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Vascular risk burden is a key player in the early progression of Alzheimer's disease☆

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ABSTRACT

Understanding whether vascular risk factors (VRFs) synergistically potentiate Alzheimer's disease (AD) progression is important in the context of emerging treatments for preclinical AD. In a group of 503 cognitively unimpaired individuals, we tested whether VRF burden interacts with AD pathophysiology to accelerate neurodegeneration and cognitive decline. Baseline VRF burden was calculated considering medical data and AD pathophysiology was assessed based on cerebrospinal fluid (CSF) amyloid-β_{1-42} ($A\beta_{1-42}$) and tau phosphorylated at threonine 181 (p-tau_{181}). Neurodegeneration was assessed with plasma neurofilament light (NfL) and global cognition with the modified version of the Preclinical Alzheimer's Cognitive Composite. The mean (SD) age of participants was 72.9 (6.1) years, and 220 (43.7%) were men. Linear mixed-effects models revealed that an elevated VRF burden synergistically interacted with AD pathophysiology to drive longitudinal plasma NfL increase and cognitive decline. Additionally, VRF burden was not associated with CSF $A\beta_{1-42}$ or p-tau_{181} changes

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over time. Our results suggest that VRF burden and AD pathophysiology are independent processes; however, they synergistically lead to neurodegeneration and cognitive deterioration. In preclinical stages, the combination of therapies targeting VRFs and AD pathophysiology might potentiate treatment outcomes.

1. Introduction

A new era of trials in individuals with preclinical Alzheimer's disease (AD) is starting, given the assumption that better outcomes could be achieved with interventions performed before the presence of extensive damage and cognitive symptoms (Cummings et al., 2021; Sperling et al., 2014). The preclinical stage of AD has been characterized by biomarker evidence of amyloid-β (Aβ) and tau pathologies in cognitively unimpaired (CU) individuals (Jack et al., 2018; Ossenkoppele et al., 2022). Individuals in this stage are at higher risk for AD clinical progression; however, many of them never progress to cognitive impairment, suggesting that other simultaneous pathological processes are involved (Dubois et al., 2021). Therefore, it is important to understand the additional factors contributing to AD progression to develop effective therapeutic strategies.

Vascular risk factors (VRFs), such as hypertension, diabetes mellitus, smoking, and hypercholesterolemia, are well-established risk factors for developing AD dementia (Anstey et al., 2007; Kivipelto et al., 2001; Luchsinger et al., 2005; Profenno et al., 2010). These conditions are associated with cerebrovascular lesions in neuropathologically-confirmed AD patients (Bangen et al., 2015; Nation et al., 2012), and the presence of these brain injuries contributes to dementia onset (Attems and Jellinger, 2014; Bangen et al., 2015; Nation et al., 2012). Furthermore, as multiple VRFs often coexist and gradually increase AD risk (Luchsinger et al., 2005), recent research focused on these conditions in combination (*i.e.*, burden) rather than individually. Nevertheless, it remains to be elucidated whether vascular risk and AD pathophysiology have additive (Pettigrew et al., 2020; Vemuri et al., 2015) or synergistic (Bos et al., 2019; Rabin et al., 2022; Rabin et al., 2018) effects on neurodegeneration and cognitive decline. Also, the direct effects of VRFs on AD pathophysiology are still not completely understood. While some studies support a possible relation with Aβ or tau deposition (Gottesman et al., 2017; Kobe et al., 2020; Rabin et al., 2019; Vemuri et al., 2017), others point to the opposite (Bangen et al., 2015; Bilgel et al., 2021; Chui et al., 2012; Lo et al., 2012; Pettigrew et al., 2020; Rabin et al., 2018).

Together with Aβ and tau biomarkers, objective measures of neurodegeneration biomarkers allow for the investigation of vascular contributions to AD clinical progression. To this end, plasma neurofilament light (NfL) has demonstrated potential utility, as it has been shown to be a noninvasive and cost-effective axonal injury biomarker to track neurodegeneration in early AD (Benedet et al., 2020; Ferreira et al., 2023; Mattsson et al., 2019). Here, we studied CU participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) with longitudinal data on plasma NfL, cognition, and cerebrospinal fluid (CSF) AD biomarkers. Using a previously proposed composite vascular risk score, we tested whether VRF burden synergistically interacts with AD pathophysiology to accelerate neurodegeneration and cognitive decline in CU individuals. Secondarily, we also assessed whether VRF burden is related to changes in Aβ and tau biomarkers over time. Interactions between VRFs and AD pathophysiology may have potential implications for clinical trials, potentially suggesting that a combination of therapies targeting Aβ and tau pathologies, as well as VRFs, may enhance treatment outcomes.

