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Original Article

Blood pressure and Alzheimer's disease biomarkers in cognitively unimpaired adults: a multicenter study

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ABSTRACT

Background: Hypertension is a modifiable risk factor for dementia, potentially influencing Alzheimer's disease (AD) pathology. Understanding this relationship is essential for developing interventions to reduce dementia risk.
Objectives: We investigated cross-sectional and longitudinal associations between blood pressure and AD biomarkers in cerebrospinal fluid (CSF) and amyloid (Aβ) positron emission tomography (PET) in cognitively unimpaired adults.
Design: Prospective observational study.
Setting: We analyzed data from cognitively unimpaired participants from three observational prospective European studies: ALFA+ (NCT02485730), EPAD-LCS (NCT02804789), and AMYPAD PNHS (EudraCT: 2018–002,277–22).
Measurements: ALFA+ participants had either CSF biomarkers (CSF Aβ42, Aβ40, p-tau181, t-tau) and/or Aβ PET data. EPAD participants had CSF biomarkers (CSF Aβ42, p-tau181, t-tau), and AMYPAD participants had Aβ PET data. All participants had available data about diabetes, use of hypertensive medication, and waist-to-hip ratio. Multivariable linear regression models were used to analyze cross-sectional associations between systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) with CSF biomarkers or Aβ PET (Centiloid units, CL); longitudinal associations were tested by means of delta CL scores between baseline and follow-up to assess Aβ PET changes over time.
Results: We included 405 participants from ALFA+ (mean age 61.1 years; 60 % female), 1104 from EPAD (mean age 64.8 years; 59.1 % female), and 340 from AMYPAD (mean age 71.8 years; 60 % female). In ALFA+, DBP was

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negatively associated with CSF Aβ40 ($p = 0.016$) and p-tau181 ($p = 0.050$), while there was a non-significant trend towards a positive association between SBP and CL over time ($p = 0.058$). In EPAD, DBP was negatively associated with CSF Aβ42 ($p < 0.001$) and p-tau181 ($p = 0.014$), while PP was positively associated with CSF Aβ42 ($p = 0.024$). In AMYPAD, SBP ($p = 0.002$) and PP ($p = 0.003$) were positively associated with CL at baseline, with a similar non-significant trend being found for DBP ($p = 0.089$). Higher DBP ($p = 0.042$) was significantly associated to increased CL over time, with a similar non-significant trend being found for SBP ($p = 0.072$). We did not find significant associations between blood pressure and longitudinal changes in CSF biomarkers.

Conclusions: Elevated blood pressure was associated with increased Aβ PET accumulation in cognitively unimpaired individuals. Further research is warranted to elucidate potential mechanisms underlying the negative associations between DBP and CSF biomarkers, which do not reflect the typical AD molecular signature. These findings highlight the relevance of high blood pressure as a potential risk factor for cognitive decline.

1. Background

Growing evidence underscores the importance of modifiable risk factors in reducing dementia risk, with lifestyle interventions showing promise in lowering cognitive impairment incidence [1–3]. Hypertension, affecting one-third of adults worldwide [4], has attracted attention for its potential role in dementia risk. Elevated blood pressure can induce structural and functional changes in cerebral vasculature, increasing the risk of acute brain injuries such as strokes, chronic small vessel disease and blood-brain barrier disruption, all of which may heighten dementia risk [5]. Moreover, midlife hypertension is linked with a higher incidence of Alzheimer's disease (AD) later in life, as well as greater AD neuropathological changes in *postmortem* studies [6,7]. Notably, antihypertensive treatment has been associated with a reduced risk of developing AD and a slower progression of the disease, suggesting a potential therapeutic avenue for modifying its course [8,9]. Nonetheless, the mechanisms underlying this association remain unclear.

Research in cognitively unimpaired populations has found associations between hypertension, elevated pulse pressure, and increased levels of phosphorylated tau (p-tau) in cerebrospinal fluid (CSF) [10–12]. Yet, some studies reported associations between hypertension and CSF AD biomarkers only in subsets of individuals not using vascular medications or with altered AD biomarkers [13–15]. Studies employing positron emission tomography (PET) to assess amyloid-beta (Aβ) burden have also shown conflicting results [16,17]. However, to our knowledge, no studies have yet integrated CSF and PET imaging data to examine longitudinal associations between blood pressure and AD pathology. To address these gaps, we investigated cross-sectional and longitudinal associations of blood pressure measures with CSF and PET AD biomarkers in cognitively unimpaired adults from the ALFA+ study and conducted the same analyses in participants from the European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD-LCS) and Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) Prognostic and Natural History Study (PNHS) with available CSF and PET biomarkers, respectively. We hypothesized that higher blood pressure levels would be linked to a greater burden of AD pathology, as measured with CSF and PET biomarkers. Since very old adults have been reported to be more vulnerable to the effect of high blood pressure on neurodegeneration [18], we also explored potential interactions between age and blood pressure on AD biomarkers.

