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BACKGROUND

Early detection of brain amyloid pathology is critical for the timely intervention in Alzheimer's disease (AD). Plasma Aβ biomarkers change early in the amyloid continuum, according to current evidence. The aim of this longitudinal study was to determine whether baseline plasma Aβ42/Aβ40 detects amyloid deposition before PET positivity.

METHODS

This study includes 164 Aβ-PET(−) (≤ 13.5 centiloids [CL]) individuals with subjective cognitive decline (SCD) from the Fundació ACE Healthy Brain Initiative (FACEHBI) cohort. Baseline plasma Aβ42/Aβ40 was measured using a mass-spectrometry based method (ABtest-MS, Araclon Biotech). Participants underwent ¹⁸F-Florbetaben PET at baseline, 2, 5, and 8 years, and annual clinical assessments up to 8 years. Participants were classified as plasma Aβ(+) or Aβ(−) using a cutoff value of 0.241 for plasma Aβ42/Aβ40. Differences in the rate of brain amyloid accumulation between plasma Aβ(+) and plasma Aβ(−) groups were assessed using linear mixed-effects models (LMEM). Progression to Aβ-PET positivity (cutoff 13.5 CL) or MCI due to AD (defined as incident MCI with concomitant Aβ-PET positivity) was evaluated based on plasma Aβ status using Kaplan-Meier and Cox proportional hazards models.

RESULTS

At baseline, plasma Aβ(+) (N=34) and plasma Aβ(−) (N=130) groups were comparable in MMSE score, APOE status, and CL values. Age and sex showed borderline differences between groups (**Table 1**). Among Aβ-PET(−) individuals, those with lower baseline Aβ42/Aβ40 ratio (plasma Aβ(+)) exhibited significantly higher rates of amyloid accumulation compared to plasma Aβ(−) subjects (interaction β = 1.99, 95% CI 1.12–2.86; P < 0.001), despite no significant differences in baseline CL values (**Figure 1**). Survival analyses confirmed earlier progression to Aβ-PET positivity (log-rank P = 0.015) and to MCI due to AD (log-rank P = 0.014) in plasma Aβ(+) participants (**Figure 2**). In Cox proportional hazards models adjusted for age, sex, APOE status, and baseline CL, plasma Aβ(+) status was associated with **increased risk of conversion to Aβ-PET positivity** (hazard ratio [HR] = 3.92, 95% CI 1.69–9.11, P = 0.001) **and to MCI due to AD** (HR = 7.11, 95% CI 1.67–30.29, P = 0.008). Integration of baseline ROC analysis¹ and longitudinal findings in Aβ-PET(−) individuals illustrates a potential plasma-based trial enrichment strategy (**Figure 3**).

1. 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.

	All participants (Aβ-PET−, n=164)	Plasma Aβ(−) (n=130)*	Plasma Aβ(+) (n=34)*	P-value†
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)	
Aβ-PET, CL	-3.73 [-7.97–1.70]	-4.08 [-8.23–1.50]	-2.14 [-6.16–5.07]	0.094
MMSE, score	29.0 [29.0–30.0]	29.0 [29.0–30.0]	29.0 [29.0–30.0]	0.836

Table 1.- Baseline characteristics of the study population. Data are shown as median [Q1–Q3] or n (%). *: Plasma Aβ(−) and Plasma Aβ(+) were defined using a threshold of 0.241. †: P values were obtained using Mann–Whitney U, χ², or Fisher's exact tests, as appropriate.