2. Materials and methods

Data used in the present retrospective cohort study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Detailed information concerning inclusion and exclusion criteria has already been described (Petersen et al., 2010). Of note, participants were recruited between the ages of 55 and 90 years, completed at least 6 years of education, were fluent in Spanish or English, had a Hachinski ischemic score less than or equal to four, and had screening/baseline MRI scans without evidence of infection, infarction, or other focal lesions (individuals with multiple lacunes or lacunes in a critical memory structure were excluded). Institutional Review Boards of all involved sites approved the ADNI study, and all research participants or their authorized representatives provided written informed consent.

2.1. Participants

We evaluated CU individuals from the ADNI cohort. All participants presented Mini-Mental State Examination (MMSE) scores $\geq$ 24 and Clinical Dementia Rating (CDR) of 0. Participants did not have any significant neurological disease. To investigate the longitudinal cognitive trajectory, we assessed 503 individuals with available baseline medical data and CSF Elecsys biomarkers ($A\beta_{1-42}$ and tau phosphorylated at threonine 181 [p-tau_{181}]), as well as longitudinal neuropsychological testing (up to 6 years). We restricted these analyses to participants with CSF collected within 1.2 years of the first neuropsychological assessment.

Analyses evaluating the longitudinal trajectories of fluid biomarkers were performed in subsamples based on specific data availability. To assess neurodegeneration over time, individuals with longitudinal plasma NfL measurements (up to 4 years) were included ($n = 269$). To assess changes in CSF AD biomarkers, individuals with longitudinal CSF $A\beta_{1-42}$ and p-tau_{181} measurements (up to 6 years) were included ($n = 284$). More details regarding patient selection criteria are provided in Supplementary Methods 1. A Detailed description of the number of participants assessed at each time-point for the longitudinal biomarkers and cognitive measures is provided in Supplementary Table 1.

2.2. VRF burden

Information regarding medical history and use of medications was assessed in ADNI records to determine VRF burden. A previously proposed composite score to estimate the lifetime risk of cardiovascular disease (Berry et al., 2012; Lloyd-Jones et al., 2006) was adapted to assess cerebrovascular injuries in AD patients (Bangen et al., 2015; Nation et al., 2012). Baseline VRF burden was calculated using the modified score (Bangen et al., 2015; Nation et al., 2012), which considers the presence or absence of history for the following conditions: (i) cardiovascular disease (coronary artery disease [myocardial infarction, angina, stent placement, angioplasty, coronary artery bypass graft, coronary insufficiency], heart failure, or intermittent claudication); (ii) hypertension (positive medical history or use of antihypertensive medications), (iii) diabetes mellitus (positive medical history or use of antidiabetic therapy), (iv) hyperlipidemia (positive medical history or use of lipid-lowering drugs); (v) stroke or transient ischemic attack (TIA); (vi) smoking (ever or never); (vii) atrial fibrillation; and (viii) left ventricular hypertrophy. The total burden was calculated by the sum of individual VRFs (Bangen et al., 2015). Further information regarding VRF burden is reported in Supplementary Methods 2. A flowchart for

medication assessment is shown in Supplementary Fig. 1. A detailed list of included drugs is reported in Supplementary Table 2.

2.3. Biomarkers

CSF $A\beta_{1-42}$, reflecting brain Aβ pathology (A), and p-tau_{181}, reflecting brain tau pathology (T), were measured using fully automated Elecsys immunoassays (Roche Diagnostics) (Bittner et al., 2016; Lifke et al., 2019). Measurements outside the analytical range (< 200 pg/mL or > 1700 pg/mL for $A\beta_{1-42}$; < 8 pg/mL or > 120 pg/mL for p-tau_{181}) were set to their respective technical limit. Plasma NfL, a marker of neurodegeneration, was analyzed using an in-house immunoassay on the Single molecule array (Simoa) platform (Quanterix Corporation) (Gisslen et al., 2016). Two individuals presenting baseline NfL concentrations three standard deviations (SD) above the mean of the population were considered outliers and excluded from the analysis assessing plasma NfL trajectory, as previously done (Ferrari-Souza et al., 2022; Ferrari-Souza et al., 2023). Impaired kidney function has been shown to influence plasma NfL levels (Stocker et al., 2023). To investigate a potential confounding effect, kidney function was assessed by the estimated glomerular filtration rate (eGFR), which was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009). To directly assess cerebrovascular disease in exploratory analyses, we quantified white matter hyperintensity (WMH) volumes using previously described automated methods (DeCarli et al., 2013; Schwarz et al., 2009).