2. Methods

2.1. Participants

The ALFA+ study (ClinicalTrials.gov ID: NCT02485730) is a unicentric, longitudinal observational study designed to explore AD early pathophysiological changes among cognitively unimpaired adults with increased genetic risk factors [19]. Participants included in this study, underwent baseline visits between and 2016 and 2020, and follow-up visits between 2019 and 2023. The European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD-LCS) (ClinicalTrials.gov ID: NCT02804789) is a multicentric European study with over 2000 participants, aiming to understand the early stages of AD and prevent dementia before symptom onset [20]. Data used in preparation of this article were obtained from the EPAD-LCS data set V.IMI (doi:10.34688/epadlcs_v.imi_20.10.30) comprising 2096 EPAD participants enrolled from 2016 to 2020, with last follow-up data being acquired during 2020. The Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) Prognostic and Natural History Study (PNHS) (EudraCT Number: 2018–002,277–22) is a large-scale longitudinal study involving different European cohorts focused on evaluating the predictive value of quantitative PET amyloid imaging for AD progression [21]. By the end of the study in 2022, 1192 prospective baseline and 227 follow-up scans had been performed. By adding 1300 PET scans that were made available through collaborations with the study parent cohorts, the PNHS study included over 2700 PET images across 1624 participants [21]. For more detailed information see supplementary material (**eMethods)**. We included cognitively unimpaired participants (CDR=0, MMSE≥27) with available AD biomarker data (CSF for ALFA+ and EPAD; PET for ALFA+ and AMYPAD), blood pressure measurements, and relevant clinical variables (**eFigure 1**). To avoid overlap, we excluded 47 participants from the EPAD cohort and 211 from the AMYPAD-PNHS cohort who had also participated in the ALFA+ study. Additionally, 158 AMYPAD participants (96 with longitudinal data) also had participated in the EPAD study, therefore these cohorts cannot be considered completely independent.

2.2. Standard protocol approvals, registrations, and patient consents

All participants provided written informed consent, and the study protocols were approved by the appropriate institutional review boards.

2.3. Clinical variables

We included participants from three cohorts with available data on systolic (SBP) and diastolic (DBP) blood pressure, waist-to-hip ratio, self-reported medical history (hypertension, diabetes, and dyslipidemia), medication use, and smoking habits (**eMethods, Supplement**). In the ALFA+ and EPAD cohorts, blood pressure was measured using an automated cuff after a 5-minute seated rest. The ALFA+ cohort included two measurements taken 10 min apart, with only the second used for the present analyses to reduce the "white coat" effect. The EPAD cohort had a single measurement available. In the AMYPAD cohort, single blood pressure records were available for a subset of participants. Pulse pressure (PP) was calculated as the difference between SBP and DBP.

2.4. CSF biomarker measurements and cutoff definitions

In the ALFA+ cohort, CSF Aβ42 and Aβ40 were measured with the NeuroToolKit, a panel of robust exploratory prototype assays, and CSF phosphorylated tau (p-tau181) and total tau (t-tau) with the Elecsys® Phospho-Tau (181P) CSF and Elecsys Total-Tau CSF immunoassays, respectively (all Roche Diagnostics International Ltd, Rotkreuz,

Switzerland). We defined Aβ positivity (*A*+) as CSF Aβ42/40<0.071 [22] In the EPAD-LCS cohort, CSF sampling followed a harmonized preclinical protocol, and analyses were performed with the fully automated Roche Elecsys System in a single laboratory (University of Gothenburg) [20,23]. We used previously validated cutoffs to define Aβ positivity (CSF Aβ42<1000 pg/ml) [23].

2.5. *Aβ PET*

In the ALFA+ cohort, [^{18}F] flutemetamol PET (FTM-PET) images were acquired and preprocessed as described previously [24]. Tracer uptake was quantified in Centiloid units (CL) using SPM12 following a validated Centiloid pipeline [25]. In the AMYPAD-PNHS, [^{18}F]florbetaben and [^{18}F]flutemetamol were used in equal representation across the study sites, with scans being acquired according to standard protocols for each tracer. CL quantification was performed following harmonized procedures across centers [26].

2.6. *Statistical Analyses*

We excluded outliers based on Tukey's criteria set at three times the interquartile range and log-transformed CL, p-tau181, t-tau and Aβ42 from ALFA+, EPAD and AMYPAD cohorts after visual inspection of histograms. We used ANOVA and Mann-Whitney U test to compare variables across cohorts. We used two-sided *t*-tests and simple correlation tests to describe univariate associations of blood pressure measurements with demographic, clinical, and AD biomarker variables within each cohort.

We used separate multivariable linear regression models to examine cross-sectional associations between blood pressure (SBP, DBP, PP) and AD biomarkers (CSF Aβ42, Aβ40, Aβ42/40 ratio, p-tau181, CL). Covariates were selected based on *a priori* knowledge [4,27,28], and included if significantly associated with blood pressure in at least two cohorts (**eFigure 2, eTable 1**). Based on these criteria, all models were adjusted by age, sex, diabetes, antihypertensive medication, and waist-to-hip ratio. To assess potential overfitting, results from unadjusted and age-/sex-adjusted models are reported.

For longitudinal analyses, delta scores were calculated by subtracting baseline from follow-up biomarker values (e.g., ΔCL = follow-up CL – baseline CL). ALFA+ and AMYPAD cohorts had two time points, while EPAD had up to three in 19.7 % of participants with longitudinal data, using the last time point as follow-up. All delta scores were normally distributed, except for ΔCL in ALFA+, which was log-transformed. Longitudinal models were adjusted with the same covariates as cross-sectional models, plus the time between baseline and follow-up. Sensitivity analyses tested the longitudinal association between CL change and baseline blood pressure in participants with CL<30, considering the plateau effect of Aβ accumulation [29].

We analyzed the interaction between age and blood pressure measures on baseline and longitudinal measures of AD biomarkers. Additionally, in the ALFA+ cohort, where total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were available, we ran interaction analyses between these measures and blood pressure to test whether cholesterol levels modify the association of blood pressure with baseline and longitudinal AD biomarkers, taking into account the physiological influence of Aβ in cholesterol dynamics [27].

Statistical analyses were conducted in RStudio 2022.12.0, with a significance threshold of $p < 0.05$. For main analyses, multiple comparisons adjustment using the Benjamini–Hochberg procedure are reported, applying FDR correction for different blood pressure measures within each cohort.

