean (SD)	60.93 (4.72)	60.59 (4.62)	63.94 (4.61)	< 0.001
Female sex, n (%)	211 (60.29)	191 (60.63)	20 (57.14)	0.827
Education (years), mean (SD)	13.53 (3.48)	13.59 (3.46)	12.91 (3.66)	0.274
<i>Genetic</i>				
<i>APOE-ε4</i> carriers, n (%)	191 (54.57)	169 (53.65)	22 (62.86)	0.390
<i>Biomarkers</i>				
Aβ-positive status, n (%)	122 (34.86)	101 (32.06)	21 (60)	0.002
Plasma p-tau217 (pg/ml), mean (SD)	0.153 (0.090)	0.149 (0.087)	0.191 (0.107)	0.009
CSF p-tau181/Aβ42 (hybrid ratio), mean (SD)	0.014 (0.011)	0.013 (0.082)	0.024 (0.022)	< 0.001
Aβ PET (Centiloids), mean (SD)	3.52 (17.25)	1.77 (14.77)	18.93 (27.44)	< 0.001
<i>Neuropsychology</i>				
MMSE, mean (SD)	29.18 (0.92)	29.21 (0.90)	28.89 (1.05)	0.048
SCD Participant, positive status, n (%)	98 (28)	83 (26.35)	15 (42.86)	0.062
SCD-Q Participant, total, mean (SD)	4.11 (4.38)	3.88 (4.25)	6.18 (5.08)	0.004
SCD Study Partner, positive status, n (%)	16 (4.57)	12 (3.81)	4 (11.43)	0.064
SCD-Q Study Partner, total, mean (SD)	1.53 (2.47)	1.40 (2.33)	2.71 (3.26)	0.003

Results presented correspond to the mean and standard deviation (SD) for continuous variables and number of observations (*n*) and percentage (%) for categorical variables. Comparisons between stable and amnestic obj-SCD groups were performed using ANOVA, chi-square (χ^2), or Fisher's Exact Test, depending on the type of variable and distribution of the data, with corresponding nominal *p*-values reported. Amnestic obj-SCD was defined using robust longitudinal neuropsychological references with a multivariate base rate threshold of significant cognitive decline. Episodic memory was evaluated with standardized neuropsychological tests (Free and Cued Selective Reminding Test; Memory Binding Test; WMS-IV: Logical Memory Subtest). The previously validated biomarker cut-off used to define A-positive status in the ALFA+ cohort was < 0.071 for the CSF A42/40 ratio. Bold text indicates a significant association (*p*-values < 0.05). A: amyloid; *APOE*: apolipoprotein E; CSF: cerebrospinal fluid; MMSE: mini-mental state examination; PET: positron emission tomography; p-tau: phosphorylated tau; SCD: subjective cognitive decline; SCD-Q: subjective cognitive decline questionnaire.

3. Results

3.1. Characteristics of the participants

A total of 350 CU participants were included in the present study, with a mean longitudinal time interval of 3.30 years (standard deviation = 0.52). According to the clinical staging criteria, 315 individuals (90%) were classified as stable, and 35 (10%) as exhibiting amnestic obj-SCD, with no participant fulfilling criteria for amnestic MCI. Baseline characteristics of the participants are presented in Table 1. Significant baseline differences were found between stable and amnestic obj-SCD groups. The group exhibiting amnestic obj-SCD was slightly older (p -value < 0.001), demonstrated a greater prevalence of A β positivity (p -value = 0.002), higher plasma p-tau217 concentration (p -value = 0.009), higher CSF p-tau181/A β 42 ratio (p -value < 0.001), higher A β PET load (p -value < 0.001), lower performance on MMSE (p -value = 0.048), and greater SCD-Q scores considering both self-reported (p -value = 0.004) and study-partner reports (p -value = 0.003), independently. No significant baseline differences were found for sex, education, APOE- ϵ 4 status, and categorically defined SCD status considering both self-reported and study-partner reports, independently. Within the subset of amnestic obj-SCD, categorically defined self-reported SCD was present in 15 out of 35 individuals (43%) at baseline, increasing to 20 out of 35 individuals (57%) at follow-up.

3.2. Robust normative longitudinal neuropsychological change

Results of AD biomarker-based robust complex SRB change indices used for clinical staging are presented in Table 2. The correlation structure among the SRB change indices confirmed moderate-to-strong within-test correlations and low-to-moderate across-test correlations; indicating that the three tests capture partially distinct aspects of episodic memory while individual variables within each test reflect slightly different components, supporting the application of the multivariate classification framework (Supplementary Figure 1). Across the full sample, the prevalence of significant decline per variable (SRB change \leq -1.645 SD [\sim 5th percentile]) ranged from approximately 5% to 9% across FCSRT, MBT, and WMS measures. The highest prevalence rates were observed for FCSRT Total Immediate Recall (8.57%), FCSRT Total Delayed Recall (8.0%), FCSRT Total Free Delayed Recall (7.71%), MBT Total Delayed Paired Recall (7.42%), and WMS Total Recognition (7.14%). Overall, SRB change indices, expressed as demographically

adjusted z-scores referenced to the A β -negative sample, ranged from approximately -0.12 to -0.04 at the full-sample level, indicating minimal average longitudinal cognitive change across the cohort. Within the stable group, SRB change indices were generally positive and centered near zero, reflecting relative cognitive stability over the study period, with most measures showing minimal improvement. In contrast, SRB change indices in the amnestic obj-SCD group were consistently negative across all measures, generally below -1 SRB change index, with mean values ranging from approximately -0.91 to -1.52, reflecting longitudinal decline. Participants classified as amnestic obj-SCD exhibited significantly lower SRB change indices than the stable group across all episodic memory measures examined (all p -values < 0.001). The most pronounced negative mean values were observed for FCSRT Total Delayed Recall (-1.52), MBT Total Delayed Paired Recall (-1.45), and MBT Total Immediate Paired Recall (-1.40). The largest group differences were observed for MBT Total Delayed Paired Recall (Cohen's d = 1.455), MBT Total Immediate Paired Recall (Cohen's d = 1.440), and MBT Total Immediate Free Recall (Cohen's d = 1.437), followed by FCSRT Total Delayed Recall (Cohen's d = 1.431) and FCSRT Total Free Delayed Recall (Cohen's d = 1.330).

3.3. Associations of amnestic obj-SCD with fluid biomarkers

Associations of amnestic obj-SCD with fluid biomarkers are presented in Fig. 1. Considering core AD biomarkers, amnestic obj-SCD was associated with higher plasma p-tau217 concentration ($\beta_{STD}[95\%CI]$ = 0.409 [0.123, 0.686]) and higher CSF p-tau181/A β 42 ratio ($\beta_{STD}[95\%CI]$ = 0.637 [0.322, 0.953]), including greater longitudinal increase of CSF p-tau181/A β 42 ratio over time ($\beta_{STD}[95\%CI]$ = 0.219 [0.053, 0.384]), compared to the stable group. Considering biomarkers of non-specific processes involved in AD pathophysiology, amnestic obj-SCD was associated with higher plasma p-tau217 concentration ($\beta_{STD}[95\%CI]$ = 0.400 [0.076, 0.723]), higher CSF NfL concentration ($\beta_{STD}[95\%CI]$ = 0.348 [0.058, 0.638]), higher plasma GFAP concentration ($\beta_{STD}[95\%CI]$ = 0.564 [0.262, 0.865]), and higher CSF GFAP concentration ($\beta_{STD}[95\%CI]$ = 0.324 [0.0027, 0.621]), compared to the stable group.

3.4. Associations of amnestic obj-SCD with neuroimaging biomarkers

Associations of amnestic obj-SCD with neuroimaging biomarkers are presented in Figs. 2 and 3. Considering core AD biomarkers, amnestic obj-SCD was associated with higher global A β PET load at baseline,

Table 2

AD Biomarker-based robust complex SRB change indices for the episodic memory battery.