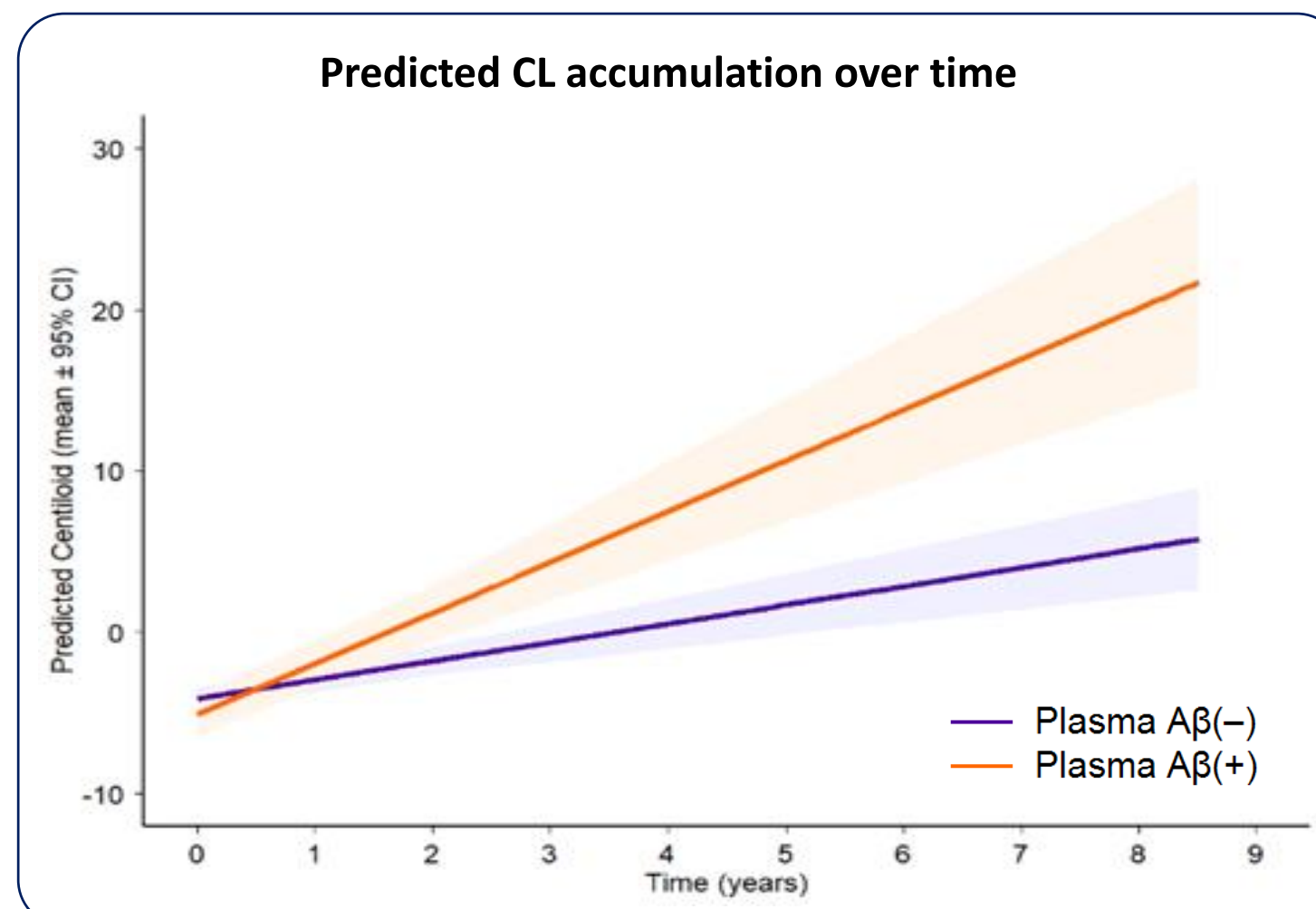


Figure 1.- Predicted longitudinal Aβ-PET burden (CL) according to baseline plasma Aβ42/Aβ40 status. Lines represent LM-estimated trajectories and shaded areas the 95% CI.