Finally, we conducted meta-analyses derived from the main study results using the metagen() function from the meta R package (version 6.5–0). Regression coefficients (β) and standard errors obtained from each cohort-specific linear model were entered as effect sizes, using the generic inverse variance method (sm = "GEN"). Heterogeneity was quantified using I^2 and τ^2.

2.7. *Data availability*

Data from the ALFA+ study that support the findings of this study are available upon reasonable request. Other data used in the preparation of this article were obtained from the AMYPAD PNHS dataset, (EPAD LCS v.IMI, https://doi.org/10.34688/epadlcs_v.imi_20.10.30) and from the Longitudinal Cohort Study (LCS), delivered by the European Prevention of Alzheimer's Disease (EPAD), and can be found in an online repository (http://epad.org/erap/).

3. Results

We included 405 participants from the ALFA+ cohort (mean [SD] age, 61.1 [4.7] years; 243 females [60.0 %]; 386 with baseline and 268 with follow-up CSF biomarkers data; 352 with baseline and 206 with follow-up Aβ PET data), 1104 participants from the EPAD-LCS cohort with baseline CSF biomarkers (mean [SD] age, 64.8 [7.1] years; 652 females [59.1 %]; 290 with longitudinal data) and 340 participants from the AMYPAD-PNHS cohort with baseline Aβ PET data (mean [SD] age, 71.8 [11.0] years; 204 females [60.0 %]; 190 with longitudinal data). Baseline characteristics of the three cohorts are summarized in Table 1. Univariate associations of blood pressure measures with AD biomarkers, clinical, genetic, and demographic variables are summarized in **eFigure 2** and **eTable 1**. Due to the high correlation between CSF p-tau181 and t-tau ($r > 0.97$ in ALFA+ and EPAD cohorts), only p-tau181 was used for the main analyses.

3.1. *Associations of blood pressure measures with Aβ and p-tau181 CSF biomarkers*

In the ALFA+ cohort, fully adjusted cross-sectional analyses exhibited negative associations of DBP with CSF Aβ40 (st. beta=−0.13, $p = 0.016$) and p-tau181 (st. beta=−0.11, $p = 0.050$), but only associations with Aβ40 survived adjustment for multiple comparisons (Table 2, Fig. 1). Conversely, neither SBP nor PP showed significant associations with CSF biomarkers. In longitudinal analyses, no significant associations were observed between blood pressure measures and longitudinal changes in CSF biomarkers (Table 3, Fig. 2).

In the EPAD cohort, DBP was negatively associated with CSF Aβ42 (st. beta=−0.13, $p < 0.001$) and p-tau181 (st. beta=−0.07, $p = 0.014$) (Table 2, Fig. 1). PP showed a positive association with CSF Aβ42 (st. beta=0.08, $p = 0.024$) and a positive non-significant association with CSF p-tau181 (st. beta=0.06, $p = 0.071$) (Table 2, Fig. 1). Significant associations survived adjustment for multiple comparisons. No significant associations were observed between baseline blood pressure measures and longitudinal changes in CSF biomarkers (Fig. 2).

In both cohorts, similar estimates were observed in models adjusted only for age and sex, with a negative non-significant association between DBP and CSF Aβ42 (st. beta=−0.10, $p = 0.053$) in the ALFA+ cohort (**eTable 2**).

We found significant interactions of age with baseline SBP ($p = 0.042$) and PP ($p = 0.040$) only in the EPAD cohort. To better interpret these interactions, we performed stratified analyses using the age median split. These analyses revealed no significant association between SBP and CSF p-tau181, while PP was significantly positively correlated with CSF p-tau181 only in the older group ($p = 0.012$). We found no significant interactions between age and blood pressure measures on longitudinal changes in CSF AD biomarkers.

To better characterize the unexpected negative associations between DBP and both CSF Aβ and p-tau181 levels, we conducted *post-hoc* analyses. First, we assessed whether the inclusion of CSF Aβ40 as a covariate in the models altered the associations of DBP with CSF Aβ42 and p-tau181 in the ALFA+ cohort, given that Aβ40 reflects overall Aβ

Table 1
Baseline characteristics of the participants from the three samples.