2.4. Cognition

The modified version of the Preclinical Alzheimer's Cognitive Composite (mPACC) (Donohue et al., 2014; Mattsson-Carlgren et al., 2020) was used as an outcome to evaluate the global cognitive trajectory of included participants as it was developed to detect cognitive changes in CU individuals with biomarker evidence of AD pathophysiology and adapted for the ADNI study. The mPACC was calculated by averaging the z-score of the following tests: MMSE, delayed recall for the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog), Logical Memory Delayed Recall, and the Trail Making Test B. Specific cognitive domains were assessed using the Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium composite scores for memory, executive function and language (Mukherjee et al., 2023).

2.5. Cutpoints

Based on previously published cutpoints, Aβ (A) positivity was defined as CSF $A\beta_{1-42}$ < 977 pg/mL, and tau (T) positivity was determined as CSF p-tau_{181} > 24 pg/mL (Blennow et al., 2019; Hansson et al., 2018). According to the 2018 NIA-AA criteria (Jack et al., 2018), the definition of preclinical AD relies on positivity for both Aβ and tau biomarkers in the absence of overt cognitive symptoms. This concept is supported by the fact approximately 25% of CU individuals older than 50 years show Aβ positivity (Jansen et al., 2022). Notably, biomarker evidence of Aβ pathology alone has relatively limited predictive accuracy for the development of cognitive impairment (Brookmeyer and Abdalla, 2018; Dubois et al., 2018). Additionally, recent evidence demonstrated that A+T + seems necessary for clinical conversion in a short-term period (Ossenkoppele et al., 2022). Therefore, in the present study, the presence of preclinical AD [(AT)+] was defined as positivity for both biomarkers (*i.e.*, A+T +), while other groups (*i.e.*, A+T-, A-T + , or A-T-) were considered as not having preclinical AD [(AT)-]. Nevertheless, to investigate potential associations in earlier and later phases of the Alzheimer's continuum, exploratory analyses were also conducted assessing Aβ (A) and tau (T) positivity separately rather than an AD pathophysiology composite [(AT)].

Neuropathologically-confirmed AD patients with two or more of the VRFs investigated are more likely to present occult cerebrovascular changes at autopsy; however, the presence of just one VRF is not necessarily associated with brain vascular lesions in these patients (Bangen et al., 2015; Nation et al., 2012). As previously done (Montagne et al., 2020; Nation et al., 2019), an elevated VRF burden (V+) was defined as a vascular score ≥ 2; individuals with a score < 2 were classified as having a low VRF burden (V-). In exploratory analyses, we divided participants into low and high WMH groups (WMH- and WMH+, respectively) based on a median split; thresholds were calculated separately in each method used to quantify WMH volume.