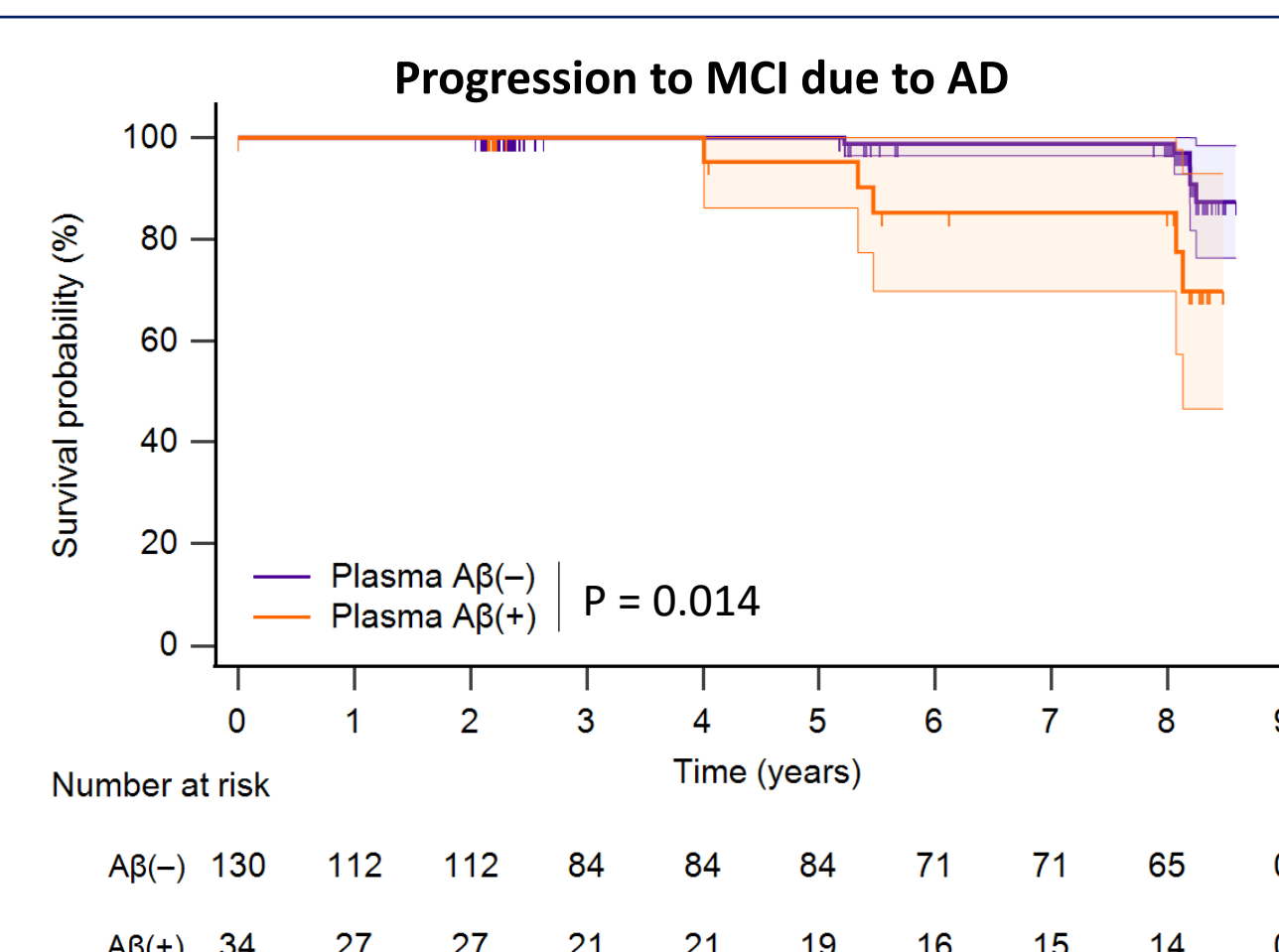