Variables	Full Sample (N = 350)			Stable (N = 315)	Amnestic obj-SCD (N = 35)	Group Comparison		
	n	SRB \leq 5th percentile, n (%)	SRB, mean (SD)	SRB, mean (SD)	SRB, mean (SD)	t-statistic	p-value	Cohen's d
FCSRT: Total Free Immediate Recall	350	19 (5.43)	-0.064 (1.046)	0.048 (0.945)	-1.069 (1.354)	4.752	< 0.001	1.125
FCSRT: Total Immediate Recall	350	30 (8.57)	-0.088 (1.132)	0.045 (0.869)	-1.282 (2.134)	3.647	< 0.001	1.251
FCSRT: Total Free Delayed Recall	350	27 (7.71)	-0.108 (1.09)	0.027 (0.974)	-1.32 (1.319)	5.868	< 0.001	1.33
FCSRT: Total Delayed Recall	350	28 (8)	-0.09 (1.205)	0.068 (0.93)	-1.517 (2.142)	4.335	< 0.001	1.431
MBT: Total Immediate Paired Recall	337	22 (6.53)	-0.049 (1.134)	0.103 (0.956)	-1.397 (1.624)	5.28	< 0.001	1.44
MBT: Total Immediate Free Recall	336	21 (6.25)	-0.048 (1.074)	0.092 (0.967)	-1.328 (1.172)	6.716	< 0.001	1.437
MBT: Total Delayed Paired Recall	337	25 (7.42)	-0.038 (1.178)	0.12 (0.966)	-1.451 (1.819)	4.958	< 0.001	1.455
MBT: Total Delayed Free Recall	334	23 (6.89)	-0.095 (1.113)	0.035 (1.005)	-1.323 (1.334)	5.589	< 0.001	1.305
WMS: Total Immediate Recall	335	22 (6.57)	-0.105 (1.029)	0.014 (0.913)	-1.167 (1.358)	4.949	< 0.001	1.223
WMS: Total Delayed Recall	336	18 (5.36)	-0.122 (1.074)	-0.009 (0.946)	-1.13 (1.543)	4.147	< 0.001	1.098
WMS: Total Recognition	336	24 (7.14)	-0.098 (1.031)	-0.006 (0.949)	-0.911 (1.348)	3.808	< 0.001	0.908

The table presents robust complex SRB change indices for the episodic memory battery. Development of these indices has been previously described (see López-Martos, D., et al., 2025). Robust longitudinal complex SRB indices reflect intra-individual cognitive change adjusted for demographics and referenced to the A β -negative sample (z-scores). For each variable, the table reports the number of observations (n), the number and percentage (%) of individuals below the 5th percentile (< -1.645 SRB), and the mean (SD) values for the full sample. Results are also stratified by group (stable, Amnestic obj-SCD), with mean (SD), t-statistic, p-value, and Cohen's d for group comparisons. Bold text indicates significant results (p-values < 0.05). A β : β -amyloid; FCSRT: Free and Cued Selective Reminding Test; MBT: Memory Binding Test; SD: standard deviation; SRB: standardized regression-based; WMS: Wechsler Memory Scale.

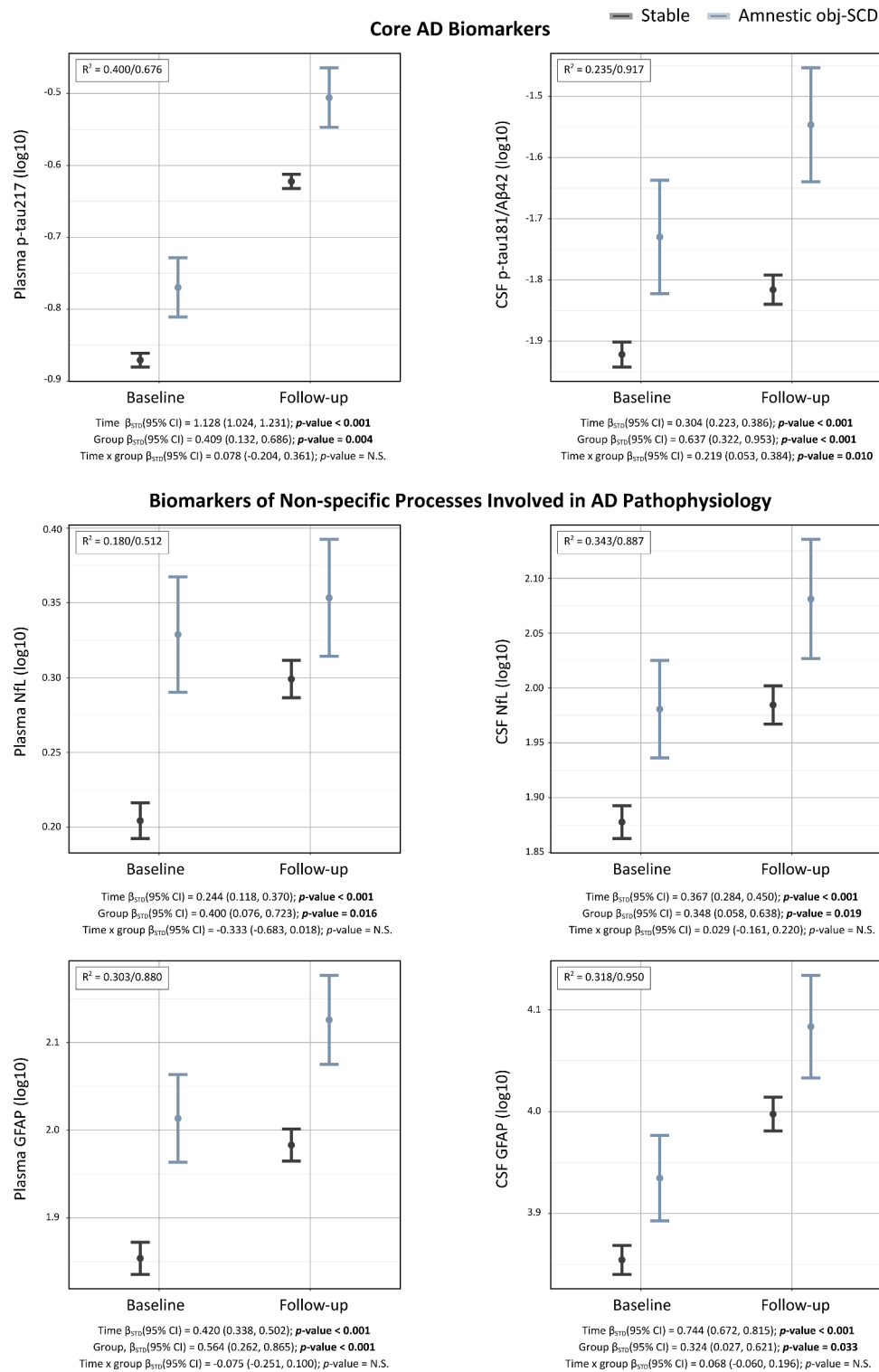


Fig. 1. Associations of amnesic obj-SCD with fluid biomarkers. Results from LME regression models show the main effect of group, time, and group \times time interaction on longitudinal plasma and CSF biomarker outcomes, including core AD markers and biomarkers of non-specific processes involved in AD pathophysiology. Data points represent predicted group means with 95% confidence intervals (CI). Model statistics include standardized β coefficients (STD β) with 95% CI, nominal p -values, and marginal/conditional R^2 . A β : β -amyloid; AD: Alzheimer's disease; CSF: cerebrospinal fluid; GFAP: glial fibrillary acidic protein; NfL: neurofilament light chain; p-tau: phosphorylated tau.

predominantly in frontoparietal regions, compared to the stable group. Longitudinally, amnesic obj-SCD showed further increases in A β PET load, following a similar but more localized pattern of accumulation, most prominently in the precuneus, compared to the stable group. Amnesic obj-SCD was also associated with higher tau PET load,

particularly in bilateral regions of the medial temporal lobe (MTL), compared to the stable group. Considering biomarkers of non-specific processes involved in AD pathophysiology, amnesic obj-SCD was associated with baseline reduced GMv, primarily in the middle cingulate cortex, with additional localized involvement of middle temporal,