2.6. Statistical analysis

We used the R Statistical Software (version 4.0.2, http://www.r-project.org/) to perform statistical analyses. Linear mixed-effects (LME)-based analyses were carried out using the "lme4" package. LME models were performed to test the existence of a synergistic relationship between VRF burden and AD pathophysiology, as well as their independent effects, on longitudinal plasma NfL levels (Model A) and global cognitive performance (Model B). To confirm the presence of a synergistic relationship, we tested whether the interaction effects of VRF burden and AD pathophysiology were greater than the sum of their independent effects (Berrington de González and Cox, 2007; Slinker, 1998; Therriault et al., 2020). For visualization purposes, graphs were plotted stratifying participants according to VRF burden and AD pathophysiology [(AT)-V-, (AT)-V+ , (AT)+V-, and (AT)+V+]. We also used LME models to determine the association of VRF burden with changes in CSF $A\beta_{1-42}$ (Model C) and p-tau_{181} levels (Model D) over time. In these analyses, both CSF $A\beta_{1-42}$ or p-tau_{181} were treated as continuous variables. Models were adjusted for age, sex, years of education, apolipoprotein E ε4 (*APOE* ε4) status, and their interactions with time (Wagner et al., 2018), to properly account for potential confounders and to avoid significance-based selection (Steyerberg, 2019). Sensitivity analyses were conducted to investigate whether kidney function and outlier exclusion could affect our plasma NfL results. Additionally, sensitivity analyses assessing plasma NfL and cognitive trajectories were performed excluding A+T- individuals from the group considered as not having preclinical AD [(AT)-]. Further analyses were conducted to test the association of VRF burden and AD pathophysiology with longitudinal trajectories in specific cognitive domains (memory, executive function, and language). Exploratory analyses were performed as follows: (i) evaluating Aβ (A) and tau (T) positivity separately rather than as an AD pathophysiology composite [(AT)]; (ii) using VRF burden and AD pathophysiology biomarkers as continuous variables rather than dichotomously; and (iii) assessing vascular burden with WMH volume instead of VRF burden. All LME models were fitted including subject-specific random slopes and intercepts and time was treated as a continuous variable (years from baseline). Additionally, continuous predictors were standardized to facilitate comparison across estimates. Statistical significance level was set as $P < 0.05$, two-tailed. We used the interactive Shiny application (available at https://atrihub.shinyapps.io/power/), which is an interface to the "longpower" R package (Iddi and Donohue, 2022), to calculate the study power for assessing our primary objectives at a 5% significance level. According to the formula of Diggle *et al.* (Diggle et al., 2002), the LME analyses (two-sided) had over 94% power for testing interactive effects of VRF burden and AD pathophysiology on plasma NfL trajectory and over 85% power for testing interactive effects of VRF burden and AD pathophysiology on cognitive trajectory.

3. Results

A total of 503 participants (mean [SD] age, 72.9 [6.1] years; 220 men [43.7%]) were assessed in this study, of whom 13.1% had CSF biomarker evidence of preclinical AD [(AT)+], and 45.9% presented an elevated VRF burden (V+). Sample demographics, biomarker and

Table 1
Demographics and key characteristics of participants[a].

	(AT)-V-	(AT)-V+	(AT)+V-	(AT)+V+
No.	238	199	34	32
Age at baseline, y	72.2 (6.3)	73.2 (6.0)	72.9 (5.9)	77.4 (5.0)
Male, No. (%)	83 (34.9)	105 (52.8)	16 (47.1)	16 (50.0)
Education, y	16.6 (2.6)	16.5 (2.6)	16.9 (2.5)	15.8 (2.2)
APOE ε4 carriers, No. (%)	57 (23.9)	54 (27.1)	22 (64.7)	18 (56.3)
Individual VRFs at baseline, No. (%)[b]				
Cardiovascular disease	2 (0.8)	31 (15.6)	0 (0.0)	8 (25.0)
Hypertension	48 (20.2)	169 (84.9)	7 (20.6)	27 (84.4)
Diabetes mellitus	1 (0.4)	40 (20.1)	0 (0.0)	4 (12.5)
Atrial fibrillation	1 (0.4)	10 (5.0)	0 (0.0)	3 (9.4)
Smoking	27 (11.3)	65 (32.7)	4 (11.8)	11 (34.4)
TIA / stroke	1 (0.4)	12 (6.0)	0 (0.0)	2 (6.3)
Hyperlipidemia	58 (24.4)	173 (86.9)	11 (32.4)	30 (93.8)
VRF burden at baseline	0.6 (0.5)	2.5 (0.7)	0.6 (0.5)	2.7 (0.5)
Medication use at baseline, No. (%)				
Lipid-lowering	49 (20.6)	149 (74.9)	9 (26.5)	27 (84.4)
Antihypertensive	47 (19.7)	155 (77.9)	7 (20.6)	24 (75.0)
Antidiabetic	1 (0.4)	31 (15.6)	0 (0)	4 (12.5)
CSF $A\beta_{1-42}$ at baseline, pg/mL	1265.1 (417.1)	1282.0 (406.7)	691.5 (165.0)	703.6 (177.9)
CSF p-tau_{181} at baseline, pg/mL	19.1 (7.4)	20.1 (7.6)	33.5 (7.2)	35.6 (10.8)
Plasma NfL at baseline, pg/mL[c]	32.3 (13.6)	33.0 (14.5)	35.6 (5.5)	41.2 (10.5)
MMSE score at baseline	29.2 (1.1)	29.0 (1.2)	29.3 (0.9)	28.9 (1.3)
mPACC score at baseline	0.5 (2.4)	-0.3 (2.6)	-0.1 (2.5)	-1.7 (2.4)
No. of cognitive assessments[d]	4.2 (1.9)	4.6 (1.9)	4.6 (1.9)	4.8 (1.8)
Follow-up, y	3.6 (1.8)	3.8 (1.8)	3.5 (1.9)	3.7 (1.8)

