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Plasma Aβ42/Aβ40 predicts longitudinal amyloid pathology and clinical progression in amyloid-PET negative individuals with subjective cognitive decline

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Abstract

Background Early detection of amyloid-β (Aβ) pathology is critical for timely intervention in Alzheimer's disease (AD). Changes in plasma Aβ42/Aβ40 levels appear early in the AD continuum, but whether they precede amyloid deposition detected by Aβ-PET requires further research.

Methods Data from 164 Aβ-PET negative (Aβ-PET(−)≤13.5 CL) individuals with subjective cognitive decline (SCD) from the Fundació ACE Healthy Brain Initiative (FACEHBI) study were included. Baseline plasma Aβ42/Aβ40 levels were quantified using mass spectrometry, and participants were classified as plasma Aβ(+) or Aβ(−) using a threshold of 0.241. Participants underwent florbetaben PET at baseline and 2, 5, and 8 years, with annual clinical assessments. Rates of brain amyloid accumulation (Centiloids, CL) and progression to Aβ-PET positive (Aβ-PET(+)) or mild cognitive impairment (MCI) due to AD (incident MCI with concomitant Aβ-PET(+)) were analyzed according to plasma Aβ status for two conversion thresholds: 22 CL and 13.5 CL.

Results Plasma Aβ(+) participants (n=34) at baseline exhibited faster amyloid accumulation than Aβ(−) individuals (n=130) (β=1.99, 95% CI 1.12–2.86; $p<0.001$), despite no significant differences in baseline CL values. At the 22 CL threshold for Aβ-PET(+) conversion, significant group differences were observed in time to event (p=0.003 for Aβ-PET(+); p=0.002 for MCI due to AD). Plasma Aβ(+) status was associated with higher risk of conversion to Aβ-PET(+) (Hazard ratio (HR): 6.86, 95% CI 2.45–19.20, $p<0.001$) and MCI due to AD (HR

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9.50, 1.98–45.65, $p=0.005$). Findings were consistent for the 13.5 CL threshold ($p=0.015$ and 0.014; HR 3.93, 1.69–9.11, $p=0.001$ and HR 7.11, 1.67–30.29, $p=0.008$, respectively).

Conclusion In a population of SCD Aβ-PET(−) participants, plasma Aβ42/Aβ40 identified individuals with emerging amyloid pathology, supporting that plasma alterations may precede PET-detectable cortical deposition. Plasma Aβ(+)/Aβ-PET(−) individuals showed increased risk of subsequent amyloid accumulation and clinical progression, consistent with an early amyloid transitional stage not yet fully captured by PET. These findings highlight the potential of plasma Aβ42/Aβ40 as a first-step screening tool for clinical trial enrichment with important implications for primary prevention trials.

Keywords Alzheimer's disease · Amyloid-β · Aβ42/Aβ40 ratio · Blood biomarkers · Plasma · PET · Mass spectrometry · Subjective cognitive decline · FACEHBI · Primary prevention trials

Abbreviations

Aβ	Amyloid-β
AD	Alzheimer's disease
APOE	Apolipoprotein E
AUC	Area Under the ROC Curve
CI	Confidence interval
CL	Centiloid
CSF	Cerebrospinal fluid
CU	Cognitively unimpaired
FACEHBI	Fundació ACE Healthy Brain Initiative
FBB	^{18}F-Florbetaben
HR	Hazard ratio
LMEM	Linear mixed-effects model
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MS	Mass spectrometry
NPV	Negative predictive value
p-tau	Phosphorylated tau
PET	Positron emission tomography
PPV	Positive predictive value
ROC	Receiver Operating Characteristic
SCD	Subjective cognitive decline
SUVR	Standard uptake value ratio

Background

Alzheimer's disease (AD) is characterized by a prolonged preclinical phase during which pathological processes develop silently for years before the onset of overt cognitive symptoms [1]. Within this continuum, amyloid-β (Aβ) accumulation represents one of the earliest detectable biological alterations, preceding tau pathology, neurodegeneration, and clinical impairment [2, 3]. Identifying individuals in these very early stages, when the first pathophysiological changes are emerging, has become a central objective in the field, as therapeutic strategies are likely to be most effective early in the disease course [4–6]. Achieving this goal may require identifying cognitively unimpaired (CU) individuals with minimal or undetectable cortical amyloid burden in vivo who are at risk

of progression [7–9]. In this context, blood-based biomarkers have emerged as promising and accessible tools, offering practical advantages over more invasive and costly approaches such as lumbar puncture or positron emission tomography (PET).

Recent advances in ultrasensitive analytical platforms have enabled the rapid development of plasma biomarkers with high analytical performance. Among them, the plasma Aβ42/Aβ40 ratio is a well-established indicator of cerebral amyloid pathology in CU individuals [10–14], and it is considered one of the earliest biomarkers to become abnormal along the AD continuum [15, 16]. While previous studies were challenged by analytical variability and overlapping Aβ42/Aβ40 values between groups [17], improvements in assay standardization and the development of high-performance immunoassays [18, 19] and mass spectrometry (MS)–based methods [20–22] have substantially enhanced their precision and reliability. As a result, improved analytical performance, together with evidence that plasma Aβ42/Aβ40 levels change very early in the disease course, has positioned this biomarker as a reliable peripheral measure of amyloid pathology and a promising tool for identifying individuals at increased risk of progression at the earliest preclinical stages.

An important unsolved question concerns the interpretation of individuals who test positive for plasma Aβ42/Aβ40 while remaining negative on Aβ-PET, the imaging reference standard for cortical amyloid burden. Such cases are frequently labeled "false positives", contributing to modest positive predictive values (PPV) in cross-sectional studies [8]. However, it remains unclear whether this apparent discordance truly reflects misclassification or instead captures a transitional biological stage in which amyloid-related alterations are detectable in peripheral fluids before reaching the threshold of cortical deposition measurable by Aβ-PET. While studies comparing cerebrospinal fluid (CSF) and PET have demonstrated that CSF biomarkers may precede PET positivity [23, 24], evidence supporting a similar temporal sequence for plasma biomarkers remains limited.

Longitudinal studies, such as our previous work [25] and others, have shown that CU individuals, including those with subjective cognitive decline (SCD), with low plasma Aβ42/Aβ40 levels are at increased risk of future conversion to Aβ-PET (+) [12, 26, 27]. They are also at a higher risk of clinical progression to mild cognitive impairment (MCI) and AD dementia [28, 29]. Nevertheless, the extent to which plasma Aβ42/Aβ40 may reflect incipient biological risk in Aβ-PET–negative (Aβ-PET(–)) individuals requires further research.

In the present study, we followed the Fundació ACE Healthy Brain Initiative (FACEHBI) cohort of individuals with SCD for up to eight years and focused on participants with baseline Aβ-PET(–), defined as ≤ 13.5 Centiloids (CL), an early amyloid deposition threshold. We examined whether baseline plasma Aβ42/Aβ40 was associated with subsequent abnormal cortical amyloid accumulation. In addition, we assessed whether plasma Aβ42/Aβ40 positivity conferred an increased risk of conversion to Aβ-PET(+), all-cause MCI, and MCI due to AD (MCI together with Aβ-PET(+)). Finally, we explored the potential implications of initial plasma Aβ42/Aβ40 assessment for optimizing participant stratification in preventive and early-intervention clinical trials.

Methods

Participants

This study included 200 Caucasian SCD participants initially enrolled in the FACEHBI cohort, an 8-year longitudinal, single-center, prospective observational study conducted at Ace Alzheimer Center Barcelona (Spain). Participants underwent annual blood collection and comprehensive neurological and neuropsychological assessments, including clinical diagnosis of SCD or MCI. Additionally, at baseline (V0) and at 2-year (V2), 5-year (V5), and 8-year (V8) follow-up visits, ^{18}F-florbetaben (FBB)-PET scans were performed to assess cortical amyloid burden. Written informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of Hospital Clinic i Provincial (Barcelona, Spain) (EudraCT: 2014–000798–38). A more detailed description of the study design has been published elsewhere, including inclusion and exclusion criteria

[30], the study procedures [13], and the criteria used for the diagnosis of SCD and MCI (Supplementary Information − Diagnosis criteria for SCD and MCI section).

^{18}F-Florbetaben positron emission tomography (FBB-PET)

Details on FBB-PET acquisition have been previously described [13]. Briefly, participants received a single intravenous 300 Mbq dose of the FBB radiotracer (NeuraCeq©). The standard uptake value ratio (SUVR) values were derived using the average uptake in magnetic resonance imaging (MRI)-defined cortical regions, normalized to the cerebellum. CL values were calculated following established published procedures [31].

Definition of Aβ-PET thresholds

Participants were classified as Aβ-PET(−) at baseline if cortical amyloid burden was ≤ 13.5CL, a threshold proposed as a marker of early amyloid accumulation during the preclinical stages of AD [32]. To define conversion to Aβ-PET(+), two thresholds were considered: 22 CL was employed to define a more advanced amyloid deposition, whereas a threshold of 13.5 CL was used to capture conversion at the earliest stages of amyloid deposition. The cutoff of 22 CL has been widely used in the literature to define abnormal amyloid levels [9, 33].