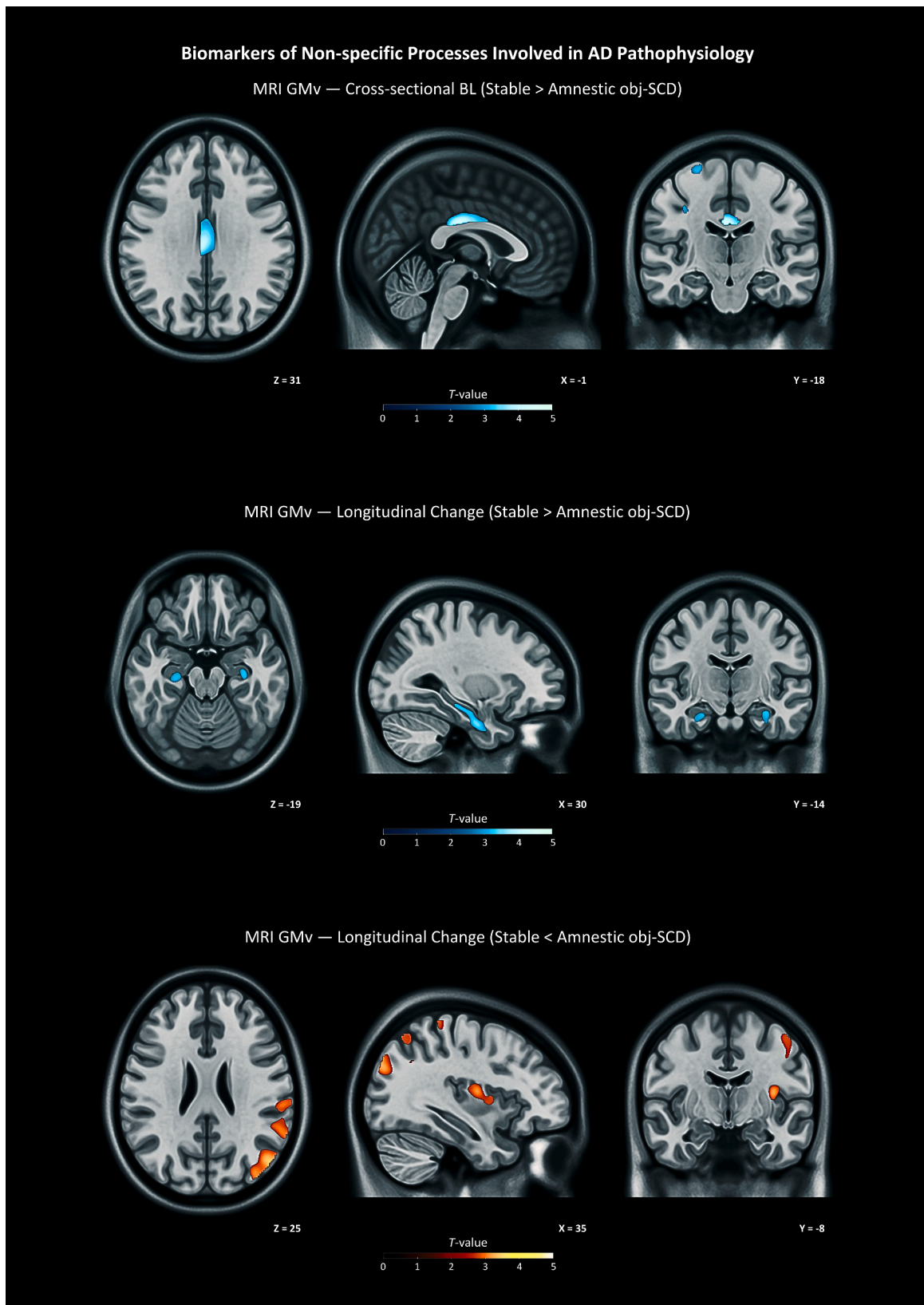
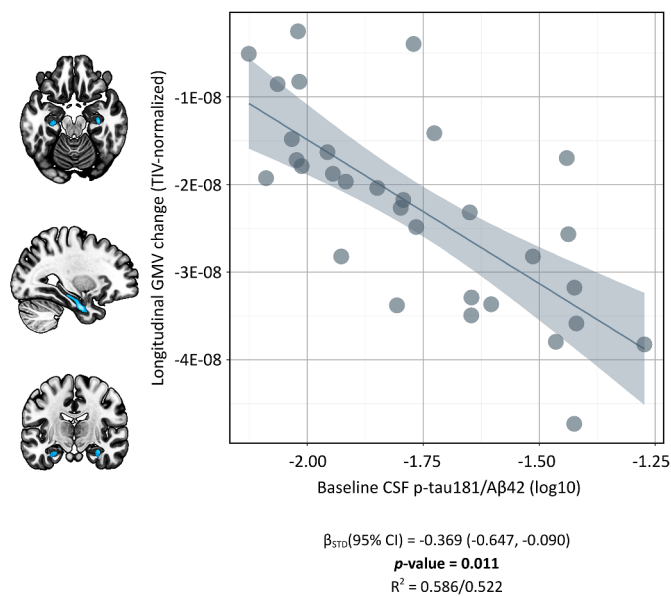


Fig. 3. Associations of amnestic obj-SCD with neuroimaging biomarkers: Non-specific processes involved in AD Pathophysiology. Results from voxel-wise regression models show the main effect of group on MRI GMv biomarker outcomes. The figure displays brain sections following anatomical convention, where the left side of the image corresponds to the left hemisphere of the brain. Color bars indicate T-values, with results shown at nominal p -values < 0.005 accounting for a cluster-size threshold of $k > 100$ voxels. AD: Alzheimer's disease; BL: Baseline; GMv: gray matter volume; MRI: magnetic resonance imaging.

A) ROIs showing longitudinal GMv reductions



B) ROIs showing longitudinal GMv increases

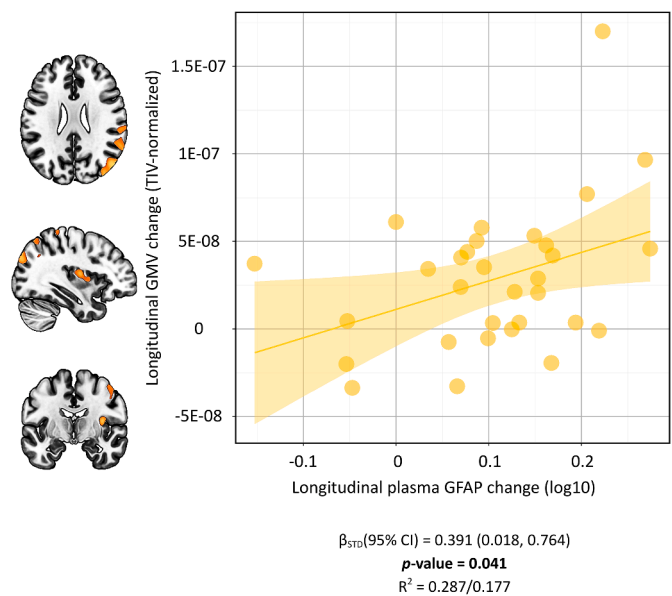


Fig. 4. Associations of fluid biomarkers with longitudinal GMv changes in amnesic obj-SCD. Results from linear regression models showing the associations between fluid biomarkers and longitudinal GMv changes within amnesic obj-SCD group, with shaded areas representing 95% confidence intervals (CI) of the predicted regression lines. Model statistics include standardized β coefficients (STD β) with 95% CI, nominal p -values, and nominal/adjusted R^2 . Models were adjusted for age, sex, and longitudinal time interval measured in years. Panel A) shows the negative association between baseline CSF p-tau181/A β 42 hybrid ratio and longitudinal GMv change in ROIs showing reductions (*i.e.*, bilateral hippocampus). Panel B) shows the positive association between longitudinal change in plasma GFAP concentration and longitudinal GMv change in ROIs showing increments (*i.e.*, neocortical regions). Mean longitudinal GMv changes by ROIs were normalized for TIV. A β : β -amyloid; CSF: cerebrospinal fluid; GFAP: glial fibrillary acidic protein; GMv: gray matter volume; p-tau: phosphorylated tau; ROIs: regions of interest; TIV: total intracranial volume.

precentral, and postcentral regions, compared to the stable group. Longitudinally, amnesic obj-SCD was associated with GMv bilateral reductions in the hippocampus, alongside GMv increases in neocortical regions, primarily involving right-lateralized parietal and occipital cortex, with additional, localized involvement of frontal and insular areas, compared to the stable group.

