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Letter to the Editor

Clarifying what BP Predicts: Commentary on CSF Aβ42/40, p-tau181, and centiloid in unimpaired populations

To the Editor,

We read the multicenter study by Osset-Malla et al. with great interest and commend the authors for assembling well-characterized, cognitively unimpaired cohorts and integrating CSF and amyloid-PET (Centiloid) to probe vascular–amyloid links before symptoms. Their harmonized models across ALFA+, EPAD-LCS, and AMYPAD-PNHS, with prespecified covariates and both cross-sectional and longitudinal analyses, make a timely and rigorous contribution to prevention research[1]. We offer the remarks below in a collegial spirit to further strengthen interpretation and clinical translation.

A notable strength is methodological consistency. Models are adjusted for age, sex, diabetes, antihypertensive medication, waist-to-hip ratio, and biomarker-acquisition interval, with sensitivity analyses for simpler specifications, which supports internal validity. Two patterns nonetheless warrant careful interpretation. Cross-sectionally, higher diastolic BP (DBP) is associated with lower CSF Aβ42 and p-tau181 in EPAD (and similarly in ALFA+), whereas pulse pressure (PP) tends to track higher CSF Aβ42; however, DBP–CSF associations attenuate after adjusting for CSF Aβ40, suggesting effects on CSF dynamics rather than canonical AD pathology [2].

On PET, AMYPAD shows that higher baseline SBP/PP relates to higher CL burden and higher baseline DBP aligns with CL increases over time; yet the pooled longitudinal meta-analysis is null, implying small effects or heterogeneity that merit targeted powering.

Measurement practice, however, could dilute signals. BP protocols differed—ALFA+ obtained two seated readings and analyzed the second, whereas EPAD generally had one reading and AMYPAD only single records for a subset—inviting nondifferential misclassification and complicating cross-cohort comparisons. Incorporating standardized devices, rest/posture periods, replicate readings, and ideally home/ambulatory BP would better capture PP and variability relevant to small-vessel injury [3].

A related implication is design clarity for incident change. The paper reports cohort-specific longitudinal findings (e.g., DBP and ΔCL in AMYPAD) but meta-analysis does not confirm a consistent slope across studies. Pre-registration of primary longitudinal endpoints, harmonized follow-up windows (with attention to the 12–50 CL "gray-zone" where accumulation is most dynamic), and power calculations anchored to expected effect sizes may sharpen inference [4].

Clinical translation will also benefit from treatment granularity. Antihypertensive use is modeled as a covariate, yet drug classes exert distinct cerebrovascular effects; stratification or interaction terms for RAAS blockers versus calcium-channel blockers, and for BP control status, could disentangle pharmacologic from hemodynamic pathways and guide trial prioritization.

Three pragmatic steps could accelerate prevention relevance. (i) Exposure harmonization: adopt unified clinic BP protocols and, where feasible, add ABPM/HBPM to quantify PP and variability.(ii) Mechanism-anchored modeling: ensure complete CSF panels with Aβ40 to test whether DBP relations reflect production/clearance, and evaluate causal pathways (e.g., PP → CSF dynamics → CL) via mediation analyses [5].(iii) Transportability: replicate in more diverse, higher-risk primary-care populations and prespecify actionable midlife targets for SBP/PP to inform biomarker-guided prevention trials.

In summary, this multimodal study links everyday BP to preclinical AD biology across independent platforms. By tightening measurement, distinguishing CSF dynamics from pathology, sharpening longitudinal design, and clarifying treatment context, the field can move from association toward actionable BP targets that plausibly delay amyloid accumulation before symptoms emerge.

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