Participants were stratified according to VRF burden and AD pathophysiology. Continuous variables are presented as mean (SD).

[a] In this table, baseline refers to the visit of first clinical assessment with neuropsychological testing.

[b] Prevalence of left ventricular hypertrophy is not displayed in the table because only one participant in the (AT)-V+ group was described to have this condition in the ADNI database.

[c] Assessed in a subset of 229 individuals who had available plasma NfL measurement at the same visit of first neuropsychological assessment.

[d] The number of cognitive assessments ranged from 2 to 8, being the median 5.

clinical characteristics are summarized in Table 1. In addition, detailed demographic information regarding subsamples used to evaluate the trajectory of plasma NfL and CSF AD biomarkers - $A\beta_{1-42}$ and p-tau_{181} – are available in Supplementary Table 3 and Supplementary Table 4. At baseline, a higher cumulative burden of VRFs was significantly associated with high WMH volume ($P < 0.001$).

3.1. VRF burden and AD pathophysiology act synergistically on plasma NfL levels

LME model coefficients for the associations among VRF burden, AD pathophysiology, and longitudinal plasma NfL can be found in Table 2, Model A. At baseline, there was a trend for the association between the presence of preclinical AD and higher concentrations of plasma NfL ($\beta = 6.23$, $P = 0.082$). On the other hand, VRF burden was not significantly associated with baseline plasma NfL levels ($P = 0.542$), nor was the interaction between VRF burden and AD pathophysiology ($P = 0.754$). Concerning plasma NfL longitudinal trajectory, there was a significant three-way interaction (VRF burden x AD pathophysiology x time; $\beta = 5.08$, $P = 0.016$), indicating that an elevated VRF burden acted synergistically with the presence of preclinical AD to increase plasma NfL concentrations longitudinally. To confirm the synergistic interaction, we found that the interaction effect of VRF burden and AD pathophysiology was greater than the sum of their independent effects (Table 3, Model A). Interestingly, VRF burden x time and AD pathophysiology x time interaction terms were not significant ($P = 0.351$ and $P = 0.793$, respectively). For results stratified by groups, see Figure 1A. Similar

Table 2
LME model coefficients.

	β (95% CI)	*T*-value	*P*-value
Model A[a]: plasma NfL ~ VRF burden x AD pathophysiology x time + covariates[e] x time			
Elevated VRF burden	1.04 (−2.32 to 4.41)	0.61	0.542
Preclinical AD	6.23 (−0.76 to 13.23)	1.75	0.082
Elevated VRF burden x preclinical AD	-1.44 (−10.44 to 7.55)	-0.31	0.754
Elevated VRF burden x time	-0.72 (−2.23 to 0.79)	-0.94	0.351
Preclinical AD x time	0.42 (−2.71 to 3.55)	0.26	0.793
Elevated VRF burden x preclinical AD x time	5.08 (0.99 to 9.17)	2.43	**0.016**
Model B[b]: mPACC ~ VRF burden x AD pathophysiology x time + covariates[e] x time			
Elevated VRF burden	-0.39 (−0.81 to 0.02)	-1.86	0.063
Preclinical AD	-0.02 (−0.81 to 0.78)	-0.04	0.969
Elevated VRF burden x preclinical AD	-0.58 (−1.70 to 0.54)	-1.01	0.312
Elevated VRF burden x time	0.05 (−0.08 to 0.18)	0.79	0.431
Preclinical AD x time	-0.22 (−0.48 to 0.04)	-1.67	0.096
Elevated VRF burden x preclinical AD x time	-0.43 (−0.79 to 0.07)	-2.34	**0.020**
Model C[c]: CSF $A\beta_{1-42}$ ~ VRF burden x time + covariates[e] x time			
Elevated VRF burden	-44.33 (−140.45 to 51.79)	-0.90	0.367
Elevated VRF burden x time	1.76 (−11.07 to 14.59)	0.27	0.789
Model D[d]: CSF p-tau_{181} ~ VRF burden x time + covariates[e] x time			
Elevated VRF burden	0.21 (−1.91 to 2.32)	0.19	0.848
Elevated VRF burden x time	-0.13 (−0.37 to 0.12)	-1.01	0.314