3.5. Exploratory analysis

The exploratory analysis was restricted to individuals exhibiting amnesic obj-SCD, associations of fluid biomarkers with longitudinal GMv change in ROIs are presented in Fig. 4 and Supplementary Table 7. ROIs were defined based on *post-hoc*, previous group-level contrasts, including ROIs showing longitudinal GMv reductions (*i.e.*, bilateral hippocampus) and ROIs showing longitudinal GMv increases (*i.e.*, neocortical regions). Within amnesic obj-SCD, higher baseline CSF p-tau181/A β 42 ratio was associated with steeper longitudinal GMv reductions in bilateral hippocampus ROIs ($\beta_{STD}[95\%CI] = -0.369 [-0.647, -0.090]$). In contrast, lower baseline plasma GFAP concentration ($\beta_{STD}[95\%CI] = -0.401 [-0.781, -0.022]$) and greater longitudinal increase in plasma GFAP concentration ($\beta_{STD}[95\%CI] = 0.391 [-0.018, 0.764]$) were both associated with steeper longitudinal GMv increments in neocortical ROIs.

4. Discussion

This study provided a comprehensive multimodal biomarker characterization of amnesic obj-SCD in aging and preclinical AD. The presence of amnesic obj-SCD was defined through robust AD biomarker-based longitudinal neuropsychological references combined with multivariate base rate thresholds of significant cognitive decline. According to the defined criteria, 10% of the present sample exhibited

amnesic obj-SCD over the 3-year follow-up. Multimodal biomarker characterization showed consistent significant associations of amnesic obj-SCD with core AD biomarkers, including diagnostic core 1 AD biomarkers (higher plasma p-tau217 concentration, higher CSF p-tau181/A β 42 ratio, and higher global A β PET burden) and prognostic core 2 AD biomarkers (higher MTL tau PET burden). Additionally, amnesic obj-SCD was significantly associated with biomarkers of non-specific processes involved in AD pathophysiology, including neurodegeneration (higher plasma and CSF NfL concentrations, reduced GMv in the middle cingulate cortex, and longitudinal bilateral GMv reductions in the hippocampus) as well as inflammation (higher plasma and CSF GFAP concentrations, as well as longitudinal GMv increases in neocortical regions). Together, these findings support obj-SCD as a transitional stage preceding MCI in the AD continuum [12], characterized by early AD-related neuropathological changes and downstream mechanisms involved in AD pathophysiology [37,38], aligning with the integrated clinical-biological staging proposed by 2024 Alzheimer's Association revised criteria [4]. This study highlights the need to strengthen current frameworks through the development of objective, standardized criteria for clinical staging, supporting early detection and risk stratification in aging and preclinical AD [2].

Amnesic obj-SCD was defined using clinically grounded methods, selected to balance sensitivity and specificity for clinical staging classification. Neuropsychological assessment incorporated comprehensive, standardized, and challenging episodic memory tests, encompassing the main variables from the FCSRT, MBT, and WMS-IV LM. Robust neuropsychological references based on AD biomarkers, which reflect deviation relative to the group with nonpathological biomarker levels, enhanced sensitivity for detecting subtle cognitive decline in preclinical AD [22,39]. Neuropsychological assessment depends on the normative references applied, with growing evidence indicating that robust normative frameworks provide higher diagnostic standards than

conventional references [17,18]. The use of demographically adjusted complex SRB longitudinal change indices, reflecting deviation from normative intra-individual cognitive variability over time, allowed to apply a cut-off consistent with clinical practice to define statistically significant longitudinal decline at the variable level (*i.e.*, SRB change \leq 5th percentile). Neuropsychological methods tracking change relative to an individual's baseline are essential, as cross-sectional assessments may be insufficient for detecting significant cognitive decline, particularly in the absence of clinical impairment. Within this framework, SRB models have been proposed as a sensitive approach for defining obj-SCD [40], and have been previously validated in both MCI and dementia stages [41]. Finally, to distinguish transitional cognitive decline from normal aging, more advanced methods than those typically used for MCI diagnosis are required. Because diagnostic accuracy and stability are influenced by the number of impaired measures being considered and specific cut-offs used [42], multivariate base rate thresholds of significant decline were employed to enhance specificity in amnesic obj-SCD determination, controlling false-positive classifications [24].

Considering core AD biomarkers, amnesic obj-SCD was associated with fluid and neuroimaging modalities. Among fluid biomarkers, amnesic obj-SCD was significantly associated with higher plasma p-tau217 concentration and CSF p-tau181/A β 42 ratio. Beyond the significant main group effect, both biomarker levels showed significant longitudinal increases across the full sample, with plasma p-tau217 exhibiting the greatest rise. However, only CSF p-tau181/A β 42 demonstrated a significant group \times time interaction, indicating greater longitudinal increase in amnesic obj-SCD. While the pronounced elevation in plasma p-tau217 indicated widespread early AD-related changes across the full sample, in consistency with its established sensitivity to underlying A β pathology in CU individuals as demonstrated in large population-based cohorts [43,44], the longitudinal increase in the CSF p-tau181/A β 42 ratio showed a closer correspondence with the memory decline characteristic of amnesic obj-SCD. This pattern is consistent with evidence indicating that plasma p-tau217 is well suited for scalable detection of early AD pathology, whereas CSF provides greater specificity, a relevant aspect for integrated clinical-biological staging [44]. These results align with previous studies linking core AD biomarkers to cognitive decline in CU population [45]. Neuroimaging biomarkers further showed significant associations of amnesic obj-SCD with A β and tau PET. Baseline A β PET load was significantly higher in amnesic obj-SCD, with a greater global burden; reflecting prominent frontoparietal deposition. Longitudinally, amnesic obj-SCD showed significant increases in A β PET load, most notably in the precuneus. Tau PET, acquired at follow-up, was also significantly higher in amnesic obj-SCD, with greater burden in bilateral MTL regions. Together, these results were consistent with AD biomarker staging [4], implicating regions affected across early-to-intermediate A β progression [46] and early MTL-restricted tau accumulation characteristic of transitional decline, prior to widespread neocortical involvement and overt clinical impairment [37,38]. Together, these findings align with the established predictive value of multimodal core AD biomarkers for cognitive decline and support their role in refining early clinical-biological staging [45], including characterization of clinical Stage 2, as reflected by amnesic obj-SCD.

Considering biomarkers of non-specific processes involved in AD pathophysiology, amnesic obj-SCD was associated with fluid and neuroimaging modalities, including neurodegeneration and inflammation. Among fluid biomarkers, amnesic obj-SCD was associated with higher neurodegeneration measured by plasma and CSF NFL concentrations, as well as higher inflammation measured by plasma and CSF GFAP concentrations. These results align with previous research linking neurodegenerative and inflammatory mechanisms with cognitive decline in CU population [47,48]. Beyond the significant group effect, all these biomarker levels showed longitudinal increases across the full sample, with plasma GFAP exhibiting the greatest rise; however, there were no significant group \times time interactions. This pattern suggests that

neurodegenerative and inflammatory processes are active early across aging and preclinical AD, but their longitudinal changes, as measured in fluid, were not specific to amnesic obj-SCD. In contrast, longitudinal increases in CSF p-tau181/A β 42 ratio were directly associated with amnesic obj-SCD, highlighting a closer link between changes in core AD biomarkers and clinical Stage 2. Neuroimaging biomarkers showed key differences in GMv. At baseline, amnesic obj-SCD was associated with reduced GMv, primarily in the middle cingulate cortex, with additional localized involvement of middle temporal, precentral, and postcentral regions. While GMv reduction in the middle cingulate cortex has not been previously reported in preclinical AD, these results suggest that such regional vulnerability may emerge earlier than widely recognized. Longitudinally, amnesic obj-SCD showed bilateral GMv reductions in the hippocampus alongside GMv increases in neocortical regions. These findings align with the early vulnerability of this MTL structure in AD, supporting the objective characterization of a subclinical amnesic syndrome [49]. The observed longitudinal GMv increases in neocortex, although not well established in current frameworks, align with studies describing non-linear or biphasic structural dynamics across the pre-clinical stage of AD [50–52]. The primary interpretation proposed in the literature involves cellular hypertrophy or neuroinflammatory responses driven by A β accumulation, preceding later neurodegenerative processes [53]; this interpretation has been discussed in the context of neuropathological evidence in CU individuals [51] and *in vivo* PET imaging of astrocytic and microglial reactivity across the AD continuum [50]. Alternative explanations, including the space-occupying effect of A β plaques and preexisting structural differences, have been proposed as possible contributing factors to observed increases in GMv or cortical thickness in preclinical AD, though their relative contributions remain uncertain.