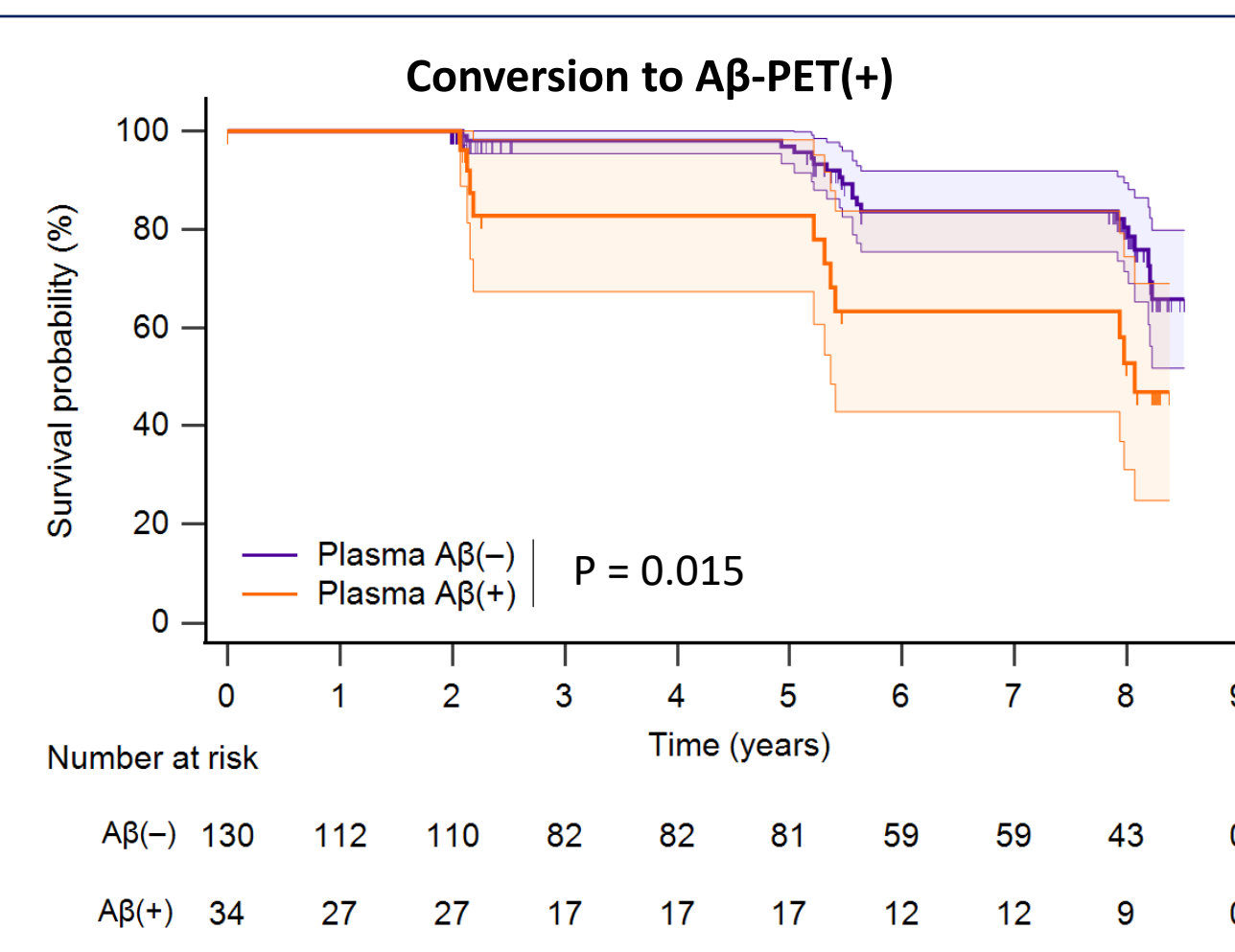