	ALFA+	EPAD	AMYPAD
Variables	**(N=405)***	**(N=1104)**	**(N=340)**
Age, mean (SD), years	61.1 (4.7)[a,b]	64.8 (7.1)[b,c]	71.8 (11.0)[a,c]
Females, N (%)	243 (60.0%)	652 (59.1%)	204 (60.0%)
***APOE-ε4* carrier, N (%)**	223 (55.1%)[a,b]	398 (36.1%)[c]	104 (30.6%)[c]
Hypertension, N (%)	127 (31.4%)	318 (28.8%)	118 (34.7%)
Anti-hypertensive treatment, N (%)	103 (25.4%)	283 (25.6%)	93 (27.4%)
Dyslipidemia, N (%)	312 (77.0%)[a,b]	369 (33.4%)[c]	101 (29.7%)[c]
Diabetes, N (%)	23 (5.7%)	75 (6.8%)	17 (5.0%)
Tobacco consumption, N (%)			
Never smoked	169 (41.7%)	499 (45.2%)	155 (45.6%)
Current smoker	52 (12.8%)[a,b]	72 (6.5%)[c]	16 (4.7%)[c]
Ex-smoker	184 (45.4%)	533 (48.3%)	169 (49.7%)
Systolic pressure, mean (SD), mmHg	127 (14.4)[a,b]	134 (17.5)[b,c]	143 (24.0)[a,c]
Diastolic pressure, mean (SD), mmHg	74.7 (9.32)[a,b]	79.1 (10.2)[c]	78.8 (10.6)[c]
Pulse pressure, mean (SD), mmHg	52.5 (12.7)[a,b]	55.0 (14.6)[b,c]	64.1 (18.8)[a,c]
High systolic pressure (≥130), N (%)	169 (41.3)[a,b]	643 (58.2)[c]	232 (68.2)[c]
High diastolic pressure (≥80), N (%)	121 (29.9)[a]	578 (52.4)[c]	147 (43.2)
High systolic and diastolic pressure, N (%)	80 (19.8)[a,b]	440 (39.9)[c]	137 (40.3)[c]
Waist-to-hip ratio, mean (SD)	0.916 (0.080)[a]	0.901 (0.096)[c]	0.914 (0.082)
CSF Aβ42, median (IQR), pg/mL	1198 (870-1650)[d]	1379 (961.9-1836.5)[d]	na
CSF Aβ40, mean (SD), ng/mL	17.3 (5.03)	na	na
CSF Aβ42/40, mean (SD)	0.075 (0.020)	na	na
CSF p-tau181, median (IQR), pg/mL	14.4 (11.1-19.2)[a]	16.1 (13-20.6)[c]	na
CSF t-tau, median (IQR), pg/mL	182 (144.9-234.9)[a]	194.2 (159.8-242.1)[c]	na
AT categories, N (%)			na
A-T-	238 (61.7%)	726 (65.8%)	na
A+T-	104 (26.9%)	263 (23.8%)	na
A-T+	13 (3.4%)[a]	72 (6.5%)[c]	na
A+T+	31 (8.0%)[a]	43 (3.9%)[c]	na
Centiloids, median (IQR)	-1.6 (-6.6-5.14)[b]	na	9 (1.3-23.8)[c]
Centiloid categories, N (%)			
Negative (≤12CL	295 (83.8%)[b]	na	191 (56.2%)[c]
Grey-zone (12-50CL)	28 (8.0%)[b]	na	101 (29.7%)[c]
Positive (≥50CL	29 (8.2%)	na	48 (14.1%)
CSF sampling interval, mean (SD), years	3.4 (0.6)	1.4 (0.5)	na
PET scans interval, mean (SD), years	3.4 (0.6)	na	1.4 (13.8)

na: Not available.
*386 with CSF data; 352 with PET data.
[a] Significantly different from EPAD; [b]Significantly different from AMYPAD; [c]Significantly different from ALFA+; [d]Not comparable due to methodological differences.

production and clearance [30]. Second, we conducted interaction analyses to determine whether Aβ positivity status influenced the relationships between DBP and CSF biomarkers in the ALFA+ and EPAD cohorts. After adjusting for CSF Aβ40, the previously significant associations between DBP and p-tau181 were no longer significant (**eTable 3**). Similarly, the non-significant negative association between DBP and CSF Aβ42, observed in models adjusted for age and sex, was attenuated after including CSF Aβ40 (**eTable 3**). Interaction analyses between DBP and Aβ status on CSF biomarkers revealed no significant results in either cohort (data not shown).

3.2. Associations of blood pressure measures with Aβ PET

In the ALFA+ cohort, fully adjusted cross-sectional analyses revealed no significant associations between CL levels and blood pressure measures (Table 2). In longitudinal analyses, increased CL were non-significantly associated with higher baseline SBP (st. beta=0.140, p = 0.058) (Table 3, Fig. 2), but this trend was not observed after correcting for multiple comparisons.

In the AMYPAD cohort, baseline CL were positively associated with SBP (st. beta=0.18, p = 0.002) and PP (st. beta=0.18, p = 0.003), and non-significantly with higher DBP (st. beta=0.09, p = 0.089) (Table 2, Fig. 1). The associations with SBP and PP remained significant after corrections for multiple comparisons. In longitudinal analyses, increased CL were significantly associated with higher baseline DBP (st. beta=0.160, p = 0.042) and marginally associated with higher baseline SBP (st. beta=0.170, p = 0.072), although these associations did not survive multiple comparisons correction (Table 3, Fig. 2).

In both cohorts, results remained consistent in models adjusted solely for age and sex (**eTable 4**). In addition, sensitivity analyses focusing on participants with baseline CL < 30 reaffirmed the positive trends and significant associations for SBP and DBP with CL accumulation over time in the ALFA+ and AMYPAD cohorts, respectively (SBP: st. beta=0.135, p = 0.084; DBP: st. beta=0.143, p = 0.032), although the trend observed between SBP and CL in the AMYPAD cohort was attenuated (st. beta=0.047, p = 0.195). Additionally, a non-significant positive association between PP and CL change was observed in the ALFA+ cohort (st. beta=0.140, p = 0.069). Conversely, no significant associations were observed in the subgroup with ≥ 30 CL in both cohorts.

We only found a significant interaction between age and baseline DBP in the ALFA+ cohort (p = 0.028), but stratified analyses by age group revealed no significant associations. We found no significant interactions between age and blood pressure measures on longitudinal changes in CSF AD biomarkers. We did not find any significant interaction between age and blood pressure on longitudinal PET changes.

We found a significant interaction between HDL and DBP on CSF Aβ42/40 levels (p = 0.008), with a positive association between DBP and CSF Aβ42/40 levels in participants with higher HDL levels, and the opposite pattern in those with lower HDL levels; however, neither association reached significance in analyses stratified by median split. We did not find any other significant interactions between cholesterol and blood pressure measures on AD biomarkers at a cross-sectional or longitudinal level.