Plasma analysis

Baseline plasma levels of Aβ40 and Aβ42 were quantified using ABtest-MS (Araclon Biotech, Zaragoza, Spain). This approach relies on an antibody-free method based on high-performance liquid chromatography combined with differential mobility spectrometry and triple quadrupole mass spectrometry (HPLC-DMS-MS/MS). Briefly, analytes were extracted directly from plasma, as no immunoprecipitation step was applied. Because enzymatic digestion was not required, measurements corresponded to the intact Aβ40 and Aβ42 peptides. Deuterated internal standards (^{2}H-Aβ40 and ^{2}H-Aβ42; Bachem AG, Bubendorf, Switzerland) were added to all samples, and the response ratios for the endogenous peptides (^{14}N-Aβ40/^{2}H-Aβ40 and ^{14}N-Aβ42/^{2}H-Aβ42) were determined by interpolation against the calibration curves. Additional methodological details, including analytical workflow, instrument settings, and data on sensitivity, parallelism, accuracy, and precision, are available in the published literature [13].

Statistical analyses

All statistical analyses and data visualization were performed using GraphPad Prism (v5.03; GraphPad Software, San Diego, CA, USA), SPSS (v18; IBM, Armonk, NY, USA), and R (v4.4.2). Statistical significance was defined as a two-sided p-value < 0.05.

Receiver operating characteristic (ROC) analysis was previously conducted [13] in the whole baseline sample (n = 200) to determine the plasma Aβ42/Aβ40 threshold that best discriminated Aβ-PET status at baseline, according to the 13.5 CL cutoff. The plasma threshold corresponding to the maximum Youden index, 0.241, was then selected to classify individuals as plasma Aβ42/Aβ40 negative ("plasma Aβ(–)", Aβ42/Aβ40 > 0.241) or positive ("plasma Aβ(+)", Aβ42/Aβ40 ≤ 0.241).

In the present study, analyses were focused on the Aβ-PET(–) group of this cohort. Within this subgroup, individuals classified as plasma Aβ(–) were considered concordant cases, while those classified as plasma Aβ(+) were considered discordant cases. Comparisons between both groups, including baseline characteristics and conversion rates, were conducted using Chi-square or Fisher's exact tests for categorical variables and Mann–Whitney U test for continuous variables.

Multiple linear regression analyses were performed to assess whether baseline plasma Aβ42/Aβ40 levels and baseline Aβ-PET burden were associated with subsequent amyloid accumulation. These analyses were repeated

in subsets of participants classified as Aβ-PET(−) using progressively higher CL thresholds (≤5, ≤10, ≤13.5, ≤22, and ≤30 CL). Three models were fitted for each threshold: Model 1 included baseline Aβ-PET (CL) as the main predictor; Model 2 included baseline plasma Aβ42/Aβ40; and Model 3 included both biomarkers. All models were adjusted for age, sex, and APOE ε4 carrier status (dichotomized as carriers or non-carriers). Interaction terms between baseline CL and plasma Aβ42/Aβ40 were initially included in Model 3. However, these interaction terms were not statistically significant across all PET thresholds and were therefore excluded from the final models.

To examine whether baseline plasma Aβ status was associated with longitudinal trajectories of Aβ-PET, linear mixed-effects models (LMEMs) were fitted. These models included subject-specific random intercepts and random slopes for time, allowing individual trajectories to vary in both baseline levels and rates of change. Fixed effects included age, sex, APOE ε4 carrier status, baseline Aβ-PET (CL) levels, plasma Aβ group, time, and the plasma Aβ group × time interaction. Time was included in the models as a continuous variable representing the exact elapsed time (in years) since baseline. The interaction term's β coefficient, 95% confidence intervals (CI), and p-value were reported. A compound symmetry covariance structure was used for the repeated measure. Despite the fact that amyloid accumulation is intrinsically non-linear, within this relatively narrow CL range, a linear approximation was chosen to characterize longitudinal amyloid accumulation. This approach provides easily interpretable slope values and a good explanation of the observed trajectories, enabling a parsimonious description of change over time.

Kaplan–Meier survival analyses were carried out to describe time to conversion to Aβ-PET(+), all-cause MCI, or MCI due to AD according to baseline plasma status, and differences between groups were assessed using the log-rank test. All survival analyses were performed separately using the two predefined thresholds for Aβ-PET conversion (22 CL and 13.5 CL). In the case of conversion to MCI due to AD, the event time was defined as the later of the two events: either the date of MCI diagnosis or the date of conversion to Aβ-PET(+). Cox proportional hazards models were used to compare conversion risk between groups. Models were fitted both unadjusted and adjusted for age, sex, APOE ε4 carrier status, and baseline Aβ-PET (CL) levels. Initially, Cox models were fitted, including an interaction term between plasma Aβ42/Aβ40 group and baseline Aβ-PET burden to assess potential effect modification by baseline amyloid levels. However, this covariate did not reach statistical significance, and it was not retained in the final models. The proportional hazards assumption was assessed using Schoenfeld residuals and visually evaluated using log-minus-log plots. Finally, to assess the robustness of interval estimates, 95% CIs for the hazard ratios (HR) were derived from 1,000 non-parametric bootstrap iterations of the Cox models.

Results

Study population

Based on the Aβ-PET threshold of 13.5 CL, 164 of the 200 FACEHBI participants were Aβ-PET(−) and constituted the study population. Within this group, 130 individuals (79.3%) were classified as plasma Aβ(−) (Aβ42/Aβ40 > 0.241), whereas 34 (20.7%) were classified as plasma Aβ(+) (Aβ42/Aβ40 ≤ 0.241).

Compared with the plasma Aβ(−) group, plasma Aβ(+) participants included a lower proportion of women (52.9% vs. 70.8%; $p = 0.049$) and were slightly older (median [Q1–Q3]: 67.5 [61.8–72.5] vs. 64.0 [60.0–69.0] years; $p = 0.051$), with differences of borderline statistical significance. As expected, given the group definition, plasma Aβ(+) participants had significantly lower plasma Aβ42 levels (62.3 [55.9–68.8] vs. 71.9 [65.6–78.7] pg/mL; $p < 0.0001$) and Aβ42/Aβ40 ratios (0.226 [0.217–0.235] vs. 0.268 [0.257–0.284]; $p < 0.0001$). Importantly, baseline cerebral amyloid burden, as measured by Aβ-PET, did not differ between plasma groups ($p = 0.094$). The two groups were otherwise well balanced with respect to APOE ε4 carrier status, educational level, global cognitive performance (Mini-Mental State Examination, MMSE), and duration of the follow-up (Table 1).

Table 1 Baseline characteristics of the Aβ-PET(−) (≤13.5 CL) study population

	All participants (Aβ-PET(−), n = 164)	Plasma Aβ(−) (n = 130)*	Plasma Aβ(+) (n = 34)*	p-value†
Demographics				
Age, years	66.0 [60.0—69.8]	64.0 [60.0—69.0]	67.5 [61.8—72.5]	0.051
Female, n (%)	110 (67.0)	92 (70.8)	18 (52.9)	**0.049**
APOE ε4, n (%)				0.129
Non-carrier	131 (79.9)	107 (82.3)	24 (70.6)	
Carrier	33 (20.1)	23 (17.7)	10 (29.4)	
Education, years	15.0 [12.0—18.0]	15.0 [12.0—18.0]	15.5 [10.8—18.5]	0.893
Neuroimaging				
Aβ-PET, CL	−3.73 [−7.97—1.70]	−4.08 [−8.23—1.50]	−2.14 [−6.16—5.07]	0.094
Plasma biomarkers				
Plasma Aβ40, pg/mL	269.26 [243.7—294.2]	266.9 [242.3—291.2]	283.2 [251.5—301.1]	0.096
Plasma Aβ42, pg/mL	70.3 [63.1—77.4]	71.9 [65.6—78.7]	62.3 [55.9—68.8]	**<0.0001**
Plasma Aβ42/Aβ40	0.261 [0.244—0.279]	0.268 [0.257—0.284]	0.226 [0.217—0.235]	**<0.0001**
Global cognition				
MMSE, score	29.0 [29.0—30.0]	29.0 [29.0—30.0]	29.0 [29.0—30.0]	0.836
Follow-up				
Follow-up duration‡, years	8.01 [4.10—8.13]	8.01 [4.17—8.13]	8.02 [3.35—8.13]	0.703
Attrition, n (%)	69 (42.1)	53 (40.8)	16 (47.1)	0.508

Data are median [Q1-Q3] values, except for the variables "female" and "APOE", which are the number of cases (%)

Abbreviations: *APOE* apolipoprotein E, *Aβ* amyloid-beta, *PET* positron emission tomography, *CL* centiloid, *MMSE* Mini-Mental State Examination

*: Plasma Aβ(−) and Plasma Aβ(+) were defined using a cutoff of Aβ42/Aβ40 > 0.241 and ≤ 0.241, respectively

†: Differences between groups (plasma Aβ(−) vs. plasma Aβ(+)) were tested using the Mann–Whitney U test, Chi-square tests or Fisher's exact test, as appropriate. Significant p-values (< 0.05) are highlighted in bold

‡: Only cases with at least one follow-up visit were included: n = 158 in the "All population" group; n = 126 in the plasma Aβ(−) group; n = 32 in the plasma Aβ(+)

During the 8-year follow-up, 69 of the 164 participants (42.1%) defined as Aβ-PET(−) at baseline discontinued the study. The reasons for participant withdrawal are provided in Supplementary Table 1. The number of dropouts per visit was as follows: V1: 6; V2: 5; V3: 22; V4: 6, V5: 10; V6: 13; V7: 4 and V8: 3. Among the 164 participants, 49% (81/164) underwent up to four Aβ-PET assessments, with an additional 21 (13%) having three scans, 37 (23%) two scans, and 25 (15%) only the baseline scan (withdrawals).