Exploratory analyses examined potential mechanisms underlying the observed longitudinal GMv changes associated with amnesic obj-SCD, providing support for the primary interpretation of neurodegenerative and neuroinflammatory responses to AD pathology. Results revealed a direct pattern of associations: the CSF p-tau181/A β 42 hybrid ratio was associated with longitudinal GMv reductions in the bilateral hippocampus, whereas plasma GFAP concentration was associated with longitudinal GMv increases in neocortical regions. These findings suggest: (i) core AD pathology contributes to the neurodegenerative mechanisms underlying the subclinical amnesic syndrome characterized by obj-SCD, consistent with evidence linking episodic memory decline to AD-related hippocampal atrophy [54], (ii) longitudinal GMv neocortical increases associated with astrocytic reactivity could reflect transient morphological changes arising as an early neuroinflammatory response to AD pathology [53]. These patterns of regional associations support the hypothesis that biphasic structural dynamics operate heterogeneously across brain regions driven by the progression of AD pathology [52], whereby A β initially accumulates in frontoparietal brain regions while medial temporal structures preferentially demonstrate subsequent tau deposition and the neurodegenerative consequences of advancing disease progression; hallmark AD pathological features associated with amnesic obj-SCD in this sample. Therefore, the present exploratory analyses indicate that the observed regional associations may arise from these particular pathological processes: specifically, plasma GFAP-related cortical GMv increases could be interpreted as a neuroinflammatory response to early A β deposition in neocortex and CSF p-tau181/A β 42-related hippocampal GMv reductions as downstream neurodegenerative mechanisms localized to medial temporal regions exhibiting heightened vulnerability to AD pathology. Together, these exploratory findings support that the multimodal, fluid and neuroimaging biomarker signature of amnesic obj-SCD reflects the convergence of these regionally heterogeneous pathological processes, integrating core AD pathology with associated inflammatory and neurodegenerative mechanisms characteristic of AD. Nevertheless, given the observational and exploratory nature of these analyses, these interpretations remain preliminary and require further prospective and

more comprehensive research aimed at clarifying the mechanisms linking pathological processes to structural brain dynamics, particularly in the context of subclinical manifestations emerging across aging and preclinical AD.

Several aspects require further development before these criteria can be translated into clinical practice, and the following limitations are particularly relevant in this regard. While the present findings advance the characterization of amnesic obj-SCD, further validation across independent cohorts is required. Amnesic obj-SCD was identified in 10% of the sample. This prevalence is consistent with the stringent clinical staging criteria defined; considering longitudinal decline < 5th percentile across multiple measures integrated with multivariate base rate thresholds, which by design target the lower tails of neuropsychological distributions [22]. Adjusting normative neuropsychological references to the biomarker-negative sample inherently increases the likelihood that individuals with AD pathology are classified as obj-SCD. These normative references were previously validated by comparing robust and conventional procedures; while robust norms identified a modestly higher proportion of individuals below the decline threshold, both frameworks showed comparable associations with AD pathology (similar in direction, magnitude, and significance), indicating that robust biomarker-based norms improved case detection sensitivity without introducing systematic bias or materially inflating associations [22]. Although this robust normative approach showed internal consistency, the prognostic value of the proposed criteria must be determined through longer follow-up; specifically, examination against longitudinal clinical progression to MCI and dementia remains essential. Together, the key strength of biomarker-based normative frameworks lies in their improved detection sensitivity, while their main limitation remains the need for external validation to establish broader applicability; anchoring normative references to plasma biomarkers will align with blood-based screening pipelines emerging in current prevention trials, potentially supporting scalable deployment without the cost and burden of PET or CSF procedures [55,56]. Clinically, operationalization of obj-SCD may support earlier detection and risk stratification but this requires further examination before routine implementation; future work should also explore more pragmatic shorter-term assessments within the 1–3 years window to enable wider research and clinical use [12]. Finally, the ALFA+ cohort consists of middle-aged CU volunteers from Barcelona, which were recruited based on AD dementia risk profile, primarily genetics (*APOE-ε4* carriership) and family history, and is characterized by high education levels and marked ethnic homogeneity. These characteristics constrain the generalizability of these findings to broader clinical populations and more demographically heterogeneous cohorts. While the biological mechanisms underlying the biomarker signatures identified here are unlikely to be unique to this sample, replication in population-based and demographically diverse cohorts would help establish the extent to which these findings generalize across varying levels of AD risk, educational background, and ethnic diversity.

The conceptualization of obj-SCD also requires detailed consideration and further examination [12]. The operational definition of MCI, which delineates the boundary of obj-SCD, directly influences prevalence estimates and prognostic interpretation. Imposing discrete diagnostic labels on a continuous disease process inevitably introduces a degree of artificial categorization, a recognized limitation of syndromic staging systems that is nonetheless necessary for operationalizing clinical assessment and establishing research classification frameworks. Prevalence of obj-SCD across other domains (e.g., dysexecutive, linguistic, mixed variants) should be addressed in future studies; which is particularly relevant considering that cognitive phenotyping distinguishing MCI subtypes has shown key differences considering the diagnostic performance of plasma AD biomarkers [57]. Crucially, diagnostic criteria and clinical staging should address the relationship between objective and subjective decline to ensure conceptual alignment with the natural course of AD [58]. In this study, individuals exhibiting amnesic obj-SCD demonstrated substantial heterogeneity in

cognitive awareness (>40% did not report SCD at follow-up), suggesting the emergence of subtle amnesic anosognosia [59]. This finding underscores a key limitation of self-reported SCD for defining Stage 2, a critical yet often neglected clinical aspect. Previous studies suggested that self-reports of SCD contribute to MCI misdiagnosis [60], while decreased cognitive awareness and anosognosia track clinical progression across the AD *continuum* [61,62]. Finally, the present study defined amnesic obj-SCD without requiring positivity for a core 1 AD biomarker, with only 60% of cases CSF Aβ-positive at baseline. Subtle cognitive decline can arise from subthreshold AD pathological processes and/or other mechanisms across aging and preclinical AD [39]. Although diagnostic guidelines emphasize clinical staging based on biologically confirmed AD, the 2024 revised criteria acknowledged substantial individual variability, recognizing that not all individuals follow the canonical temporal sequence of biological and clinical events in AD. This highlights the need for further research on vulnerability and resilience mechanisms, as well as the role of comorbid pathologies in AD [4].

5. Conclusion

In conclusion, this study provided a multimodal biomarker characterization of amnesic obj-SCD, defined using robust longitudinal neuropsychological references with multivariate base-rate thresholds of significant cognitive decline. The observed biomarker profile supports obj-SCD as a transitional stage preceding MCI in the AD *continuum*, associated with early AD-related neuropathological changes and downstream mechanisms involved in AD pathophysiology, aligning with the integrated clinical-biological staging proposed by the 2024 Alzheimer's Association revised criteria. These findings underscore the need to develop objective, standardized clinical staging criteria, supporting early detection and risk stratification in aging and preclinical AD.

Data availability

The data that support the findings of this study are available from the corresponding authors, D.L.-M., O.G.-R. or G.S.-B., on reasonable requests.

