

Midlife Cardiovascular Risk And Amyloid Status Interact To Accelerate Cognitive Decline In Cognitively Unimpaired Individuals

Lídia Mulet-Pons^{1,2}, Gonzalo Sánchez-Benavides^{1,2}, David López-Martos^{1,2}, Ana Fernández-Arcos^{1,2}, Juan Domingo Gispert^{1,3}, Gemma Salvadó^{1,2,4}, Oriol Grau-Rivera^{1,5}.

(1) BarcelonaBeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain; (2) Hospital del Mar Research Institute, Barcelona, Spain; (3) Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable, Instituto de Salud Carlos III, Madrid, Spain; (4) Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Lund, Sweden; (5) Servei de Neurologia, Hospital del Mar, Barcelona, Spain.

Background

- Cardiovascular risk factors (CVRF) during midlife have a significant impact on the development of dementia in late life [1], but whether early Alzheimer's disease (AD) pathology modifies this relationship remains controversial [2].
- Therefore, understanding the mechanisms through which these CVRF contribute to cognitive decline and whether these effects are modified by early AD pathology is essential for effectively addressing them during midlife and reducing the risk of dementia later in life.

Aim

To examine whether baseline midlife CVRF predict cognitive decline over 6 years in a cognitively unimpaired cohort at risk for AD, and to examine whether this association is independent of underlying AD pathology.

Method

Participants and longitudinal study design

269 cognitively unimpaired participants from the ALFA+ cohort [3] (Figure 1).

Vascular risk factors (CVRF)

➤ The Framingham Risk Score (FRS)

10-year risk for developing a cardiovascular disease [5]: Sex, age, total and high-density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetes status.

➤ Status in six vascular risk factors

We assessed the status of specific CVRF associated with AD [6] to explore vascular mechanisms underlying cognitive trajectories:

- Hypertension, dyslipidemia, diabetes, obesity, smoking, and physical inactivity, based on clinical measures (blood pressure, total and LDL cholesterol, HbA1c levels, moderated and high physical activity), treatment, or self-reported diagnosis.

Cognition

Preclinical Alzheimer's Cognitive Composite (PACC)

The primary cognitive outcome was PACC [7] including immediate and delayed episodic memory, semantic fluency and speed of processing.

We used the mean and standard deviation from a baseline CSF biomarker-negative group (A-T-[N]-) as reference (n = 248).

CSF biomarkers

We used NeuroToolKit and Elecsys® immunoassays to measure cerebrospinal fluid biomarkers: Amyloid- β (A β)42, A β 40, pTau181, Neurofilament light (NfL). Amyloid status was defined by validated A β 42/40 ratio cutoff [4].

Statistical analyses

Main outcome: PACC Main predictors: CVRF Moderator: A β status

- Linear mixed-effects models (lme4) with random intercepts and slopes examined associations between baseline CVRF and longitudinal PACC change.
- An interaction with baseline A β positivity was included to test moderation effects.
- Sensitivity analyses to assess the robustness of the results: (1) adjustment for CSF pTau181 and NfL and (2) exclusion of outliers.
- All models were adjusted for age, sex, education, and APOE ϵ 4 status.
- Significance was set at $p < 0.05$ (FDR-corrected when applicable).

Results

- At baseline, participants had low-to-moderate vascular risk (FRS $\sim$ 10%), with dyslipidemia being the most prevalent vascular risk factor, with low AT(N) pathology (Table 1).
- Over 3.2–6.6 years of follow-up, the average cognitive trajectory is stable ($\beta = 0.012$, SE = 0.017, $t(290.974) = 0.688$, $p = 0.492$). However, 36.6% of participants showed cognitive decline.

(1) Baseline vascular risk, particularly hypertension, predicted cognitive decline

- Higher baseline FRS was significantly associated with faster PACC decline (Figure 2A). Among CVRF, only hypertension predicted PACC decline (Figure 2B). Findings were robust in sensitivity analyses.