Association of baseline Aβ-PET and plasma Aβ42/Aβ40 with longitudinal cortical amyloid accumulation across different negative thresholds

Multiple linear regression analyses were performed across Aβ-PET(−) populations defined by progressively higher CL thresholds, to examine the association between baseline biomarkers and subsequent amyloid accumulation (Table 2). Baseline Aβ-PET levels were not significantly associated with amyloid accumulation in the lowest CL ranges (≤5 and ≤10 CL). Coefficients became significant only when the assessed thresholds included higher baseline CL values (Table 2, Model 1). In contrast, baseline plasma Aβ42/Aβ40 levels were consistently associated with amyloid accumulation across all CL thresholds, including those with minimal baseline amyloid burden (≤5 and ≤10 CL) (Table 2, Model 2). When both biomarkers were included simultaneously in the model (Table 2, Model 3), plasma Aβ42/Aβ40 remained independently associated with amyloid accumulation across thresholds, whereas the association with baseline Aβ-PET was again restricted to populations including higher baseline CL levels (13.5 CL or higher). A visualization of the standardized regression coefficients across the different CL thresholds is provided in Supplementary Fig. 1.

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Table 2 Multiple linear regression models of amyloid change across Aβ-PET thresholds

		Model 1			**Model 2**			**Model 3**					
		Aβ-PET (CL)			**Plasma Aβ42/Aβ40**			**Aβ-PET (CL)**			**Plasma Aβ42/Aβ40**		
Aβ-PET Cutoff (CL)	N	B (95% CI)	B	p-value	B (95% CI)	β	p-value	B (95% CI)	β	p-value	B (95% CI)	β	p-value
≤5	141	0.017 (−0.048–0.081)	0.047	0.610	−16.94 (−32.05 to −1.82)	−0.216	**0.028**	0.028 (−0.037–0.092)	0.077	0.397	−17.88 (−33.18 to −2.59)	−0.228	**0.022**
≤10	153	0.038 (−0.022–0.098)	0.109	0.217	−22.03 (−36.71 to −7.35)	−0.267	**0.004**	0.050 (−0.009–0.108)	0.144	0.095	−23.64 (−38.33 to −8.94)	−0.286	**0.002**
≤13.5	164	0.059 (0.004–0.115)	0.180	**0.036**	−23.48 (−38.02 to −8.93)	−0.278	**0.002**	0.060 (0.007–0.113)	0.183	**0.028**	−23.63 (−37.97 to −9.29)	−0.279	**0.001**
≤22	175	0.080 (0.033–0.128)	0.276	**0.001**	−24.83 (−39.59 to −10.08)	−0.284	**0.001**	0.067 (0.020–0.115)	0.230	**0.006**	−20.67 (−35.38 to −5.95)	−0.237	**0.006**
≤30	179	0.068 (0.023–0.113)	0.250	**0.003**	−26.06 (−40.86 to −11.26)	−0.292	**0.001**	0.057 (0.013–0.101)	0.211	**0.011**	−23.14 (−37.83 to −8.44)	−0.260	**0.002**

Regression coefficients (B) with 95% confidence intervals (CI), standardized beta coefficients (β), and p-values are shown for multiple linear regression models evaluating the association between baseline biomarkers and change in global Centiloid (CL) values from baseline to last follow-up. Analyses were conducted in subsets of participants classified as Aβ-PET(−) using different baseline Centiloid thresholds (≤5, ≤10, ≤13.5, ≤22, and ≤30 CL). Model 1 included baseline Aβ-PET, Model 2 included baseline plasma Aβ42/Aβ40, and Model 3 included both biomarkers. All models were adjusted for age, sex, and APOE ε4 carrier status. Significant p-values (<0.05) are highlighted in bold

Association of baseline Aβ42/Aβ40 status with longitudinal Aβ-PET deposition

LMEM were used to examine whether baseline plasma Aβ42/Aβ40 status was associated with longitudinal changes in cerebral amyloid burden over the 8-year follow-up. Aβ-PET burden increased over time in plasma Aβ(−) individuals at a rate of 1.16 CL/year (95% CI 0.78–1.54; $p<0.001$). Plasma Aβ(+) individuals showed a significantly steeper rate of amyloid accumulation compared with plasma Aβ(−) individuals (interaction β = 1.99, 95% CI 1.12–2.86; $p<0.001$), corresponding to an estimated annual increase of approximately 3.13 CL/year (Fig. 1).

Conversion to Aβ-PET(+) and to MCI due to AD

The proportional hazards assumption was met for models evaluating conversion to Aβ-PET(+) and to MCI due to AD, as indicated by non-significant Schoenfeld residual tests and approximately parallel log-minus-log survival curves. Conversions were assessed using two different amyloid positivity thresholds:

Conservative amyloid threshold

When conversion to Aβ-PET(+) was evaluated using a conservative amyloid threshold of 22 CL, 21 individuals converted during the follow-up. Among them, a higher proportion of converters was observed in the plasma Aβ(+) group (9/34, 26.5%) compared with the plasma Aβ(−) group (12/130, 9.2%; $p=0.007$). Kaplan–Meier curves showed significant differences between groups (log-rank $p=0.003$) (Fig. 2A). In addition, Cox regression models indicated an increased risk of conversion to Aβ-PET(+) in plasma Aβ(+) participants (unadjusted HR = 3.46, 95% CI 1.45–8.23, $p=0.005$), which remained significant after adjustment for covariates (HR = 6.86, 95% CI 2.45–19.20, $p<0.001$). Bootstrap analyses under the 22 CL threshold yielded 95% CIs (2.91–51.4) consistent with the primary Cox estimates.

Plasma Aβ(+) participants also showed a higher frequency of conversion to MCI due to AD (5/34, 14.7% vs. 3/130, 2.3%; $p=0.007$) and a significantly higher cumulative probability of conversion over time (log-rank $p=0.002$; Fig. 2B). Moreover, positive baseline plasma Aβ42/Aβ40 status was associated with an increased risk of conversion during follow-up (unadjusted HR = 7.21, 95% CI 1.72–30.18, $p=0.007$), independent of age, sex, APOE ε4 status, and baseline Aβ-PET burden (adjusted HR = 9.50, 95% CI 1.98–45.65, $p=0.005$). In this case,

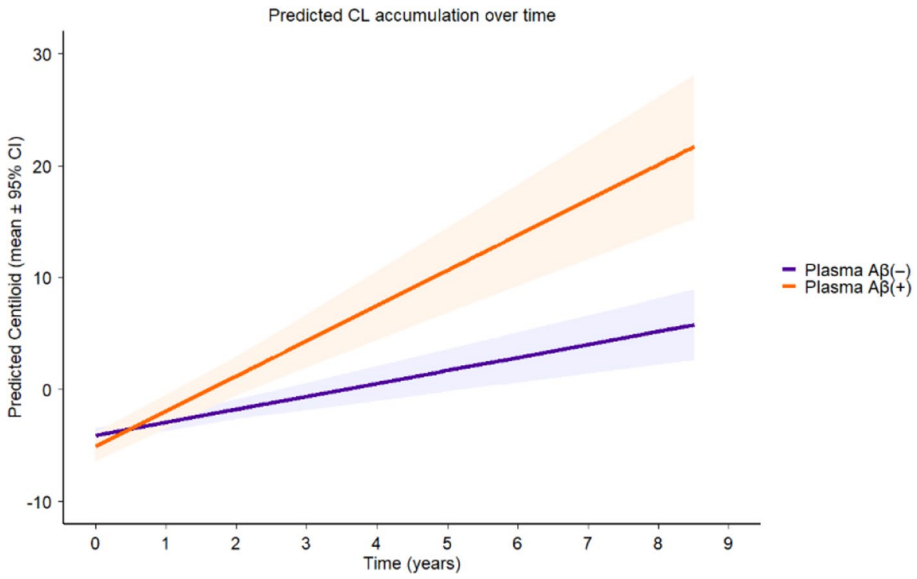

Fig. 1 Longitudinal trajectories of Aβ-PET burden according to baseline plasma Aβ42/Aβ40 status. Predicted Centiloid (CL) values over time (years) derived from linear mixed-effects models are shown for plasma Aβ(−) and plasma Aβ(+) groups. Solid lines represent model-estimated mean trajectories, and shaded areas indicate 95% confidence intervals