Funding

The research leading to these results has received funding from “la Caixa” Foundation under agreement LCF/PR/SC22/68000001, the Alzheimer's Association, and an international anonymous charity foundation through the TriBEKa Imaging Platform project (TriBEKa-17-519007). R.C. received funding from the MCIN/AEI/10.13039/501100011033/FEDER, EU, through the project PID2021-125433OA-I00 and from the grant RYC2021-031128-I, funded by MCIN/AEI/10.13039/501100011033 and the European Union NextGenerationEU/PRTR; M.S.-C. received funding from the ERC under the EU's Horizon 2020 research and innovation program (grant no. 948677), ERA PerMed-ERA NET and the Generalitat de Catalunya (Departament de Salut) through project no. SLD077/21/000001, projects PI19/00155 and PI22/00456, funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the EU (FEDER), and from a fellowship from ‘la Caixa’ Foundation (ID 100010434) and the EU's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie (grant no. 847648 (LCF/BQ/PR21/11840004)); A.B.-S. received funding from the Alzheimer's Association Clinician Scientist Fellowship (AACSF) Program, through the grant AACSF-23-1145154; H.Z. is a Wallenberg Scholar and a Distinguished Professor at the Swedish Research Council supported by grants from the Swedish Research Council (#2023-00356, #2022-01018 and #2019-02397), the European Union's Horizon Europe research and innovation programme under grant agreement No 101053962, Swedish State Support for Clinical Research (#ALFGBG-

71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, #ADSF-21-831377-C, and #ADSF-24-1284328-C), the European Partnership on Metrology, co-financed from the European Union's Horizon Europe Research and Innovation Programme and by the Participating States (NEuroBioStand, #22HLT07), the Bluefield Project, Cure Alzheimer's Fund, the Olav Thon Foundation, the Erling-Persson Family Foundation, Familjen Rönströms Stiftelse, Familjen Beiglers Stiftelse, Stiftelsen för Gamla Tjänarinnor, Hjärfonden, Sweden (#FO2022-0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre, the UK Dementia Research Institute at UCL (UKDRI-1003), and an anonymous donor; K.B. is supported by the Swedish Research Council (#2017-00915 and #2022-00732), the Swedish Alzheimer Foundation (#AF-930351, #AF-939721, #AF-968270, and #AF-994551), Hjärfonden, Sweden (#ALZ2022-0006, #FO2024-0048-TK-130 and FO2024-0048-HK-24), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (#ALFGBG-965240 and #ALFGBG-1006418), the European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236), the Alzheimer's Association 2021 Zenith Award (ZEN-21-848495), the Alzheimer's Association 2022-2025 Grant (SG-23-1038904 QC), La Fondation Recherche Alzheimer (FRA), Paris, France, the Kirsten and Freddy Johansen Foundation, Copenhagen, Denmark, Familjen Rönströms Stiftelse, Stockholm, Sweden, and an anonymous philanthropist and donor; J.D.G. was supported by the Spanish Ministry of Science and Innovation (RYC-2013-13054), received research support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking AMYPAD (grant agreement 115952), EIT Digital (grant 2021), and from Ministerio de Ciencia y Universidades (grant agreement RTI2018-102261); O. G.-R. was supported by the Spanish Ministry of Science, Innovation and Universities (Juan de la Cierva program IJC2020-043417-I), funded by MCIN/AEI/10.13039/501100011033 and the European Union Next-GenerationEU/PRTR, Instituto de Salud Carlos III (ISCIII) through the projects "PI19/00117" and "PI24/00116" and co-funded by the European Union/FEDER. OG-R also receives funding from F. Hoffmann-La Roche Ltd, and has given lectures in symposia sponsored by Roche Diagnostics, S.L.U; G.S.-B. was supported by the Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union/FSE+, supported by MCIN/AEI/10.13039/501100011033, through the project PID2020-119566RA-I00 and grant CP23/00039.

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

The authors declare that no generative AI or AI-assisted technologies were used in the manuscript preparation process.

CRediT authorship contribution statement

David López-Martos: Writing – original draft, Writing – review & editing, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Raffaele Cacciaglia:** Writing – review & editing, Software, Data curation. **Marc Suárez-Calvet:** Writing – review & editing, Data curation. **Gemma Salvadó:** Writing – review & editing, Data curation. **Mahnaz Shekari:** Writing – review & editing, Data curation. **Armand González-Escalante:** Writing – review & editing, Data curation. **Marta Milà-Alomà:** Writing – review & editing, Data curation. **Anna Bruguat-Serrat:** Writing – review & editing, Data curation. **Carolina Minguillon:** Writing – review & editing, Project administration. **Matteo Tonietto:** Writing – review & editing, Resources. **Edilio Borroni:** Writing – review & editing,

Resources. **Gregory Klein:** Writing – review & editing, Resources. **Clara Quijano-Rubio:** Writing – review & editing, Resources. **Gwendlyn Kollmorgen:** Writing – review & editing, Resources. **Henrik Zetterberg:** Writing – review & editing, Resources. **Kaj Blennow:** Writing – review & editing, Resources. **Juan Domingo Gispert:** Writing – review & editing, Data curation. **Oriol Grau-Rivera:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Gonzalo Sánchez-Benavides:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

DL-M, RC, MS, AG-E, MM-A, AB-S, and CM have nothing to disclose; MS-C has served as a consultant and at advisory boards for Roche Diagnostics International Ltd and Grifols S.L., has given lectures in symposia sponsored by Roche Diagnostics, S.L.U and Roche Farma, S.A., and was granted with a project funded by Roche Diagnostics International Ltd; GS has received speaker fees from Springer, GE Healthcare, Biogen, Esteve and Adium and she serves on the advisory board of Johnson&Johnson; MT is a full-time employee and own stock in F. Hoffmann-La Roche Ltd; EB was a full-time employee in F. Hoffmann-La Roche Ltd; GK is a full-time employee and own stock in F. Hoffmann-La Roche Ltd; CQ-R is a full-time employee of Roche Diagnostics International Ltd, Rotkreuz, Switzerland; GK is a full-time employee of Roche Diagnostics GmbH, Penzberg, Germany; HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optocentrics, Passage Bio, Pinteun Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and is a shareholder of MicThera (outside submitted work); KB has served as a consultant and at advisory boards for Abbvie, AC Immune, ALZPath, AriBio, Beckman-Coulter, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Neurimmune, Novartis, Ono Pharma, Prothena, Quanterix, Roche Diagnostics, Sunbird Bio, Sanofi and Siemens Healthineers, has served at data monitoring committees for Julius Clinical and Novartis, has given lectures, produced educational materials and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai and Roche Diagnostics, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper; JDG receives research funding from Roche Diagnostics and GE Healthcare and has given lectures at symposia sponsored by Biogen and Philips; OG-R receives research funding from Roche Pharma; GS-B worked as a consultant for Roche Farma, S.A. Given M.S.-C. and H.Z. role as Editorial Board members, they had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor.

Acknowledgments

This publication is part of the ALFA study. The authors would like to express their most sincere gratitude to the ALFA project participants and relatives without whom this research would not have been possible. The authors also thank Roche Diagnostics International Ltd for providing the kits used to measure CSF biomarkers, the laboratory technicians at the Clinical Neurochemistry Laboratory in Mölndal, Sweden, for performing the analyses, Eli Lilly and Company for providing the measurements of

the in-house assay for plasma p-tau217, GE Healthcare for supplying the [¹⁸F]flutemetamol doses, and F. Hoffmann-La Roche Ltd for sponsoring the tau PET study.

COBAS and ELECSYS are trademarks of Roche. All other product names and trademarks are the property of their respective owners. The NeuroToolKit is a panel of exploratory prototype assays designed to robustly evaluate biomarkers associated with key pathologic events characteristic of AD and other neurological disorders, used for research purposes only and not approved for clinical use (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). The Elecsys β -Amyloid(1–42) CSF and Elecsys Phospho-Tau (181P) CSF assays are approved for clinical use.

Collaborators of the ALFA study are: Federica Anastasi, Annabella Beteta, Marta del Campo, Lidia Canals, Alba Cañas, Irene Cumplido-Marinero, Carme Deulofeu, Ruth Dominguez, María Emilio, Karine Fauria, Ana Fernández-Angulo, Sherezade Fuentes, Marina García, Patricia Genius, Laura Hernández, Felipe Hernández-Viadel, Gema Huesa, Jordi Huguet, Laura Iglesias, Esther Jiménez, Ferran Lugo, Paula Marne, Tania Menchón, José Luis Molinuevo, Paula Ortiz-Romero, Wiesje Pelkmans, Albina Polo, Sandra Pradas, Blanca Rodríguez-Fernández, Iman Sadeghi, Lluís Solsona, Anna Soteras, Laura Stankeviciute, Núria Tort-Colet, Marc Vilanova, Natalia Vilor-Tejedor.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.tjpad.2026.100612](https://doi.org/10.1016/j.tjpad.2026.100612).