VRF burden refers to a dichotomous variable (V- *vs.* V+), as well as AD pathophysiology [(AT)- *vs.* (AT)+]. Continuous predictors were standardized prior to model entry. CI = confidence interval.

[a] Marginal R^2: 0.32; Conditional R^2: 0.79.

[b] Marginal R^2: 0.21; Conditional R^2: 0.74.

[c] Marginal R^2: 0.15; Conditional R^2: 0.92.

[d] Marginal R^2: 0.10; Conditional R^2: 0.98.

[e] Potential confounders included in the models as covariates are the following: age, sex, years of education, and *APOE* ε4 status.

results were observed in sensitivity analysis adjusting for kidney function (indexed by the eGFR; Supplementary Table 5) and including outliers (Supplementary Fig. 2). Consistent findings were also observed in sensitivity analysis excluding A+T- individuals from the group categorized as not having preclinical AD (Supplementary Fig. 3A).

3.2. VRF burden and AD pathophysiology act synergistically on cognitive decline

Coefficients from LME models assessing the associations among VRF burden, AD pathophysiology, and longitudinal cognitive decline are shown in Table 2, Model B. We observed a trend for the association of worse baseline cognitive performance with an elevated VRF burden ($\beta = -0.39$, $P = 0.063$). In contrast, no relation was detected with AD pathophysiology ($P = 0.969$) or with VRF burden x AD pathophysiology interaction ($P = 0.312$). Regarding cognitive trajectory, the three-way interaction (VRF burden x AD pathophysiology x time) was significant for predicting longitudinal cognitive decline ($\beta = -0.43$, $P = 0.020$), statistically supporting the notion that simultaneously having an elevated VRF burden and the presence of preclinical AD accelerates the rates of cognitive decline more than the added impact of these conditions (*i.e.*, synergy). Noteworthy, the interactive effect of VRF burden and AD pathophysiology was greater than the sum of their independent effects, confirming the presence of a synergistic relationship rather than the presence of additive effects (Table 3, Model B). Even though VRF burden was not associated with changes in cognition over time (*i.e.*, VRF burden x time interaction term was not significant; $P = 0.431$), we detected a trend for the impact of the presence of preclinical AD on the

Table 3
Independent and interactive effects of VRF burden and AD pathophysiology on longitudinal plasma NfL and cognitive trajectories.

Model (outcome)	Independent VRF burden effect	Independent AD pathophysiology effect	Sum of independent effects	VRF burden and AD pathophysiology interaction effect
Model A (plasma NfL)[a]	-0.72	0.42	-0.30	5.08
Model B (mPACC)[b]	0.05	-0.22	-0.17	-0.43

Absolute values of the β coefficients from LME models testing the presence of synergistic interactions between VRF burden and AD pathophysiology. The independent effects correspond to the absolute β coefficients of the two-way interactions of VRF burden with time and AD pathophysiology with time. The interaction effects correspond to the absolute β coefficients of the three-way interactions of VRF burden and AD pathophysiology with time. Noteworthy, VRF burden refers to a dichotomous variable (V- *vs.* V+), as well as AD pathophysiology [(AT)- *vs.* (AT)+].

[a] Model A: plasma NfL ~ VRF burden x AD pathophysiology x time + age x time + sex x time + years of education x time + *APOE* ε4 status x time.

[b] Model B: mPACC ~ VRF burden x AD pathophysiology x time + age x time + sex x time + years of education x time + *APOE* ε4 status x time.