3.3. Meta-analysis of blood pressure and AD biomarkers across cohorts

In meta-analyses of cross-sectional results, higher DBP was significantly associated with lower CSF Aβ42 (β = –0.00250, 95 % CI: –0.00358 to –0.00142, p < 0.001) and lower p-tau (β = –0.00130, 95 % CI: –0.00214 to –0.00047, p = 0.002). Additionally, higher PP was associated with higher CSF Aβ42 (β = 0.00096, 95 % CI: 0.00015 to 0.00176, p = 0.020) and higher p-tau (β = 0.00071, 95 % CI: 0.00008 to 0.00134, p = 0.027). Associations with CL were not statistically significant, although a trend was observed for PP (β = 0.00466, 95 % CI: –0.00018 to 0.00950, p = 0.059). Across these analyses, heterogeneity was minimal (I^2 = 0 %). Forest plots of these analyses are shown in **eFigure 3**. In longitudinal analyses, no statistically significant associations were observed between baseline blood pressure and changes in Aβ42, p-tau, or CL values. Heterogeneity was low across most models (I^2 = 0–75 %), and no model showed evidence of substantial inconsistency across cohorts. Forest plots are shown in **eFigure 4**.

Table 2
Cross-sectional associations between blood pressure and AD biomarkers.

	CSF log(Aβ42)		CSF Aβ42/40		CSF Aβ40		CSF log(p-tau181)		log (centiloids)	
	std.β (95% CI)	p_{unc} (p_{FDR})	*std.β (95% CI)*	p_{unc} (p_{FDR})	*std.β (95% CI)*	p_{unc} (p_{FDR})	*std.β (95% CI)*	p_{unc} (p_{FDR})	*std.β (95% CI)*	p_{unc} (p_{FDR})
ALFA+										
SBP	-0.01 (-0.12, 0.09)	0.808 (0.808)	-0.03 (-0.13, 0.08)	0.627 (0.941)	-0.00 (-0.11, 0.10)	0.963 (0.963)	-0.00 (-0.11, 0.10)	0.956 (0.956)	0.04 (-0.07, 0.15)	0.480 (0.720)
DBP	-0.08 (-0.19, 0.03)	0.139 (0.417)	0.00 (-0.11, 0.11)	0.987 (0.987)	-0.13 (-0.24, -0.02)	**0.016 (0.048)**	-0.1 (-0.21, -0.00)	**0.050** (0.150)	-0.01 (-0.12, 0.10)	0.861 (0.861)
PP	0.04 (-0.06, 0.15)	0.441 (0.417)	-0.0 (-0.13, 0.07)	0.575 (0.941)	0.09 (-0.02, 0.19)	0.100 (0.150)	0.07 (-0.03, 0.17)	0.186 (0.279)	0.05 (-0.06, 0.16)	0.363 (0.720)
EPAD										
SBP	-0.03 (-0.09, 0.04)	0.406 (0.406)	na	na	na	na	-0.00 (-0.06, 0.06)	0.973 (0.973)	na	na
DBP	-0.13 (-0.19, -0.07)	**<0.001 (<0.001)**	na	na	na	na	-0.07 (-0.13, -0.01)	**0.014 (0.042)**	na	na
PP	0.08 (0.01, 0.14)	**0.024 (0.036)**	na	na	na	na	0.06 (-0.00, 0.12)	0.071 (0.106)	na	na
AMYPAD										
SBP	na	na	na	na	na	na	na	na	0.18 (0.07, 0.29)	**0.002 (0.004)**
DBP	na	na	na	na	na	na	na	na	0.09 (-0.01, 0.19)	**0.089 (0.089)**
PP	na	na	na	na	na	na	na	na	0.18 (0.06, 0.29)	**0.003 (0.004)**

SBP: Systolic blood pressure (mmHg), DBP: Diastolic blood pressure (mmHg), PP: Pulse pressure (mmHg), p_{unc}: uncorrected p-values, p_{FDR}: FDR-corrected p-values. All models are adjusted by age, sex, diabetes, antihypertensive medication and waist-hip-ratio.

4. Discussion

This study including cognitively unimpaired participants from the ALFA+, EPAD, and AMYPAD cohorts revealed two main findings: (1) higher blood pressure measures were both cross-sectionally and longitudinally associated with a greater burden of amyloid pathology, as measured by PET, and (2) DBP was negatively associated both with CSF levels of Aβ42 and p-tau181 at baseline, but these associations disappeared after adjusting by CSF Aβ40, potentially reflecting a non-specific effect on CSF dynamics. Meta-analyses confirmed several of these findings across cohorts. In cross-sectional analyses, higher DBP was significantly associated with lower CSF Aβ42 and p-tau181, and PP was positively associated with both biomarkers. SBP showed a trend toward a positive association with amyloid PET burden. In contrast, meta-analyses of longitudinal data revealed no statistically significant associations, although some trends were observed in individual cohorts.

4.1. Association between blood pressure and CSF biomarkers

Increased arterial pulsatility from arterial stiffening, often linked to hypertension, may impair the clearance of interstitial waste, including Aβ and tau [31]. High PP has been associated with increased p-tau181 and decreased Aβ42 in CSF [12], although other studies did not find significant cross-sectional associations between blood pressure and CSF biomarkers [13,14]. Contrary to our initial hypothesis that higher blood pressure would correspond to the typical AD CSF profile (increased p-tau181 and decreased Aβ42) our cross-sectional analyses revealed negative associations between DBP and both Aβ and tau CSF biomarkers in the ALFA+ and EPAD cohorts. Meta-analysis of these results confirmed significant negative associations between DBP and both Aβ42 and p-tau181 and showed a positive association between PP and both CSF biomarkers. These findings were consistent with cohort-specific results and suggest a robust cross-sectional relationship between blood pressure and CSF AD biomarkers. However, none of these associations were observed in the longitudinal meta-analyses, indicating that these effects may reflect momentary physiological interactions or nonspecific alterations in CSF dynamics rather than progressive AD pathology.