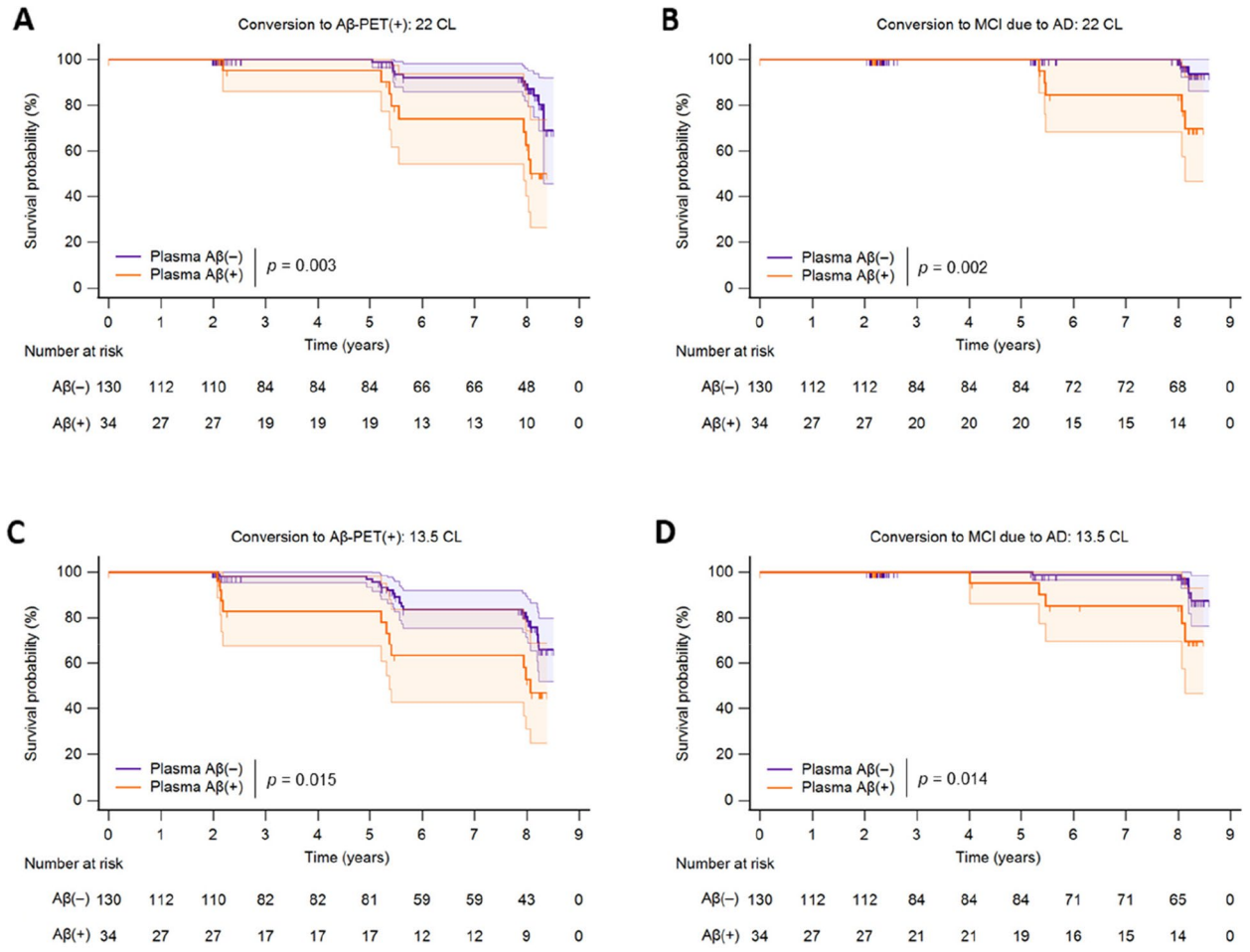

Fig. 2 Kaplan–Meier curves for conversion to Aβ-PET(+) and MCI due to AD. Curves show the fraction of participants remaining Aβ-PET(–) (**A** and **C**) or remaining SCD and Aβ-PET(–) (**B** and **D**) according to plasma Aβ42/Aβ40 status. Panels **A** and **B** correspond to the conservative cutoff of amyloid positivity (22 CL) while panels **C** and **D** correspond to the early cutoff of amyloid positivity (13.5 CL). Plasma Aβ(–) and plasma Aβ(+) groups were defined based on a baseline plasma Aβ42/Aβ40 cutoff of 0.241. Vertical tick marks on lines indicate censored observations. Log-rank test p-values are shown. Tables below the plots display the number of participants at risk of conversion at each time point

after bootstrap resampling, the 95% CI was wide (1.49–155.44) due to a low number of events, although the effect remained consistent.

Early amyloid threshold

Survival analyses were repeated using an early threshold for conversion to Aβ-PET(+) (13.5 CL). In this case, 31 individuals converted to Aβ-PET(+) during the follow-up: 20/130 (15.4%) in the plasma Aβ(−) group and 11/34 (32.4%) in the plasma Aβ(+) group ($p=0.018$). Kaplan–Meier curves demonstrated a higher cumulative probability of conversion among plasma Aβ(+) individuals (log-rank $p=0.015$; Fig. 2C). In addition, plasma Aβ(+) status was associated with an increased risk of conversion to Aβ-PET(+) (HR = 2.42, 95% CI 1.16 − 5.07, $p=0.019$), which remained significant after adjustment for covariates (HR = 3.93, 95% CI 1.69 − 9.11, $p=0.001$). Bootstrap-derived CI (95% CI 1.58–15.97) supported the robustness of the association.

Conversion to MCI due to AD was also more frequent in the plasma Aβ(+) group (5/34, 14.7%) than in the plasma Aβ(−) group (5/130, 3.9%; $p=0.024$) when the early cutoff of conversion was considered. Kaplan–Meier analysis showed significant differences in time to conversion between groups (log-rank $p=0.014$; Fig. 2D) and

Cox models indicated an increased risk for future conversion to MCI due to AD in the plasma Aβ(+) group (unadjusted HR = 4.17, 95% CI 1.21–14.41, p = 0.024; adjusted HR = 7.11, 95% CI 1.67–30.29, $p = 0.008$). Again, bootstrap CI were wide (95% CI: 1.12–108.32) due to the low number of events, but the effect remained consistent.

Table 3 summarizes conversion frequencies and Cox analyses using both the conservative (22 CL) and early (13.5 CL) amyloid positivity thresholds.

Conversion to all-cause MCI

For all-cause MCI conversion, the primary predictor (plasma Aβ group) satisfied the proportional hazards assumption ($p = 0.39$), whereas deviations were observed for age ($p = 0.005$) and APOE genotype ($p = 0.028$), yielding a significant global test. As these variables were included as adjustment covariates and the main exposure fulfilled the proportional hazards assumption, estimates for the association between plasma status and all-cause MCI were interpreted with caution but considered informative.

Conversion to all-cause MCI occurred in 30/130 (23.1%) plasma Aβ(−) participants and 6/34 (17.6%) plasma Aβ(+) participants (Supplementary Table 2). Between-group differences in conversion rates were not statistically significant ($p = 0.542$). Consistent with this, time-to-event analyses showed no evidence of group differences in Kaplan–Meier estimates (log-rank $p = 0.722$; Supplementary Fig. 2) or in Cox regression models (unadjusted HR = 0.85, 95% CI 0.36–2.05, $p = 0.722$; adjusted HR = 0.80, 95% CI 0.32–1.99, $p = 0.633$).

Implications for clinical trial enrichment

Based on the combined diagnostic and prognostic findings of this study, we next explored the potential clinical utility of plasma Aβ42/Aβ40 as a first-line screening tool to support recruitment for clinical trials. Specifically, we integrated the results of the ROC analysis performed in the full cohort at baseline [13] with the longitudinal analyses conducted in Aβ-PET(−) individuals to illustrate how plasma testing could be incorporated into real-world trial enrichment strategies (Fig. 3).

In the full cohort of 200 individuals with SCD, baseline plasma Aβ42/Aβ40 would stratify participants into 135 plasma Aβ(−) (67.5%) and 65 plasma Aβ(+) (32.5%) individuals [25]. Given the high negative predictive value

Table 3 Conversion rates and survival analyses by plasma Aβ status

		Conservative threshold for Aβ-PET positivity (> 22.0 CL)					**Early threshold for Aβ-PET positivity (> 13.5 CL)**				
		Plasma Aβ(–) (n = 130)	**Plasma Aβ(+) (n = 34)**	**Conversion status**	**Cox analysis**		**Plasma Aβ(–) (n = 130)**	**Plasma Aβ(+) (n = 34)**	**Conversion status**	**Cox analysis**	
		n (%)	**n (%)**	***p*-value***	**HR (95% CI)**	***p*-value**	**n (%)**	**n (%)**	***p*-value***	**HR (95% CI)**	***p*-value**
Conversion to Aβ-PET(+)	Withdrawals	18 (13.9)	7 (20.6)	**0.007**	6.86 (2.45—19.20)	**< 0.001**	18 (13.9)	7 (20.6)	**0.018**	3.93 (1.69—9.11)	**0.001**
	Converters	12 (9.2)	9 (26.5)				20 (15.4)	11 (32.4)			
	Non-Converters	100 (76.9)	18 (52.5)				92 (70.8)	16 (47.1)			
Conversion to MCI due to AD	Withdrawals	18 (13.9)	7 (20.6)	**0.007**	9.50 (1.98—45.65)	**0.005**	18 (13.9)	7 (20.6)	**0.024**	7.11 (1.67—30.29)	**0.008**
	Converters	3 (2.3)	5 (14.7)				5 (3.9)	5 (14.7)			
	Non-Converters	109 (76.9)	22 (64.7)				107 (82.3)	22 (64.7)			