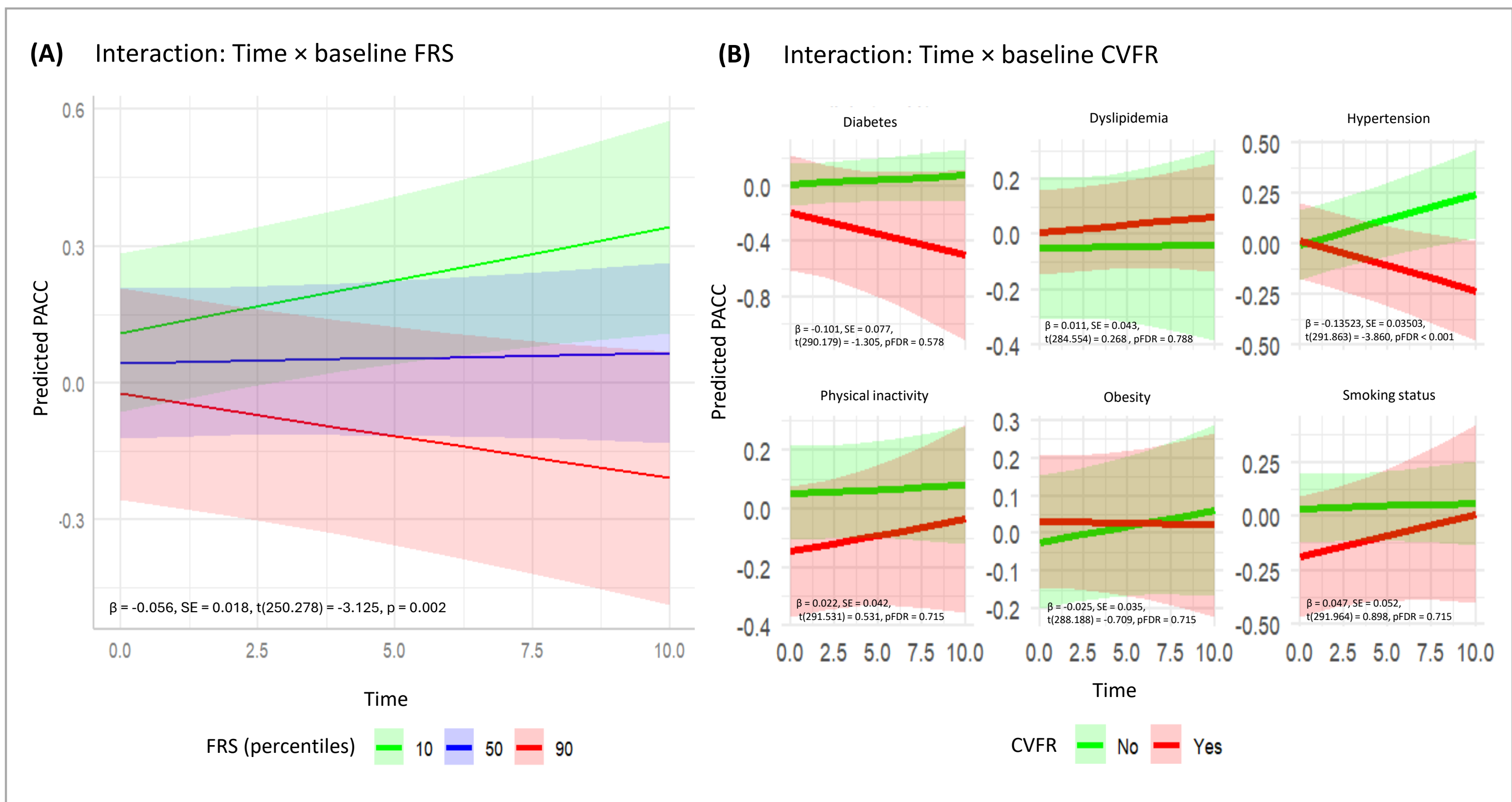


Figure 2. Regression plots show predicted PACC trajectories from linear mixed-effects models, illustrating interactions between time and baseline CVRF. In (A) percentiles were used only for visualization.

(2) A β positivity moderated the associations between baseline vascular risk and cognitive decline

- The association between higher FRS and hypertension with faster PACC decline was stronger in A β + than in A β - participant (Figure 3A and 3B). Findings remained after adjustment for pTau181 and NfL.
- The interaction between FRS and A β status became stronger and significant after excluding influential participants ($\beta = -0.109$, CI = [-0.181, -0.038], $p = 0.002$; N = 14 excluded).