Figure 2.- Kaplan–Meier curves for conversion to Aβ-PET(+) (top) and MCI due to AD (bottom) according to plasma Aβ status.

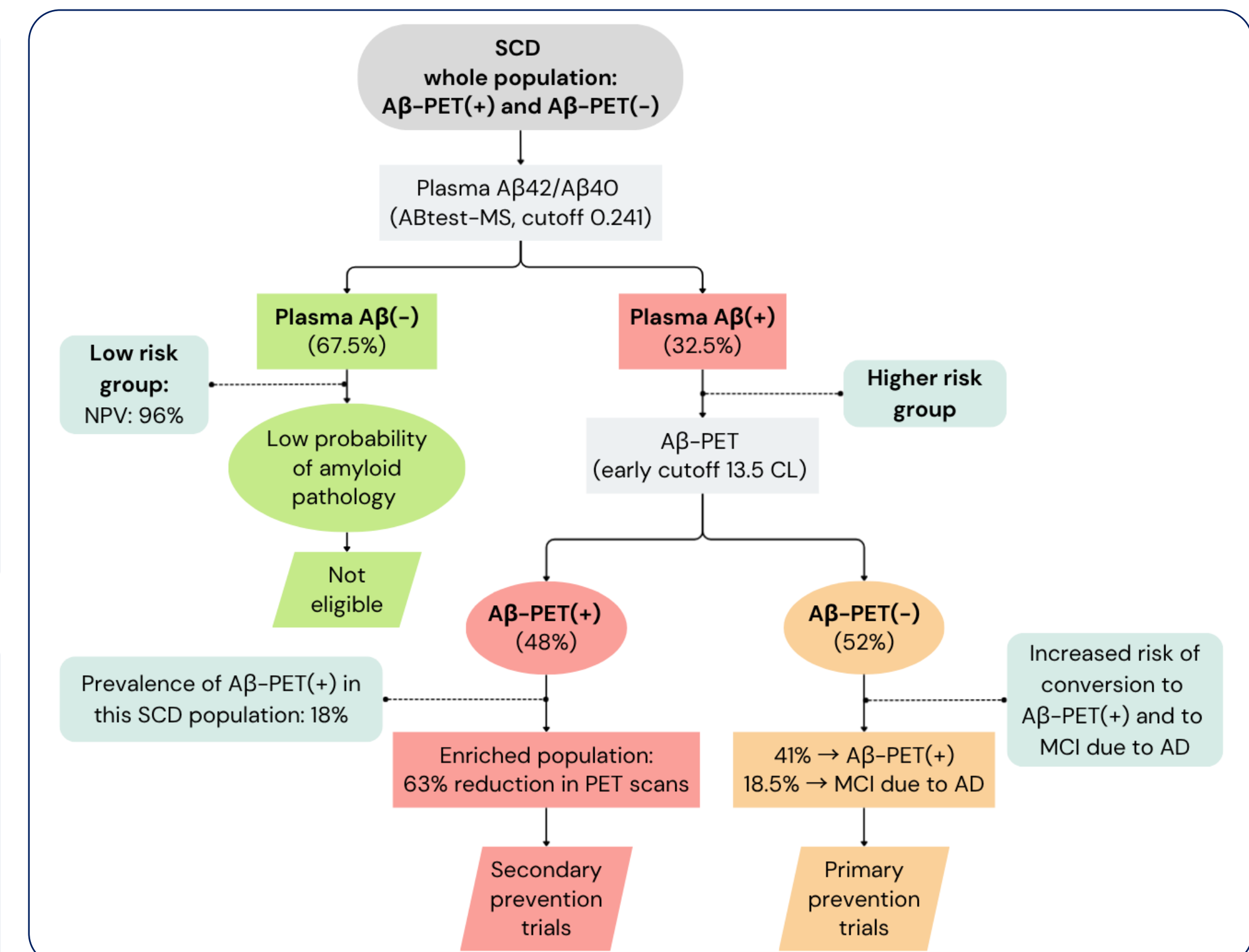


Figure 3. Plasma-based screening strategy for recruitment in primary and secondary prevention clinical trials. Plasma Aβ42/Aβ40 is used as a first-line screening tool in a cohort of SCD participants. Given its high negative predictive value, most plasma Aβ(−) individuals are correctly classified as amyloid pathology-negative and are therefore not eligible for AD clinical trials. Among plasma Aβ(+) individuals, Aβ-PET confirmation identifies candidates for secondary prevention trials, substantially reducing PET utilization. Importantly, plasma Aβ(+)/Aβ-PET(−) individuals represent a high-risk preclinical population with increased likelihood of future amyloid accumulation and clinical progression. This group is suitable for primary prevention strategies aimed at delaying or preventing amyloid accumulation.

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CONCLUSIONS

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.