Conversion counts to Aβ-PET(+) and to MCI due to AD are presented as n (%) with percentages calculated, using the total number of participants in each group

*P-values in the "conversion status" column correspond to Fisher's exact test comparing converters versus non-converters among participants with available follow-up data (withdrawals excluded). Cox regression models (HR with 95% CI) adjusted for age, sex, APOE-ε4 status and baseline Aβ-PET (CL) are depicted. Results are presented for both conservative and early thresholds used for defining conversion to Aβ-PET(+)

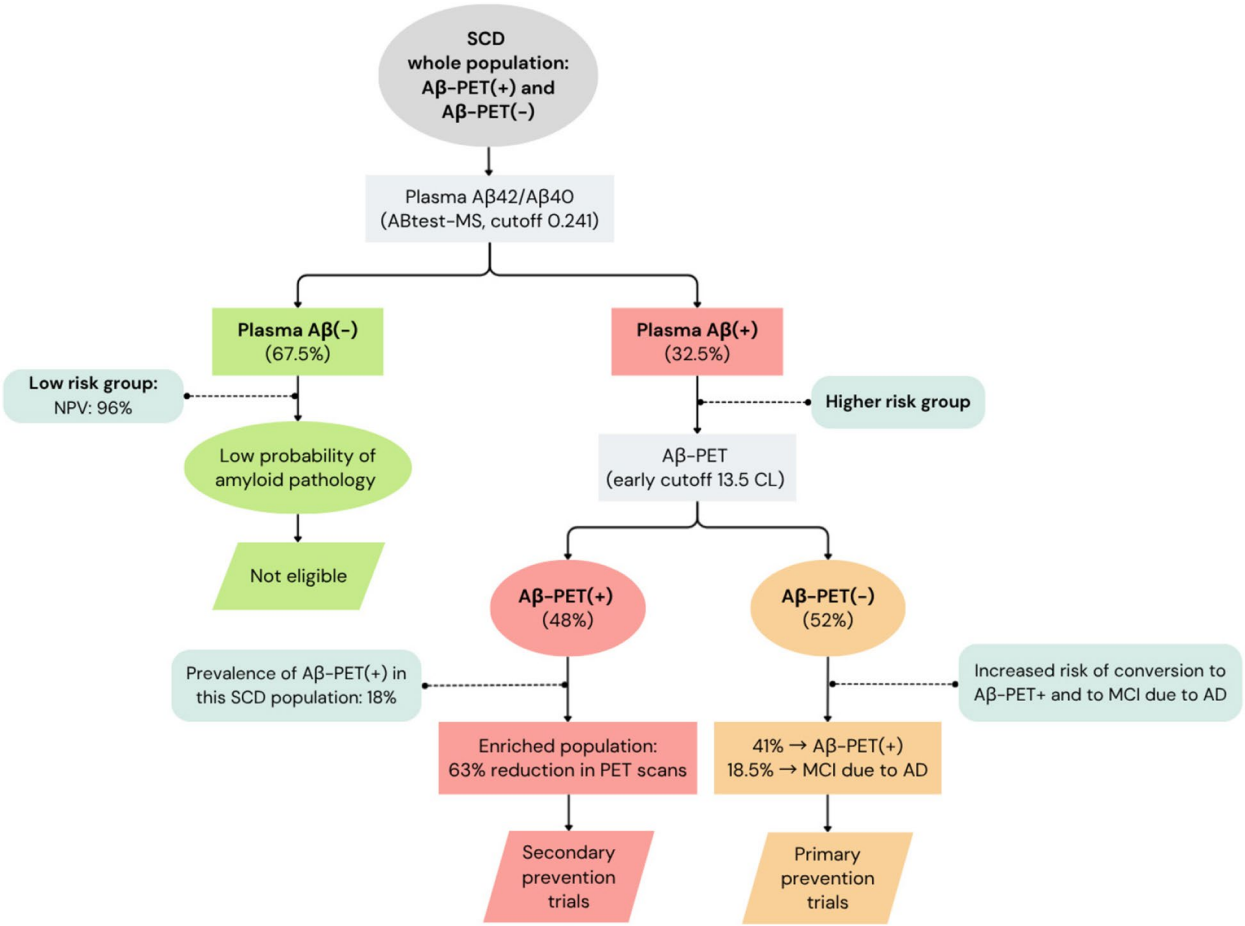

Fig. 3 Plasma-based screening strategy for recruitment in primary and secondary prevention clinical trials. Proposed stepwise screening strategy using plasma Aβ42/Aβ40 to enrich clinical trial populations and optimize Aβ-PET utilization

(NPV) of the plasma assay (96%), the large majority of plasma Aβ(−) participants would be correctly classified as amyloid-negative. These ruled-out individuals would therefore be unlikely to exhibit imminent amyloid pathology and may not require further biomarker-based screening at this stage.

Among the plasma Aβ(+) subjects, Aβ-PET imaging would confirm cerebral amyloid deposition in 31 individuals (31/65: 48% plasma true positives). This stepwise strategy would substantially enrich the population in Aβ-PET(+) individuals. Compared with an alternative direct PET-based screening strategy, which would require approximately 172 scans to identify 31 amyloid-positive individuals based on the observed prevalence (18%), plasma prescreening would reduce PET utilization by about 63%. These amyloid-positive individuals would represent optimal candidates for secondary prevention trials targeting downstream pathological processes.

On the other hand, 34 plasma Aβ(+) individuals (34/65: 52%) would test Aβ-PET(−) at baseline. Despite the absence of detectable cortical amyloid pathology, this group would exhibit a substantially increased risk of future progression, compared to plasma Aβ(−). Among those with longitudinal PET follow-up (n = 27, Table 2), 41% (11/27) converted to Aβ-PET(+) and 18.5% (5/27) progressed to MCI due to AD. These individuals would therefore constitute a high-risk preclinical population, detectable through the plasma Aβ42/Aβ40 analysis, suitable for primary prevention strategies aimed at delaying or preventing amyloid accumulation.

Discussion

In this 8-year longitudinal study of individuals with SCD from the FACEHBI cohort, we specifically focused on those with negative baseline Aβ-PET status, defined using an early amyloid deposition threshold of 13.5 CL. Our analyses showed that, within this Aβ-PET(–) population, plasma Aβ(+) participants exhibited steeper longitudinal increases in cortical amyloid burden, along with a significantly higher risk of conversion to Aβ-PET(+) and to MCI due to AD. These findings suggest that plasma Aβ42/Aβ40 positivity identified individuals in early amyloid transition despite PET negativity. Importantly, in a screening context for clinical trials, assessing plasma Aβ42/Aβ40 as an initial step may help rule out individuals at low risk of amyloid pathology, reducing the number of PET scans required to identify Aβ-PET(+) individuals. Furthermore, this approach might optimize selection for primary prevention trials by identifying those at higher risk of future progression, rather than assuming that all Aβ-PET(−) participants have the same risk.

The use of 13.5 CL to define the Aβ-PET(−) group is based on previous evidence from FBB-PET showing that this threshold captures the earliest stages of amyloid deposition and is therefore suitable for identifying individuals with emerging Aβ pathology [32]. This threshold has been previously applied in the FACHEBI cohort [13, 25] and is consistent with other studies supporting values around 12 CL as indicative of early amyloid-related changes. For example, La Joie et al. [34], optimally detected Consortium to Establish a Registry for Alzheimer's Disease (CERAD) moderate-to-frequent neuritic plaques at a cutoff of 12.2 CL. Salvadó et al., reported optimal agreement with CSF Aβ42 at 12 CL and proposed this value as a transition point between absent and subtle amyloid pathology [35]. Similarly, Milà-Alomà et al., subsequently used a threshold of≥12 CL to identify CU individuals with early Aβ aggregation [36].

The objective of the present study was to assess whether plasma Aβ42/Aβ40 was associated with subsequent amyloid outcomes independently of baseline cortical amyloid burden. In our cohort, plasma Aβ(−) and plasma Aβ(+) groups had comparable baseline CL levels, suggesting that both groups were at a similar initial stage of cortical amyloid pathology detectable by PET. Nevertheless, baseline CL levels were systematically accounted for in all analyses.

When examining the association between baseline plasma Aβ42/Aβ40 and baseline CL with subsequent cortical amyloid changes, the standardized effect size of plasma exceeded that of baseline PET across the Aβ-PET(−) spectrum. Both variables were associated with amyloid accumulation in populations including higher CL levels (≤13.5,≤22 and≤30 CL), suggesting that they may capture partially distinct components of the amyloid process. However, in individuals with very low baseline amyloid levels (≤5 and≤10 CL), baseline CL values were not associated with future accumulation. Baseline plasma Aβ remained associated, even after adjusting for baseline PET burden, reflecting an earlier change in plasma. Consistently, plasma Aβ(+) individuals exhibited a significantly faster rate of amyloid deposition than plasma Aβ(−) participants, diverging over time despite their comparable baseline cortical burden assessed by Aβ-PET. This pattern is consistent with an accelerated pathological process within the plasma Aβ(+)/PET(−) group and supports the notion that plasma Aβ42/Aβ40 captures very early amyloid changes that are not yet detectable with conventional PET, suggesting that it may act as an earlier biomarker of incipient amyloid pathology than PET imaging.