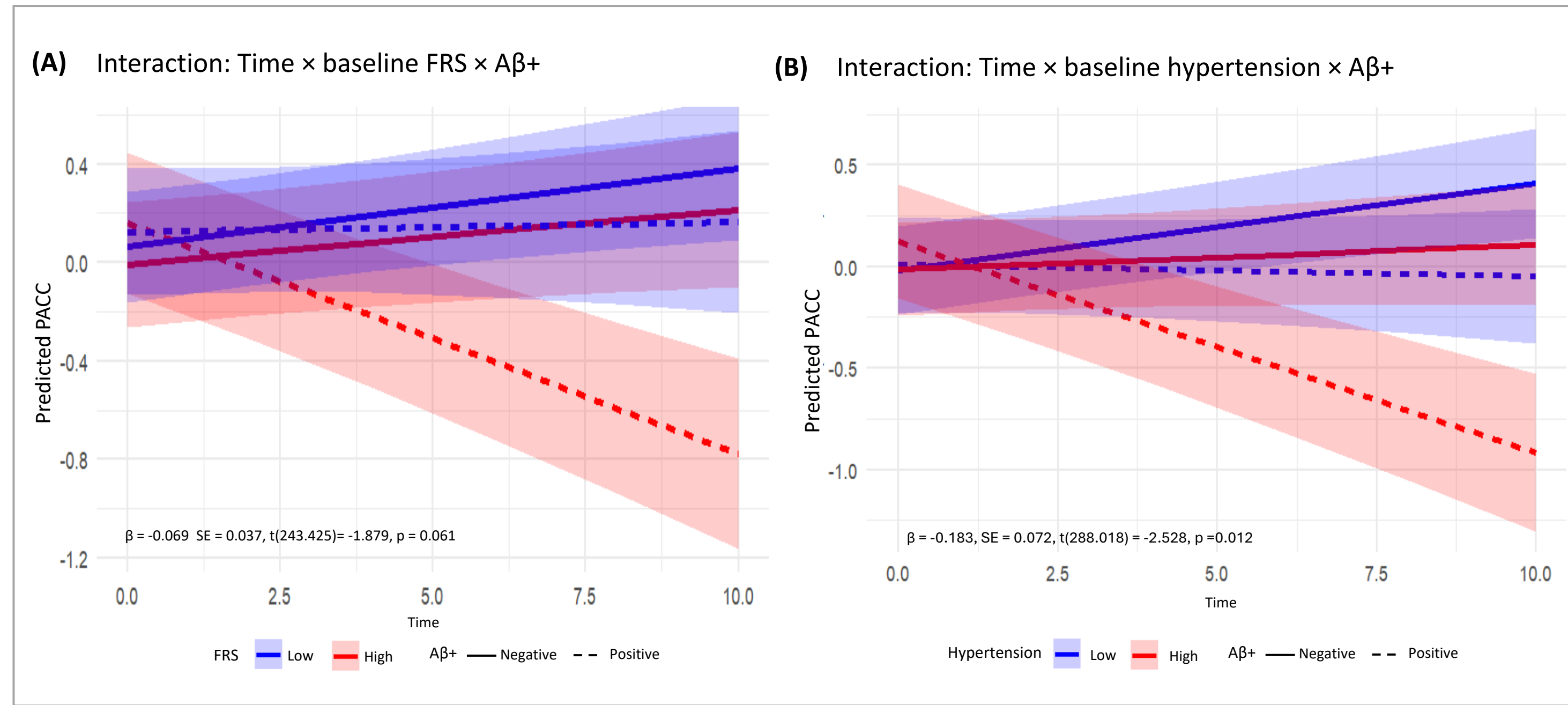


Figure 3. Regression plots show predicted PACC trajectories from linear mixed-effects models, illustrating interactions between time, baseline CVRF and A β status. In (A) FRS groups were created solely for visualization purposes: low FRS $<10\%$ and high FRS $>10\%$.

	N	Summary statistics ¹
Age at baseline	292	60.7 $\pm$ 4.6
Years of education	292	14 $\pm$ 4
Sex	292	174 (60%) females
APOE- ϵ 4 carriers	292	157 (54%) yes
FRS at baseline	261	12% $\pm$ 7%
Hypertension at baseline	292	123 (42%) yes
Diabetes at baseline	292	16 (5.5%) yes
Dyslipidemia at baseline	292	231 (79%) yes
Smoking at baseline	292	38 (13%) yes
Obesity at baseline	292	122 (42%) yes
Inactivity at baseline	292	64 (22%) yes
CSF A β 42/40 (+) at baseline	278	94 (34%) yes
CSF pTau181 at baseline	278	1.17 $\pm$ 0.17
CSF NFL at baseline	278	81 $\pm$ 29
PACC at baseline	292	0.04 $\pm$ 0.67
PACC at 3-y follow-up	292	0.09 $\pm$ 0.67
PACC at 6-y follow-up	292	0.06 $\pm$ 0.82

Table 1. Descriptive statistics at baseline and cognitive outcomes across visits. ¹Mean $\pm$ SD for continuous variables; N (%) for categorical variables.

Conclusions

- ➔ Midlife vascular risk was associated with cognitive decline over 6.6 years of follow-up in cognitively unimpaired individuals.
- ➔ Hypertension emerged as a key mechanism linking midlife vascular risk to cognitive decline.
- ➔ A β pathology moderated the associations between vascular risk and cognitive decline, such that A β + was associated with accelerated decline.
- ➔ This moderating effect was independent of concomitant pathologies, including pTau and NfL.

- ➔ Overall, this findings suggest a synergistic effect between vascular risk and A β pathology, indicating that management of midlife vascular risk may help preserve cognition in individuals with early A β accumulation.

Further directions

- ➔ Vascular risk factors are linked to cerebrovascular co-pathology (V) in AD: cerebral small vessel disease, blood-brain barrier dysfunction, cerebral hypoperfusion, atherosclerosis... which may impair glymphatic clearance and promoting neuroinflammation, reactive glia and metabolic stress.
- ➔ Investigate how cerebrovascular co-pathology (V) affect disease progression.

➔ References

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Contact
lmulet@barcelonabeta.org
linkedin.com/in/lidia-mulet-pons-0182b715a

www.barcelonabeta.org

barcelonaβeta
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