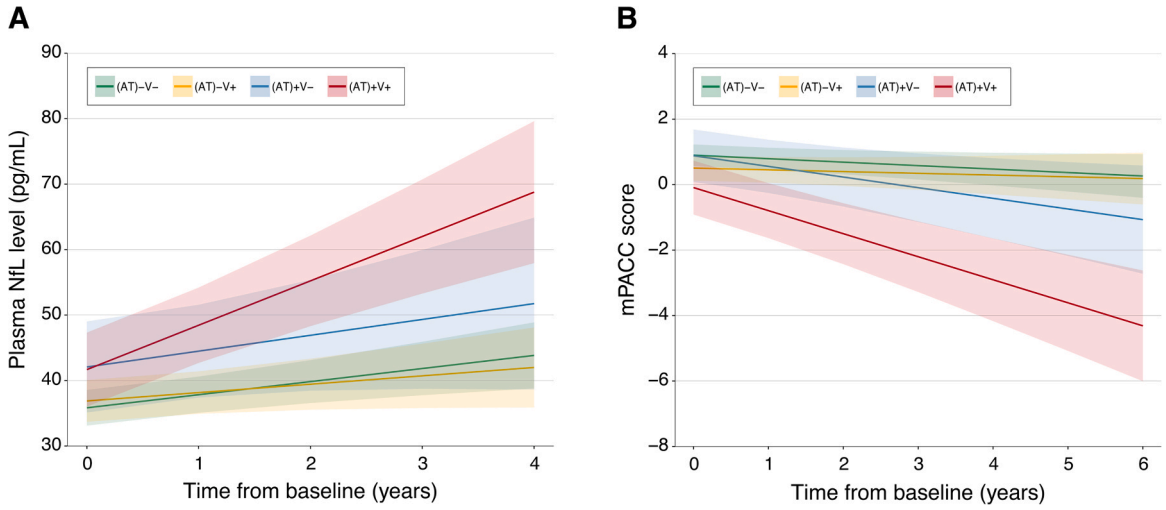

Fig. 1. Elevated VRF burden accelerates neurodegeneration and cognitive decline in individuals with preclinical AD. Mean predicted trajectories and 95% confidence interval (CI) estimated from LME models according to baseline VRF burden and AD pathophysiology. (**A**) Longitudinal neurodegeneration measured by plasma NfL levels over a 4-year follow-up period and (**B**) longitudinal cognitive trajectory indexed by the mPACC score over a 6-year follow-up period. Each model was adjusted for age, sex, years of education, *APOE* ε4 status, and their interaction with time.

rate of cognitive decline (*i.e.*, AD pathophysiology x time interaction term; $\beta = -0.22$, $P = 0.096$). For results stratified by groups, see Figure 1B. We found consistent results in the sensitivity analysis that excluded A+T individuals from the group classified as not having preclinical AD (Supplementary Fig. 3B). Further analyses assessing cognitive domains revealed a significant interaction between VRF burden and AD pathophysiology on longitudinal decline in memory function (Supplementary Fig. 4A), but not in executive (Supplementary Fig. 4B) or language functions (Supplementary Fig. 4C).