Consistently, plasma Aβ(+) status was associated with a higher risk of conversion to Aβ-PET(+) and to MCI due to AD. These associations remained statistically significant after adjustment for demographics and baseline CL levels. The persistence of the plasma effect, even adjusting for baseline Aβ-PET, indicates that the association of plasma Aβ status with conversion is independent of baseline amyloid burden as measured by PET. Furthermore, the absence of a significant interaction between plasma status and baseline amyloid burden suggests that the plasma association is comparable across the full spectrum of Aβ-PET(–) individuals. Importantly, similar associations were observed when conversion to Aβ-PET(+) was either defined using a broadly used cutoff for abnormal Aβ-PET (22 CL) or an earlier (13.5 CL) threshold. Conversion to 22 CL reflects a more advanced stage of amyloid accumulation, indicating that baseline plasma Aβ42/Aβ40 identifies individuals at risk of reaching

clinically relevant levels of amyloid burden. Notably, the persistence of the association when using the lower 13.5 CL threshold further indicates that plasma Aβ42/Aβ40 is informative of increased risk of early conversion.

Taken together, these results suggest that plasma Aβ42/Aβ40 captures early dynamic aspects of amyloid pathology that are not fully reflected by Aβ-PET. Rather than merely mirroring subtle baseline cortical differences, plasma positivity appears to identify a biologically active transitional stage characterized by accelerated amyloid accumulation and a greater likelihood of clinical progression. Plasma Aβ42/Aβ40 showed no association with conversion to all-cause MCI, which was not unexpected, as the plasma-based tool used is specifically related to cerebral amyloid pathology. In our cohort, 72% of individuals who converted to all-cause MCI did not exhibit amyloid positivity on Aβ-PET imaging during follow-up, suggesting predominantly non-AD etiologies. Accordingly, the lack of association with all-cause MCI likely reflects outcome heterogeneity rather than limited performance of the plasma biomarker.

Direct comparison of our findings with previous studies is challenging due to differences in the thresholds used to define Aβ-PET(−) and conversion to Aβ-PET(+). Nevertheless, other studies have reported results consistent with ours. In a cohort composed predominantly of CU individuals, Schindler et al. [12] showed that participants with a negative baseline amyloid PET scan (SUVR < 1.42 for Pittsburgh Compound B (PiB) and < 1.22 for AV45) but positive plasma Aβ42/Aβ40 had a 15-fold greater risk of subsequent conversion to PET positivity than those with negative plasma levels. Similarly, Janelidze et al. [27] reported that in CU participants with subthreshold baseline amyloid burden (< 40 CL), plasma Aβ42/Aβ40 levels were associated with longitudinal increases in Aβ-PET signal. They also found significant associations when lower (< 20 CL and < 12 CL) Aβ-PET thresholds were applied, but with smaller effect sizes. More recently, Feizpour et al. [8] reported across three international cohorts that plasma Aβ42/Aβ40 positivity predicted PET conversion in CU individuals with very low baseline amyloid levels (< 5 CL), although no added predictive value was observed in those with higher subthreshold levels (5–20 CL). By focusing on individuals with SCD and using a low-burden threshold to identify Aβ-PET(–) individuals, our study extends these findings by showing that plasma Aβ42/Aβ40 is associated with accelerated amyloid accumulation.

Importantly, we additionally examined clinical progression from SCD to MCI due to AD as a downstream outcome to evaluate whether plasma Aβ42/Aβ40 screening status relates not only to underlying amyloid pathology, but also to subsequent clinical disease expression. Plasma Aβ(+) individuals showed a higher risk of progression to MCI due to AD compared with plasma Aβ(−), supporting the clinical relevance of this biomarker-based stratification beyond its association with amyloid burden. In this context, progression to MCI due to AD represents a clinically defined stage consistent with underlying AD pathology, thereby providing evidence that plasma Aβ-based screening captures individuals at increased risk of clinically manifest disease. While prior longitudinal studies have linked plasma Aβ42/Aβ40 to cognitive decline and clinical conversion in CU individuals, these have largely been conducted in mixed amyloid populations [37–39]. To our knowledge, no prior longitudinal studies have specifically assessed clinical progression from CU/SCD to MCI in cohorts restricted to Aβ-PET(−) individuals; however, these findings warrant replication in larger cohorts, particularly given the low number of conversion events in our study.

Longitudinal modeling of amyloid trajectories has suggested that plasma Aβ alterations may precede measurable brain amyloid accumulation by Aβ-PET [15, 16]. In a natural history analysis, Burnham et al. [40] reported that the trajectory of plasma Aβ preceded that of Aβ-PET by a median of approximately six years, suggesting that plasma changes may arise before conventional PET positivity. More recently, Cánovas et al. [41] described a steep decline in plasma Aβ42/Aβ40 occurring at an Aβ-PET burden of approximately 15 CL and characterized a transitional phase between 10 and 15 CL, with plasma abnormalities emerging slightly (~2 years) before PET reaches conventional positivity thresholds (20 CL). Notably, this transitional window overlaps closely with the early cutoff (13.5 CL) applied in our study to define PET negativity at baseline. Together, our findings are consistent with these observations and support the hypothesis that plasma Aβ42/Aβ40 captures early biological shifts that precede the initial phases of PET-detectable amyloid accumulation.

The present study focused exclusively on plasma Aβ42/Aβ40. Other blood-based biomarkers, particularly p-tau217, have also emerged as promising tools in the field. However, within the framework of the amyloid cascade hypothesis, altered tau phosphorylation occurs downstream of initial amyloid deposition [42, 43]. Thus, as an earlier marker, plasma Aβ42/Aβ40 may be particularly well suited to detect incipient changes during the earliest phases of the disease. In line with this, Feizpour et al. [8] have suggested that plasma Aβ42/Aβ40 may better capture *future* amyloid positivity due to its earlier trajectory, whereas p-tau217 may be more effective for pre-screening in trials targeting *current* pathology. Similarly, Schindler et al. [44] reported that among individuals with low PET burden (≤20 CL), Aβ42/Aβ40 levels showed the strongest association with low levels of cortical amyloid compared with other leading plasma biomarkers, including p-tau217. Using the same threshold to define Aβ-PET amyloid status (20 CL), Gogola et al. [45] found significant associations between baseline Aβ42/Aβ40 with future progression from Aβ-PET(−) to Aβ-PET(+) in individuals with plasma A(+) without dementia, but no significant associations were observed for p-tau217. Additionally, Cogswell et al. [9] observed no evidence of interaction when both biomarkers were included in the same models, supporting complementary rather than competing roles. This is consistent with additional studies suggesting that the combination of Aβ42/Aβ40 and p-tau217 may improve the prediction of Aβ-PET progression among Aβ(−) individuals [27, 46], in line with the concept that these biomarkers may capture distinct stages along the AD continuum, reflecting complementary aspects of early pathological processes [47]. Future studies directly comparing and integrating Aβ42/Aβ40 and p-tau217 within the same early PET–negative populations will be essential to clarify their respective contributions and determine whether combined approaches further enhance early risk stratification.

Finally, our findings have potential implications for trial design, particularly in the context of biomarker-based recruitment strategies in CU individuals. As disease-modifying therapies increasingly target early stages of AD [48], the identification of CU individuals at the highest risk of progression has become a central objective of prevention trials. In this regard, the high NPV observed in our cohort supports the use of plasma Aβ42/Aβ40 as a practical rule-out biomarker of cortical amyloid pathology. Excluding individuals unlikely to harbor significant amyloid pathology at the time of screening allows PET imaging to be applied in a more targeted manner, substantially reducing the logistical and economic burden associated with PET-based recruitment. Individuals with concordant plasma Aβ(+)/PET(+) profiles would represent candidates for secondary prevention trials targeting downstream disease mechanisms.

Of particular relevance, however, are plasma Aβ(+)/PET(–) individuals. In the absence of plasma prescreening, these participants would typically be classified as amyloid-negative and excluded from amyloid-focused studies. Our longitudinal findings suggest that this group may represent a biologically active transitional stage characterized by increased risk of subsequent amyloid accumulation and clinical progression. These results support the value of plasma Aβ42/Aβ40-based screening as a tool for clinical trial enrichment, extending beyond the identification of amyloid-positive individuals to the enrichment of cohorts with a higher likelihood of subsequent clinical progression. The identification of such high-risk yet Aβ-PET(–) individuals may therefore open a window for primary prevention approaches, targeting the earliest detectable phase of amyloid dysregulation before conventional imaging thresholds are reached. Overall, these data support the integration of plasma Aβ42/Aβ40 as a first-line screening tool to optimize trial enrichment strategies, enhance the efficiency of PET-based screening, and enable the identification of individuals who may benefit from intervention at the very earliest stages of disease. Finally, this tool could also have potential utility in future clinical settings as a large-scale screening approach for CU individuals at risk of progression, as individuals with a positive plasma result could benefit from closer monitoring and/or earlier intervention.