Similar findings of negative associations between DBP and CSF p-tau181, and no correlations with Aβ40 or Aβ42 levels have been reported elsewhere [18,32].

Notably, PP showed a positive correlation with Aβ42 and p-tau181 in the EPAD cohort, but with a smaller effect size than DBP, suggesting DBP as the main driver of these associations. In this regard, an interaction model with age revealed a significant association between PP and p-tau181 only in the older group in EPAD, suggesting that PP might contribute to AD risk only in persons 65 or older.

4.2. Association between blood pressure and Aβ PET

Prior studies on amyloid PET and blood pressure in non-demented adults have yielded conflicting outcomes. Some reported a positive association between SBP and Aβ deposition [17], while others found no association [16,33,34], or only observed positive links in subgroups like *APOE-ε4* carriers [35,36]. Our findings in the AMYPAD cohort provide new evidence, showing positive associations between higher blood pressure and Aβ deposition at baseline (SBP, DBP and PP) and over time (SBP and DBP). A similar trend was observed in the ALFA+ cohort, with SBP showing a positive association with longitudinal Aβ accumulation. These results were partially supported by the meta-analyses, which revealed a cross-sectional trend toward a positive association between SBP and amyloid PET burden ($\beta = 0.00377$, $p = 0.070$), though not statistically significant. No significant longitudinal associations were observed in the pooled meta-analyses, suggesting that while cohort-specific trends may exist, between-study variation and small pooled effect sizes may have limited statistical power at the meta-analytic level.

These findings support a direct link between elevated blood pressure and AD pathology. Discrepancies across ALFA+ and AMYPAD cohorts may stem from differences in age, cardiovascular burden and stages in the preclinical AD *continuum*. Additionally, methodological variations, such as the periods studied, exposure variable definitions, and cohort characteristics, may contribute to prior inconsistencies in the literature and between previous studies and ours.

Post-hoc analyses in the ALFA+ cohort showed that, adjusting for Aβ40, negative associations between DBP and Aβ42 and p-tau181 were no longer significant, which would suggest a nonspecific effect of DBP

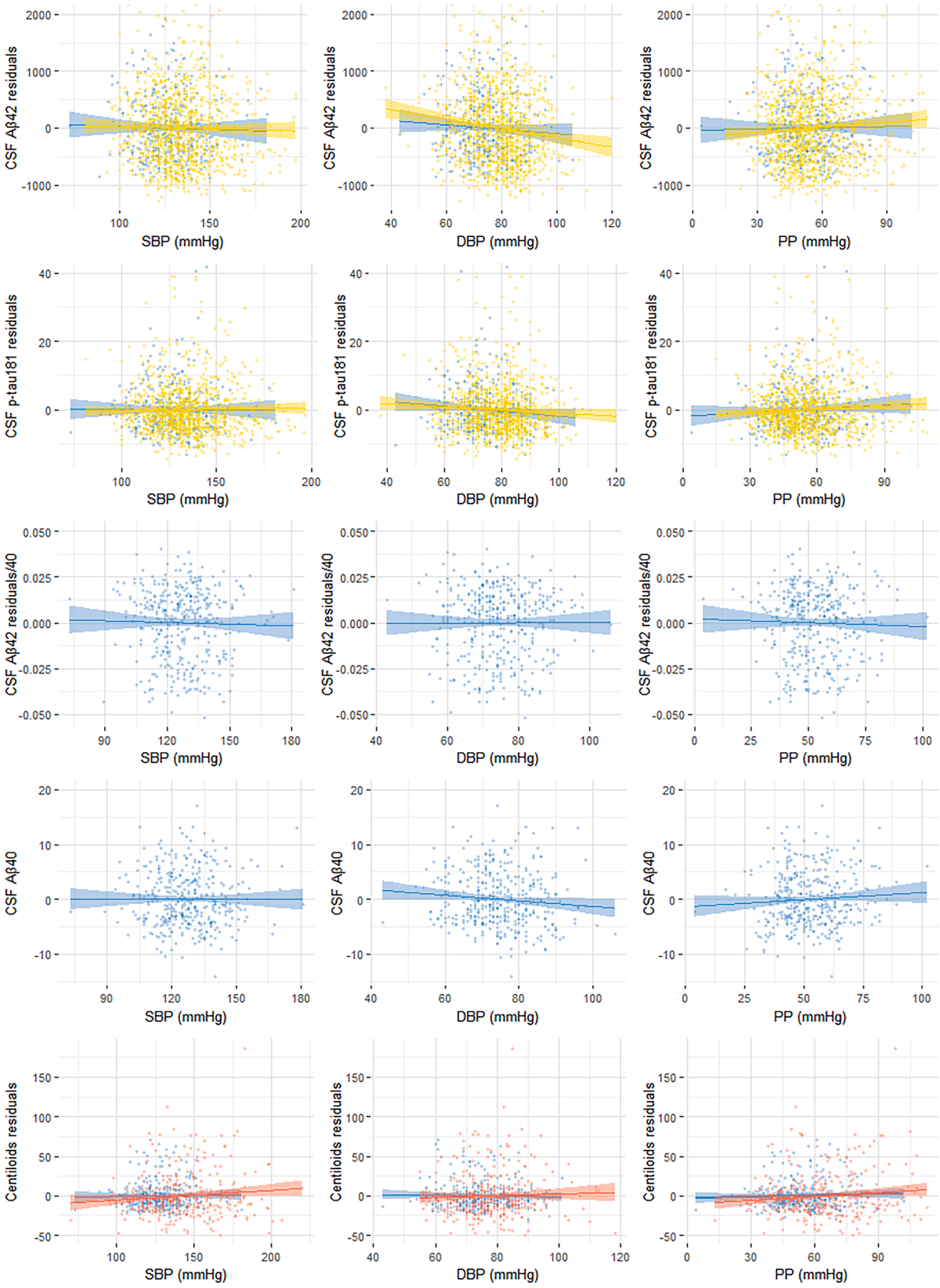

Fig. 1. Cross-sectional associations between blood pressure and AD biomarkers.
Figure shows cross-sectional associations between blood pressure and residuals of CSF and amyloid PET biomarkers in the ALFA+ (blue), EPAD (yellow), and AMYPAD (red) cohorts. Residuals are derived from general linear models adjusted for age, sex, diabetes, waist-to-hip ratio, and antihypertensive medication. CL: Centiloids.