References

- Jack CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):257–62. <https://doi.org/10.1016/j.jalz.2011.03.004>.
- Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):280–92. <https://doi.org/10.1016/j.jalz.2011.03.003>.
- Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018;14(4):535–62. <https://doi.org/10.1016/j.jalz.2018.02.018>.
- Jack CR, Andrews JS, Beach TG, 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>.
- Grober E, Lipton RB, Sperling RA, et al. Associations of stages of objective memory impairment with Amyloid PET and structural MRI: the A4 study. *Neurology* 2022;98(13):E1327–36. <https://doi.org/10.1212/WNL.000000000200046>.
- Insel PS, Donohue MC, Sperling R, Hansson O, Mattsson-Carlsson N. The A4 study: β -amyloid and cognition in 4432 cognitively unimpaired adults. *Ann Clin Transl Neurol* 2020;7(5):776–85. <https://doi.org/10.1002/acn3.51048>.
- Vannini P, Hanseeuw B, Munro CE, et al. Anosognosia for memory deficits in mild cognitive impairment: insight into the neural mechanism using functional and molecular imaging. *Neuroimage Clin* 2017;15:408–14. <https://doi.org/10.1016/j.nicl.2017.05.020>.
- Cacciamani F, Houot M, Gagliardi G, et al. Awareness of cognitive decline in patients with Alzheimer's Disease: a systematic review and meta-analysis. *Front Aging Neurosci* 2021;13. <https://doi.org/10.3389/fnagi.2021.697234>.
- Dubois B, Villain N, Schneider L, et al. Alzheimer Disease as a clinical-biological construct: an International Working Group recommendation. *JAMA Neurol* 2024;81:1304–11. <https://doi.org/10.1001/jamaneurol.2024.3770>.
- Kiselica AM, Atkins KJ, Han SD, et al. Reactions of clinical neuropsychologists to the Alzheimer's Association workgroup's draft diagnostic and staging criteria for Alzheimer's disease. *J Alzheimers Dis* 2024;102(3):877–84. <https://doi.org/10.1177/13872877241292089>.
- Kiselica AM, Gaynor LS, Atkins KJ. IWG and AA Criteria—Where the differences matter. *JAMA Neurol* 2025;82:628–9. <https://doi.org/10.1001/jamaneurol.2025.0775>.
- Thomas KR, Edmonds EC. Objective criteria for subtle cognitive decline in aging and preclinical Alzheimer disease. *Neurology* 2025;104(9):e213536. <https://doi.org/10.1212/WNL.000000000213536>.
- Hanseeuw BJ, Betensky RA, Jacobs HIL, et al. Association of amyloid and Tau with cognition in preclinical Alzheimer disease: a longitudinal study. *JAMA Neurol* 2019;76(8):915–24. <https://doi.org/10.1001/jamaneurol.2019.1424>.
- Donohue MC, Sperling RA, Petersen R, Sun CK, Weiner M, Aisen PS. Association between elevated brain amyloid and subsequent cognitive decline among cognitively normal persons. *JAMA* 2017;317(22):2305–16. <https://doi.org/10.1001/jama.2017.6669>.
- Kiselica AM, Karr JE, Mikula CM, et al. Recent advances in neuropsychological test interpretation for clinical practice. *Neuropsychol Rev* 2024;34(2):637–67. <https://doi.org/10.1007/s11065-023-09596-1>.
- Grober E, Mowrey W, Katz M, Derby C, Lipton RB. Conventional and robust norming in identifying preclinical dementia. *J Clin Exp Neuropsychol* 2015;37(10):1098–106. <https://doi.org/10.1080/13803395.2015.1078779>.
- Hassenstab J, Chasse R, Grabow P, et al. Certified normal: Alzheimer's disease biomarkers and normative estimates of cognitive functioning. *Neurobiol Aging* 2016;43:23–33. <https://doi.org/10.1016/j.neurobiolaging.2016.03.014>.
- Bos I, Vos SJB, Jansen WJ, et al. Amyloid- β , tau, and cognition in cognitively normal older individuals: examining the necessity to adjust for biomarker status in normative data. *Front Aging Neurosci* 2018;10. <https://doi.org/10.3389/fnagi.2018.00193>.
- Kaser AN, Kaplan DM, Goette W, Kiselica AM. The impact of conventional versus robust norming on cognitive characterization and clinical classification of MCI and dementia. *J Neuropsychol* 2023;17(1):108–24. <https://doi.org/10.1111/jnp.12289>.
- Duff K. Current topics in science and practice evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods. *Arch Clin Neuropsychol* 2012;27(3):248–61. <https://doi.org/10.1093/arclin/acr120>.
- Borland E, Edgar C, Stomrud E, Cullen N, Hansson O, Palmqvist S. Clinically relevant changes for cognitive outcomes in preclinical and prodromal cognitive stages: implications for clinical Alzheimer trials. *Neurology* 2022;99(11):E1142–53. <https://doi.org/10.1212/WNL.000000000200817>.
- López-Martos D, Brugalat-Serrat A, Suárez-Calvet M, et al. Robust longitudinal neuropsychological norms in Spanish individuals with nonpathological Alzheimer's disease biomarkers. *Neuropsychology* 2025;39:517–37. <https://doi.org/10.1037/neu0001013>.
- Brooks BL, Iverson GL, White T. Substantial risk of "Accidental MCI" in healthy older adults: base rates of low memory scores in neuropsychological assessment. *J Int Neuropsychol Soc* 2007;13(3):490–500. <https://doi.org/10.1017/S1355617707070531>.
- Kiselica AM, Webber TA, Bengtson JF. Using multivariate base rates of low scores to understand early cognitive declines on the uniform data set 3.0 Neuropsychological Battery. *Neuropsychology* 2020;34(6):629–40. <https://doi.org/10.1037/neu0000640>.
- Molinuevo JL, Gramunt N, Gispert JD, et al. The ALFA project: a research platform to identify early pathophysiological features of Alzheimer's disease. *Alzheimers Dement (N Y)*. 2016;2(2):82–92. <https://doi.org/10.1016/j.trci.2016.02.003>.
- Milà-Alomà M, Salvadó G, Gispert JD, et al. Amyloid beta, tau, synaptic, neurodegeneration, and glial biomarkers in the preclinical stage of the Alzheimer's continuum. *Alzheimers Dement* 2020;16(10):1358–71. <https://doi.org/10.1002/alz.12131>.
- Suárez-Calvet M, Karikari TK, Ashton NJ, et al. Novel tau biomarkers phosphorylated at T181, T217 or T231 rise in the initial stages of the preclinical Alzheimer's continuum when only subtle changes in A β pathology are detected. *EMBO Mol Med* 2020;12(12). <https://doi.org/10.15252/emmm.202012921>.
- Thijssen EH, La Joie R, Strom A, et al. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. *Lancet Neurol* 2021;20(9):739–52. [https://doi.org/10.1016/S1474-4422\(21\)00214-3](https://doi.org/10.1016/S1474-4422(21)00214-3).
- Shekari M, Vázquez García D, Collij LE, et al. Stress testing the centiloid: precision and variability of PET quantification of amyloid pathology. *Alzheimers Dement* 2024;20(8):5102–13. <https://doi.org/10.1002/alz.13883>.
- Peña-Casanova J, Gramunt-Fombuena N, Quiñones-Úbeda S, et al. Spanish multicenter normative studies (NEURONORMA project): norms for the re-ostertih complex figure (copy and memory), and free and cued selective reminding test. *Arch Clin Neuropsychol* 2009;24(4):371–93. <https://doi.org/10.1093/arclin/acp041>.
- Gramunt N, Sánchez-Benavides G, Buschke H, et al. The memory binding test: development of two alternate forms into Spanish and Catalan. *J Alzheimers Dis* 2016;52(1):283–93. <https://doi.org/10.3233/JAD-151175>.
- Wechsler D. Wechsler memory scale-IV. Spanish edition. *Pearson Clinical & Talent Assessment*; 2013.
- Morris JC. The Clinical Dementia Rating (CDR) current version and scoring rules. *Neurology* 1993;43(11):2412. <https://doi.org/10.1212/WNL.43.11.2412-a>.
- Blesa R, Pujol M, Aguilar M, et al. Clinical validity of the 'mini-mental state' for Spanish speaking communities. *Neuropsychologia* 2001;39(11):1150–7. [https://doi.org/10.1016/S0028-3932\(01\)00055-0](https://doi.org/10.1016/S0028-3932(01)00055-0).
- Rami L, Mollica MA, García-Sánchez C, et al. The subjective cognitive decline questionnaire (SCD-Q): a validation study. *J Alzheimers Dis* 2014;41(2):453–66. <https://doi.org/10.3233/JAD-132027>.
- Oltra-Cucarella J, Sánchez-SanSegundo M, Rubio-Aparicio M, Arango-Lasprilla JC, Ferrer-Cascales R. The association between the number of neuropsychological measures and the base rate of low scores. *Assessment* 2021;28(3):955–63. <https://doi.org/10.1177/1073191119864646>.
- Therriault J, Schindler SE, Salvadó G, et al. Biomarker-based staging of Alzheimer disease: rationale and clinical applications. *Nat Rev Neurol* 2024;20(4):232–44. <https://doi.org/10.1038/s41582-024-00942-2>.
- Therriault J, Pascoal TA, Lussier FZ, et al. Biomarker modeling of Alzheimer's disease using PET-based Braak staging. *Nat Aging* 2022;2(6):526–35. <https://doi.org/10.1038/s43587-022-00204-0>.