CU individuals with biomarker evidence of amyloid pathology are conceptualized differently across current frameworks, including those proposed by the National Institute on Aging and the Alzheimer's Association [49], and the International Working Group [50]. However, these frameworks converge in not recommending a clinical diagnosis of AD in CU individuals on the basis of biomarker positivity alone. In this context, the present findings should be interpreted within a risk stratification and enrichment framework, aimed at identifying individuals at increased likelihood of early amyloid accumulation and subsequent clinical progression, rather than as a

diagnostic approach. These considerations are particularly relevant for the design of prevention and early intervention trials. In the future, if disease-modifying therapies demonstrate efficacy in the preclinical stage, current conceptual boundaries may require further refinement.

Several strengths of this study should be highlighted. First, plasma Aβ42/Aβ40 was quantified using a MS–based method, which is known to provide reliable performance in the quantification of Aβ peptides [51]. Second, the Aβ42/Aβ40 ratio is less affected by comorbid conditions such as renal dysfunction or body mass index than other plasma biomarkers associated with AD pathology, such as p-tau, neurofilament light chain (NfL), or glial fibrillary acidic protein (GFAP) [52, 53], supporting its suitability for investigating very early amyloid-related changes. Third, we focused on a cohort of Aβ-PET(–) individuals with SCD, a population characterized by self-perceived cognitive changes not yet detectable on standardized neuropsychological tests [54]. This group represents a particularly relevant stage for studying early pathological processes, as individuals who are within a potential window for preventive intervention. Fourth, the FACEHBI cohort was extensively characterized, and all samples were collected, processed, and analyzed at a single center following standardized protocols. This reduces inter-site variability and minimizes methodological heterogeneity unrelated to the underlying disease process. In addition, the longitudinal design included up to four Aβ-PET assessments per participant, providing a more detailed characterization of amyloid trajectories than is typically available in cohorts with only two imaging timepoints. Fifth, PET negativity at baseline was defined using an early and relatively stringent cutoff (13.5 CL), ensuring the inclusion of individuals with very low cortical amyloid burden and strengthening the focus on the earliest phases of amyloid accumulation. Finally, the association of plasma Aβ42/Aβ40 with longitudinal conversion to Aβ-PET(+) was evaluated using two complementary thresholds, a threshold reflecting a more advanced amyloid accumulation and an earlier threshold capturing very initial changes, confirming the robustness of our findings across the spectrum of amyloid progression.

Limitations

This study has several limitations that should be acknowledged. First, it was conducted in a single-center cohort of modest size composed exclusively of Caucasian individuals with SCD and relatively high educational attainment. Although this homogeneous design reduces methodological variability and potential confounding factors, it may limit the generalizability of the findings to more heterogeneous populations. Replication in larger, multicenter cohorts including individuals with diverse ethnic, educational, clinical and socioeconomic backgrounds will be necessary to confirm the robustness and external validity of the results, and assess their broader applicability to other settings.

In addition, the relatively low number of clinical progression events warrants cautious interpretation of the effect size estimates. This study was exploratory. The cutoff used in this cohort should be validated in independent cohorts to confirm its generalizability.

A MS−based assay was used to measure Aβ42/Aβ40. Although using this method has analytical advantages, its widespread implementation is somewhat limited due to technical complexity and accessibility, requiring centralized sample analyses in a reference laboratory.

Finally, the present analyses focused on plasma Aβ42/Aβ40 given its well-established role as an early marker of amyloid pathology. While this approach aligns with the objective of identifying individuals at the earliest stages of disease, future studies should assess whether the inclusion of additional amyloid-related biomarkers, such as p-tau217, further improves risk prediction or refines stratification models.

Conclusion

Our study shows that plasma Aβ42/Aβ40 detects emerging amyloid pathology in Aβ-PET(−) SCD individuals, suggesting the notion that plasma alterations precede detectable changes on PET imaging. Plasma Aβ(+)/PET(−) individuals, who are at a higher risk of developing cortical amyloid pathology and subsequent cognitive decline, appear to represent an early amyloid transitional stage, in which pathological processes are already underway but not yet captured by PET imaging. Our results further support the potential use of plasma Aβ42/Aβ40 as a first-step screening tool for clinical trials, with plasma Aβ(+)/PET(−) individuals representing particularly suitable candidates for primary prevention approaches targeting the earliest detectable phase of amyloid accumulation.

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Authors' contributions NF analysed and interpreted the data, contributed to the study concept and design, performed the statistical analysis and drafted the manuscript. MP analysed and interpreted the data, substantially contributed to the study concept and design, and substantively revised the manuscript for intellectual content. LS acquired and interpreted the data and revised the manuscript for intellectual content. JL, JPT, AS, OSG and AC interpreted the data and revised the manuscript for intellectual content. JT, MA, LLT, MJG, AR, XM, MB and MM substantially contributed to the study concept and design and substantively revised the manuscript for intellectual content. JAA: acquired, analysed and interpreted the data, substantially contributed to the study concept and design, and substantively revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate All participants gave written informed consent according to the principles of the Declaration of Helsinki. The FACEHBI, FACEHBI-2 and FACEHBI-3 study protocols (which included visits 0, 1 and 2, visits 3, 4 and 5, and visits 6, 7, and 8 respectively) were approved by the ethics committee of the Hospital Clínic i Provincial and Hospital Universitari de Bellvitge (Barcelona, Spain), respectively.

Consent for publication Not applicable.

Competing interests NF, MP, LS, JL and JAA are full-time employees of Araclon Biotech-Grifols. JT is a full-time employee of Grifols.
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References

1. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. Alzheimers Dement. 2015;12(3):292–323.
2. Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207–16.
3. Sperling R, Mormino E, Johnson K. The evolution of preclinical Alzheimer's disease: implications for prevention trials. Neuron. 2014;84(3):608–22.
4. McDade E, Bateman RJ. Stop Alzheimer's before it starts. Nature. 2017;547(7662):153–5.
5. Aisen PS, Jimenez-Maggiora GA, Rafii MS, Walter S, Raman R. Early-stage Alzheimer disease: getting trial-ready. Nat Rev Neurol. 2022;18(7):389–99.
6. Hampel H, Au R, Mattke S, van der Flier WM, Aisen P, Apostolova L, et al. Designing the next-generation clinical care pathway for Alzheimer's disease. Nat Aging. 2022;2(8):692–703.
7. Ashton NJ, Pascoal TA, Karikari TK, Benedet AL, Lantero-Rodriguez J, Brinkmalm G, et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. Acta Neuropathol. 2021;141(5):709–24.
8. Feizpour A, Doré V, Bourgeat P, Doecke JD, Canovas R, Laws SM, et al. Plasma Aβ42/40 predicts progression from Aβ-amyloid negative to positive PET scans. J Prev Alzheimers Dis. 2026;13(2):100455.
9. Cogswell PM, Wiste HJ, Weigand SD, Therneau TM, Griswold ME, Braunstein JB, et al. Plasma Alzheimer's disease biomarker relationships with incident abnormal amyloid PET. Alzheimers Dement. 2025;21(2):e14629.
10. Palmqvist S, Janelidze S, Stomrud E, Zetterberg H, Karl J, Zink K, et al. Performance of fully automated plasma assays as screening tests for Alzheimer disease-related β-amyloid status. JAMA Neurol. 2019;76(9):1060–9.
11. Winston CN, Langford O, Levin N, Raman R, Yarasheski K, West T, et al. Evaluation of Blood-Based Plasma Biomarkers as Potential Markers of Amyloid Burden in Preclinical Alzheimer's Disease. J Alzheimers Dis. 2023;92(1):95–107.
12. Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Li Y, Gordon BA, et al. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. Neurology. 2019;93(17):e1647–59.
13. Pascual-Lucas M, Allué JA, Sarasa L, et al. Clinical performance of an antibody-free assay for plasma Aβ42/Aβ40 to detect early alterations of Alzheimer's disease in individuals with subjective cognitive decline. Alzheimers Res Ther. 2023;15(1):2.
14. Allué JA, Pascual-Lucas M, Sarasa L, Castillo S, Sarasa M, Sáez ME, et al. Clinical utility of an antibody-free LC-MS method to detect brain amyloid deposition in cognitively unimpaired individuals from the screening visit of the A4 Study. Alzheimers Dement (Amst). 2023;15(2):e12451.
15. Palmqvist S, Insel PS, Stomrud E, Janelidze S, Zetterberg H, Brix B, et al. Cerebrospinal fluid and plasma biomarker trajectories with increasing amyloid deposition in Alzheimer's disease. EMBO Mol Med. 2019;11(12):e11170.
16. Hansson O. Biomarkers for neurodegenerative diseases. Nat Med. 2021;27(6):954–63.
17. Rabe C, Bittner T, Jethwa A, Suridjan I, Manuilova E, Friesenhahn M, et al. Clinical performance and robustness evaluation of plasma amyloid-β42/40 prescreening. Alzheimers Dement. 2023;19(4):1393–402.
18. Palmqvist S, Stomrud E, Cullen N, Janelidze S, Manuilova E, Jethwa A, et al. An accurate fully automated panel of plasma biomarkers for Alzheimer's disease. Alzheimers Dement. 2023;19(4):1204–15.
19. Martínez-Dubarbie F, Guerra-Ruiz A, López-García S, Lage C, Fernández-Matarrubia M, Infante J, et al. Accuracy of plasma Aβ40, Aβ42, and p-tau181 to detect CSF Alzheimer's pathological changes in cognitively unimpaired subjects using the Lumipulse automated platform. Alzheimers Res Ther. 2023;15(1):163.
20. Kirmess KM, Meyer MR, Holubasch MS, Knapik SS, Hu Y, Jackson EN, et al. The PrecivityAD™ test: Accurate and reliable LC-MS/MS assays for quantifying plasma amyloid beta 40 and 42 and apolipoprotein E proteotype for the assessment of brain amyloidosis. Clin Chim Acta. 2021;519:267–75.
21. West T, Kirmess KM, Meyer MR, Holubasch MS, Knapik SS, Hu Y, et al. A blood-based diagnostic test incorporating plasma Aβ42/40 ratio, ApoE proteotype, and age accurately identifies brain amyloid status: findings from a multi cohort validity analysis. Mol Neurodegener. 2021;16(1):30.
22. Allué JA, Sarasa L, Fandos N, Gonzalo R, Sabido-Vera R, Loscos J, et al. Clinical validation of a plasma-based antibody-free LC-MS method for identifying CSF amyloid positivity in mild cognitive impairment. Front Aging Neurosci. 2025;17:1681516.
23. Palmqvist S, Mattsson N, Hansson O, Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid analysis detects cerebral amyloid-β accumulation earlier than positron emission tomography. Brain. 2016;139(4):1226–36.
24. Li Y, Yen D, Hendrix RD, Gordon BA, Dlamini S, Barthélemy NR, et al. Timing of biomarker changes in sporadic Alzheimer's disease in estimated years from symptom onset. Ann Neurol. 2024;95(5):951–65.
25 Fandos N, Pascual-Lucas M, Sarasa L, Terencio J, Sáez ME, Tartari JP, et al. Plasma Aβ42/Aβ40 determined by mass spectrometry is associated with longitudinal changes in amyloid accumulation, brain atrophy, and conversion to mild cognitive impairment due to Alzheimer's disease in individuals with subjective cognitive decline: 5-year follow-up of the FACEHBI cohort. J Prev Alzheimers Dis. 2026;13(3):100465.