Table 3
Longitudinal associations between blood pressure and AD biomarkers.

	Δ Aβ42		Δ Aβ42/40		Δ Aβ40		Δ p-tau181		Δ centiloids	
	std.β (95%CI)	p_{unc} (p_{FDR})	*std.β (95%CI)*	p_{unc} (p_{FDR})	*std.β (95%CI)*	p_{unc} (p_{FDR})	*std.β (95%CI)*	p_{unc} (p_{FDR})	*std.β (95%CI)*	p_{unc} (p_{FDR})
ALFA+										
SBP	0.02	0.813	0.07	0.277	0.01	0.910	0.04	0.534	0.14	0.058
	(-0.12, 0.15)	(0.813)	(-0.06, 0.20)	(0.575)	(-0.12, 0.14)	(0.910)	(-0.09, 0.18)	(0.534)	(-0.00, 0.28)	(0.174)
DBP	-0.05	0.468	0.03	0.639	-0.04	0.544	-0.07	0.300	0.05	0.487
	(-0.19, 0.09)	(0702)	(-0.10, 0.17)	(0.639)	(-0.17, 0.09)	(0.897)	(-0.21, 0.07)	(0.450)	(-0.10, 0.20)	(0.487)
PP	0.05	0.468	0.06	0.383	0.03	0.598	0.09	0.176	0.11	0.117
	(-0.08, 0.18)	(0.702)	(-0.07, 0.18)	(0.575)	(-0.09, 0.16)	(0.897)	(-0.04, 0.22)	(0.450)	(-0.03, 0.26)	(0.176)
EPAD										
SBP	0.06	0.376	na	na	na	na	0.07	0.245	na	na
	(-0.07, 0.18)	(0.564)					(-0.05, 0.20)	(0.368)		
DBP	0.09	0.152	na	na	na	na	0.08	0.156	na	na
	(-0.03, 0.20)	(0.456)					(-0.03, 0.20)	(0.368)		
PP	0.00	0.995	na	na	na	na	0.02	0.739	na	na
	(-0.13, 0.13)	(995)					(-0.11, 0.15)	(0.739)		
AMYPAD										
SBP	na	na	na	na	na	na	na	na	0.17	0.072
									(-0.02, 0.35)	(0.108)
DBP	na	na	na	na	na	na	na	na	0.16	0.042
									(0.01, 0.32)	(0.108)
PP	na	na	na	na	na	na	na	na	0.09	0.356
									(-0.10 – 0.27)	(0.356)

Δ: longitudinal changes (delta score), SBP: Systolic blood pressure (mmHg), DBP: Diastolic blood pressure (mmHg), PP: Pulse pressure (mmHg), punc: uncorrected p-values, pFDR: FDR-corrected p-values. [a]Δ centiloids were log transformed for AMYPAD data. All models are adjusted by age, sex, diabetes, antihypertensive medication, waist-hip-ratio and time between CSF/PET acquisition.

on CSF clearance, influencing various CSF protein concentrations, including AD biomarkers. The lack of interactions between Aβ status and DBP further supports this hypothesis, ruling out the possibility that the associations were driven by individuals with abnormal Aβ levels. Although our findings do not support a clear pathophysiological link between DBP and CSF AD biomarkers, we cannot entirely dismiss this possibility. Elevated DBP might impair CSF protein clearance from the interstitial fluid compartment to the CSF, potentially resulting in negative correlations between CSF Aβ species and p-tau181 levels and DBP. This would be consistent with findings linking elevated DBP to reduced brain perfusion [37], as well as positive associations between DBP and increased Aβ PET burden found in our cross-sectional and longitudinal analyses. However, meta-analysis results did not show any significant longitudinal associations between blood pressure and CSF biomarkers, suggesting that observed cohort-level trends may not generalize across populations. These null findings could reflect subtle and variable effects across cohorts, as well as differences in follow-up durations and biomarker measurement procedures. Our findings are in line with mixed results from previous studies on the impact of hypertension on CSF AD biomarkers change. While one study found no association between midlife hypertension and longitudinal changes in CSF AD biomarkers [38], another observed that hypertension was linked to a quicker increase in t-tau and p-tau181 levels over time, but only in individuals who were both *A+* and *T+* [13], and recent research noted steeper increases in p-tau181 and t-tau among older adults with uncontrolled hypertension [10].

Altogether, our findings suggest that different potential mechanisms may underlie the relationship between blood pressure and CSF/PET AD biomarkers, with DBP potentially influencing CSF dynamics across individuals within or not the AD *continuum*. This could help explain why robust cross-sectional associations were identified via meta-analysis, while longitudinal associations remained non-significant, despite a larger sample size. The nonspecific impact of DBP on CSF dynamics may obscure any true longitudinal progression effect of AD pathology. However, these findings need to be validated in other large cohorts. Also, we cannot exclude that CSF dynamic disturbance could be related to the presence of cerebrovascular disease among individuals with higher DBP levels.