- [39] López-Martos D, Suárez-Calvet M, Milà-Alomà M, et al. Longitudinal associations of multimodal core 1 Alzheimer disease biomarkers with cognition in aging and preclinical Alzheimer disease. *Neurology* 2025;105(9). <https://doi.org/10.1212/WNL.0000000000214308>.
- [40] Kiselica AM, Kaser AN, Webber TA, Small BJ, Bengte JF. Development and preliminary validation of standardized regression-based change scores as measures of transitional cognitive decline. *Arch Clin Neuropsychol* 2025;40:1146–57. <https://doi.org/10.1093/arclin/aca015>.
- [41] Duff K, Sevigny-Resetto D. Validation of regression-based change formulae for mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement (Amst)* 2024;16(3):e70008. <https://doi.org/10.1002/dad2.70008>.
- [42] Simone G, Michele R, Federica DS, Giulia L, Antonio G, Elena R. Conventional and neuropsychological criteria for mild cognitive impairment show similar prognostic value for dementia across 12 years in a non-clinical setting. *Sci Rep* 2025;15(1):19827. <https://doi.org/10.1038/s41598-025-04275-y>.
- [43] Palmqvist S, Warmenhoven N, Anastasi F, et al. Plasma phospho-tau217 for Alzheimer's disease diagnosis in primary and secondary care using a fully automated platform. *Nat Med* 2025;31:2036–43. <https://doi.org/10.1038/s41591-025-03622-w>.
- [44] Salvadó G, Janelidze S, Bali D, et al. Plasma phosphorylated tau 217 to identify preclinical Alzheimer disease. *JAMA Neurol* 2025;82(11):1122–34. <https://doi.org/10.1001/jamaneurol.2025.3217>.
- [45] Ossenkoppele R, Salvadó G, Janelidze S, et al. Plasma p-tau217 and tau-PET predict future cognitive decline among cognitively unimpaired individuals: implications for clinical trials. *Nat Aging* 2025;5:883–96. <https://doi.org/10.1038/s43587-025-00835-z>.
- [46] Mattsson N, Palmqvist S, Stomrud E, Vogel J, Hansson O. Staging β -amyloid pathology with amyloid positron emission tomography. *JAMA Neurol* 2019;76(11):1319–29. <https://doi.org/10.1001/jamaneurol.2019.2214>.
- [47] Mielke MM, Syrjanen JA, Blennow K, et al. Plasma and CSF neurofilament light: relation to longitudinal neuroimaging and cognitive measures. *Neurology* 2019;93(3):e252–60. <https://doi.org/10.1212/WNL.00000000000007767>.
- [48] Pereira JB, Janelidze S, Smith R, et al. Plasma GFAP is an early marker of amyloid- β but not tau pathology in Alzheimer's disease. *Brain* 2021;144(11):3505–16. <https://doi.org/10.1093/brain/awab223>.
- [49] Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013;12(2):207–16. [https://doi.org/10.1016/S1474-4422\(12\)70291-0](https://doi.org/10.1016/S1474-4422(12)70291-0).
- [50] Gispert JD, Rami L, Sánchez-Benavides G, et al. Nonlinear cerebral atrophy patterns across the Alzheimer's disease continuum: impact of APOE4 genotype. *Neurobiol Aging* 2015;36(10):2687–701. <https://doi.org/10.1016/j.neurobiolaging.2015.06.027>.
- [51] Fortea J, Vilaplana E, Alcolea D, et al. Cerebrospinal fluid β -amyloid and phospho-tau biomarker interactions affecting brain structure in preclinical Alzheimer disease. *Ann Neurol* 2014;76(2):223–30. <https://doi.org/10.1002/ana.24186>.
- [52] Pegueroles J, Vilaplana E, Montal V, et al. Longitudinal brain structural changes in preclinical Alzheimer's disease. *Alzheimers Dement* 2017;13(5):499–509. <https://doi.org/10.1016/j.jalz.2016.08.010>.
- [53] Salvadó G, Shekari M, Falcon C, et al. Brain alterations in the early Alzheimer's continuum with amyloid- β , tau, glial and neurodegeneration CSF markers. *Brain Commun* 2022;4(3). <https://doi.org/10.1093/braincomms/fcac134>.
- [54] Mormino EC, Kluth JT, Madison CM, et al. Episodic memory loss is related to hippocampal-mediated β -amyloid deposition in elderly subjects. *Brain* 2009;132(5):1310–23. <https://doi.org/10.1093/brain/awn320>.
- [55] Raffi MS, Sperling RA, Donohue MC, et al. The AHEAD 3-45 study: design of a prevention trial for Alzheimer's disease. *Alzheimers Dement* 2023;19(4):1227–33. <https://doi.org/10.1002/alz.12748>.
- [56] Yaari R, Holdridge KC, Williamson M, et al. Donanemab in preclinical Alzheimer's disease: screening and baseline data from TRAILBLAZER-ALZ 3. *Alzheimers Dement* 2025;21(9):e70662. <https://doi.org/10.1002/alz.70662>.
- [57] Bouteloup V, Villain N, Vidal JS, et al. Cognitive phenotyping and interpretation of Alzheimer blood biomarkers. *JAMA Neurol* 2025;82:506–15. <https://doi.org/10.1001/jamaneurol.2025.0142>.
- [58] Cappa SF, Ribaldi F, Chicherio C, Frisoni GB. Subjective cognitive decline: memory complaints, cognitive awareness, and metacognition. *Alzheimers Dement* 2024;20:6622–31. <https://doi.org/10.1002/alz.13905>.
- [59] López-Martos D, Suárez-Calvet M, Milà-Alomà M, et al. Awareness of episodic memory and meta-cognitive profiles: associations with cerebrospinal fluid biomarkers at the preclinical stage of the Alzheimer's continuum. *Front Aging Neurosci* 2024;16. <https://doi.org/10.3389/fnagi.2024.1394460>.
- [60] Edmonds EC, Delano-Wood L, Galasko DR, Salmon DP, Bondi MW. Subjective cognitive complaints contribute to misdiagnosis of mild cognitive impairment. *J Int Neuropsychol Soc* 2014;20(8):836–47. <https://doi.org/10.1017/S135561771400068X>.
- [61] Therriault J, Ng KP, Pascoal TA, et al. Anosognosia predicts default mode network hypometabolism and clinical progression to dementia. *Neurology* 2018;90(11):e932–9. <https://doi.org/10.1212/WNL.00000000000005120>.
- [62] Hanseeuw BJ, Scott MR, Sikkes SAM, et al. Evolution of anosognosia in Alzheimer's disease and its relationship to amyloid. *Ann Neurol* 2020;87(2):267–80. <https://doi.org/10.1002/ana.25649>.