26. Pereira JB, Janelidze S, Stomrud E, Palmqvist S, van Westen D, Dage JL, et al. Plasma markers predict changes in amyloid, tau, atrophy and cognition in non-demented subjects. Brain. 2021;144(9):2826–36.
27. Janelidze S, Barthélemy NR, Salvadó G, Schindler SE, Palmqvist S, Mattsson-Carlgren N, et al. Plasma phosphorylated Tau 217 and Aβ42/40 to predict early brain Aβ accumulation in people without cognitive impairment. JAMA Neurol. 2024;81(9):947–57.
28. Cullen NC, Leuzy A, Janelidze S, Palmqvist S, Svenningsson AL, Stomrud E, et al. Plasma biomarkers of Alzheimer's disease improve prediction of cognitive decline in cognitively unimpaired elderly populations. Nat Commun. 2021;12(1):3555.
29. Verberk IMW, Slot RE, Verfaillie SCJ, Heijst H, Prins ND, van Berckel BNM, et al. Plasma Amyloid as Prescreener for the Earliest Alzheimer Pathological Changes. Ann Neurol. 2018;84(5):648–58.
30 Rodriguez-Gomez O, Sanabria A, Perez-Cordon A, et al. FACEHBI: A Prospective Study of Risk Factors, Biomarkers and Cognition in a Cohort of Individuals with Subjective Cognitive Decline. Study Rationale and Research Protocols. J Prev Alzheimers Dis. 2017;4(2):100–8.
31. Rowe CC, Doré V, Jones G, Baxendale D, Mulligan RS, Bullich S, et al. (18)F-Florbetaben PET beta-amyloid binding expressed in Centiloids. Eur J Nucl Med Mol Imaging. 2017;44(12):2053–9.
32. Bullich S, Roé-Vellvé N, Marquié M, Landau SM, Barthel H, Villemagne VL, et al. Early detection of amyloid load using 18F-florbetaben PET. Alzheimers Res Ther. 2021;13(1):67.
33. Jack CR Jr, Therneau TM, Weigand SD, Wiste HJ, Knopman DS, Vemuri P, et al. Prevalence of biologically vs clinically defined Alzheimer spectrum entities using the National Institute on Aging-Alzheimer's Association research framework. JAMA Neurol. 2019;76(10):1174–83.
34. La Joie R, Ayakta N, Seeley WW, Borys E, Boxer AL, DeCcarli C, et al. Multisite study of the relationships between antemortem [11C]PIB-PET Centiloid values and postmortem measures of Alzheimer's disease neuropathology. Alzheimers Dement. 2018;15(2):205–16.
35. Salvadó G, Molinuevo JL, Brugulat-Serrat A, Falcon C, Grau-Rivera O, Suárez-Calvet M, et al. Centiloid cut-off values for optimal agreement between PET and CSF core AD biomarkers. Alzheimers Res Ther. 2019;11(1):27.
36. Milà-Alomà M, Ashton NJ, Shekari M, Salvadó G, Ortiz-Romero P, Montoliu-Gaya L, et al. Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease. Nat Med. 2022;28(9):1797–1801. Erratum in: Nat Med. 2022;28(9):1965.
37. Cogswell PM, Wiste HJ, Therneau TM, Griswold ME, Mattsson-Carlgren N, Palmqvist S, et al. Association of plasma Alzheimer's disease biomarkers with cognitive decline in cognitively unimpaired individuals. Alzheimers Dement. 2025;21(9):e70625.
38. Trieu C, van Harten AC, van Leeuwenstijn MSSA, Schlüter LM, Boonkamp L, Aladdin A, et al. Longitudinal blood-based biomarkers and clinical progression in subjective cognitive decline. JAMA Netw Open. 2025;8(12):e2545862.
39. Shen XN, Li JQ, Wang HF, Li HQ, Huang YY, Yang YX, et al. Alzheimer's Disease Neuroimaging Initiative. Plasma amyloid, tau, and neurodegeneration biomarker profiles predict Alzheimer's disease pathology and clinical progression in older adults without dementia. Alzheimers Dement (Amst). 2020;12(1):eb12104.
40. Burnham SC, Fandos N, Fowler C, Pérez-Grijalba V, Dore V, Doecke JD, et al. Longitudinal evaluation of the natural history of amyloid-β in plasma and brain. Brain Commun. 2020;2(1):fcaa041.
41 Cánovas R, Cox T, Doré V, Bourgeat P, Fripp J, Feizpour A, et al. When Does Alzheimer's Disease Start? Plasma Aβ42/40 Assays Show Steep Changes at Aβ-PET Centiloid 15, Mean Age of 66 Years. Ann Neurol. 2026;99(5):1327–42.
42. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med. 2016;8(6):595–608.
43. Zou K, Abdullah M, Michikawa M. Current biomarkers for Alzheimer's disease: from CSF to blood. J Pers Med. 2020;10(3):85.
44. Schindler SE, Petersen KK, Saef B, Tosun D, Shaw LM, Zetterberg H, et al. Head-to-head comparison of leading blood tests for Alzheimer's disease pathology. Alzheimers Dement. 2024;20(11):8074–96.
45. Gogola A, Cohen AD, Lopresti BJ, Ikonomovic MD, Snitz B, Tudorascu D, et al. Plasma amyloid-β predicts amyloid-β accumulation in PET A- non-demented participants. J Alzheimers Dis. 2026;110(3):1166–74.
46. Rissman RA, Langford O, Raman R, Donohue MC, Abdel-Latif S, Meyer MR, et al. Plasma Aβ42/Aβ40 and phospho-tau217 concentration ratios increase the accuracy of amyloid PET classification in preclinical Alzheimer's disease. Alzheimers Dement. 2024;20(2):1214–24.
47. Kang H, Yoo H, Lee J, Yoon S, Zetterberg H, Blennow K, et al. Plasma phosphorylated tau 217 and amyloid-β 42/40 for amyloid risk in subgroups. Alzheimers Res Ther. 2025;17(1):184.
48. Rafii MS, Sperling RA, Donohue MC, Zhou J, Roberts C, Irizarry MC, et al. The AHEAD 3–45 study: design of a prevention trial for Alzheimer disease. Alzheimers Dement. 2023;19(4):1227–33.
49. Jack CR Jr, 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(8):2121–4.
50. Dubois B, Villain N, Schneider L, Fox N, Campbell N, Galasko D, et al. Alzheimer disease as a clinical-biological construct-an international working group recommendation. JAMA Neurol. 2024;81(12):1304–11.

51. Janelidze S, Teunissen CE, Zetterberg H, Allué JA, Sarasa L, Eichenlaub U, et al. Head-to-head comparison of 8 plasma amyloid-β 42/40 assays in Alzheimer disease. JAMA Neurol. 2021;78(11):1375–82.
52. Pichet Binette A, Janelidze S, Cullen N, Dage JL, Bateman RJ, Zetterberg H, et al. Confounding factors of Alzheimer's disease plasma biomarkers and their impact on clinical performance. Alzheimers Dement. 2023;19(4):1403–14.
53. Lehmann S, Schraen-Maschke S, Vidal JS, Allinquant B, Bombois S, Gabelle A, et al. Plasma Aβ42/Aβ40 ratio is independent of renal function. Alzheimers Dement. 2023;19(6):2737–9.
54. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement. 2014;10(6):844–52.

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