This study has several strengths. Firstly, its large sample size increases the reliability of the findings. Secondly, insights from the ALFA+ cohort, comprising individuals at heightened risk of AD dementia, shed light on early disease mechanisms. Thirdly, the use of PET and CSF biomarkers allowed a comprehensive assessment of AD pathology. Limitations include the potential lack of generalizability due to the highly educated, healthy population in the ALFA+ cohort and the low prevalence of cardiovascular risk factors among participants from the three cohorts, compared to epidemiological data from the general population [39]. Although both CSF and PET AD biomarkers were assessed, future studies should encompass measures of tau PET as well. Additionally, differences in blood pressure measurement procedures may also account for inconsistencies across cohorts. Unfortunately, CSF levels of Aβ40 were not available for the EPAD cohort; thus, we couldn't formally test whether inclusion of Aβ40 as a surrogate of brain clearance would attenuate the association between DBP and Aβ42 in the EPAD cohort. Lastly, not all findings withstood multiple comparison corrections, though some were replicated across two cohorts.

5. Conclusion

Our study reveals that higher blood pressure is significantly associated with an increased burden of AD pathology and amyloid deposition over time. Additionally, the observed negative associations between DBP and CSF biomarkers suggest a nonspecific impact on CSF dynamics, a finding that warrants careful consideration in future research. These results emphasize the importance of managing hypertension during midlife as a potential strategy for AD prevention.

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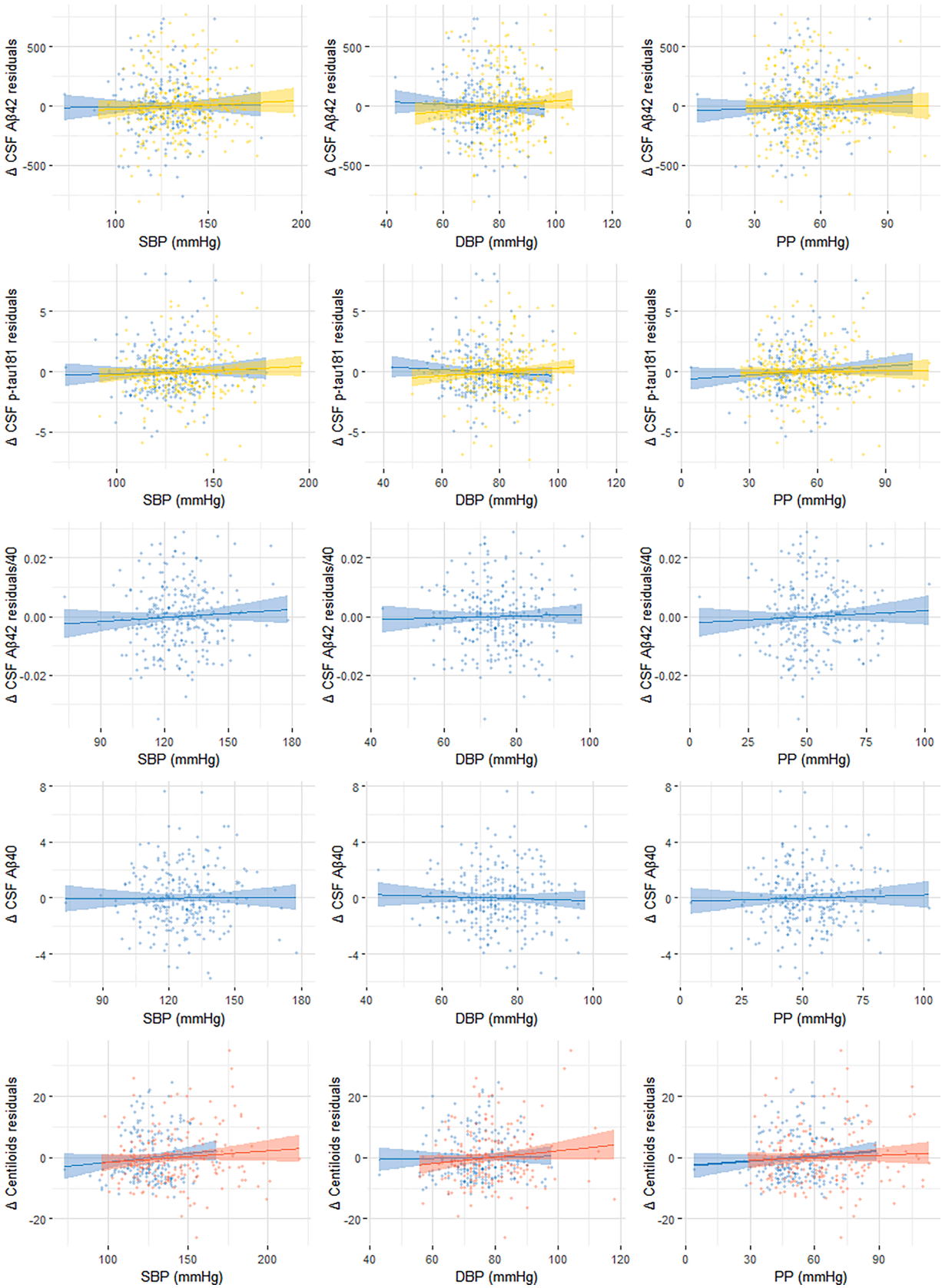

Fig. 2. Longitudinal associations between blood pressure and AD biomarkers.
Figure shows associations between blood pressure and residuals of longitudinal change in CSF and amyloid PET biomarkers in the ALFA+ (blue), EPAD (yellow), and AMYPAD (red) cohorts. Residuals are estimated using general linear models adjusted for age, sex, diabetes, waist-to-hip ratio, antihypertensive medication, and time interval between visits. CL: Centiloids.

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Declaration of competing interest

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Supplementary materials

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