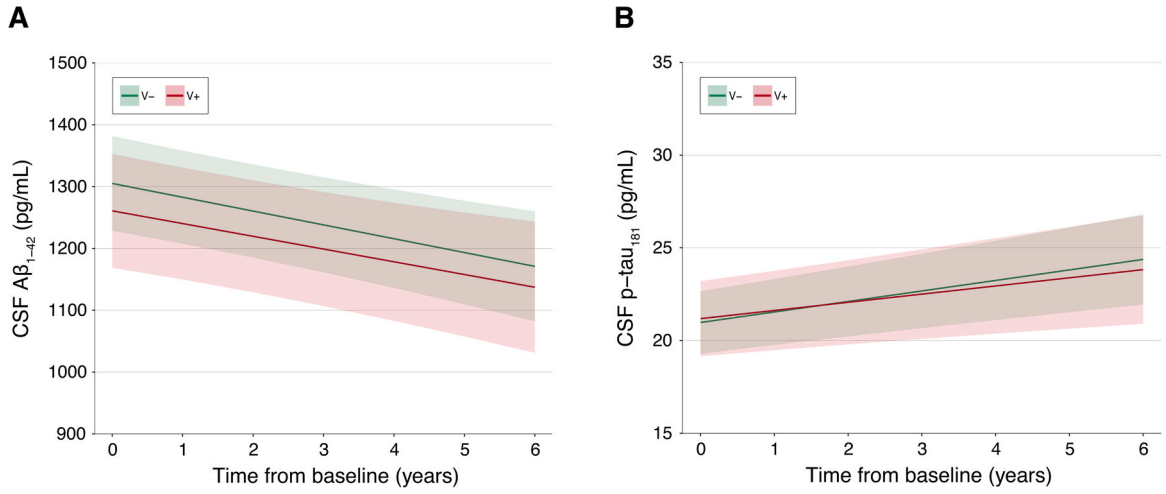

Fig. 2. VRF burden is not associated with changes over time in CSF $A\beta_{1-42}$ and p-tau_{181} levels. Mean predicted trajectories and 95% confidence interval (CI) estimated from LME models according to baseline VRF burden. (**A**) CSF $A\beta_{1-42}$ longitudinal trajectory over a 6-year follow-up and (**B**) CSF p-tau_{181} longitudinal trajectory over a 6-year follow-up period. Each model was adjusted for age, sex, years of education, *APOE* ε4 status, and their interaction with time.

3.3. VRF burden is not associated with CSF AD biomarkers

In LME models evaluating CSF $A\beta_{1-42}$ and p-tau_{181} trajectories, neither the main effect of VRF burden nor the VRF burden x time interaction was significant (Figure 2A and Model C in Table 2 for CSF $A\beta_{1-42}$ and Figure 2B and Model D in Table 2 for p-tau_{181}; all $P \geq 0.314$). Hence, VRF burden was not associated with baseline CSF $A\beta_{1-42}$ and p-tau_{181} levels nor with changes in its levels over time.

3.4. Exploratory analyses

We conducted exploratory analyses to better investigate the effects of VRF burden and AD pathophysiology on longitudinal plasma NfL and cognition. In the model assessing Aβ (A) and tau (T) positivity separately, we observed that only the A+T + V+ group presented significantly higher plasma NfL increase over 4 years in comparison to the reference group (Supplementary Fig. 5A). Using a similar model, we found that the A+T-V-, A+T + V-, and A+T + V+ groups had significantly higher cognitive decline over 6 years in comparison to the reference group, with the A+T + V+ group showing the highest rates of cognitive deterioration (Supplementary Fig. 5B). LME models using CSF AD biomarkers as continuous variables revealed that a significant interaction between CSF $A\beta_{1-42}$ and CSF p-tau_{181} on longitudinal plasma NfL increase and cognitive decline in individuals with an elevated VRF burden but not in individuals with a low VRF burden (Supplementary Table 6 for plasma NfL and Supplementary Table 7 for mPACC). Analyses assessing VRF burden as the cumulative burden of VRFs are shown in Supplementary Fig. 6 for longitudinal plasma NfL and cognitive trajectories. Furthermore, models testing the effects of the cumulative burden of VRFs on longitudinal CSF $A\beta_{1-42}$ and p-tau_{181} levels are displayed in Supplementary Fig. 7. In relation to our main analyses, similar results were observed when evaluating vascular burden with WMH volume instead of VRF burden (Supplementary Figs. 8 and 9). Altogether, the exploratory analyses further support our previous findings that vascular burden does not directly influence AD pathophysiology; however, these conditions jointly potentiate longitudinal neurodegeneration and cognitive deterioration.

4. Discussion

We showed that VRF burden interacts synergistically with AD pathophysiology to drive longitudinal increases in plasma NfL levels, as well as longitudinal decline in mPACC scores in CU older adults. However, VRF burden was not associated with changes in CSF AD biomarkers. These findings suggest that the impact of VRF burden on neurodegeneration and cognitive decline varies according to AD pathophysiology status in CU individuals.

Our results suggest that VRF burden and AD pathophysiology are synergistically associated with longitudinal neurodegeneration measured by plasma NfL. Recent observations indicated that vascular risk and Aβ are interactively related to longitudinal brain atrophy in CU individuals (Rabin et al., 2022). Accordingly, although assessing a different neurodegeneration biomarker, it was reported that CU individuals with an elevated Framingham Risk Score present higher rates of increase in CSF total tau (t-tau) levels only when having abnormal Aβ and tau biomarkers at baseline (Bos et al., 2019). Given that the association was restricted to the A+T + group, this finding further supports the notion of an interactive association between vascular risk and AD pathophysiology. Our results are also in agreement with cross-sectional evidence showing that vascular risk amplifies AD pathophysiology impact on axonal damage, as indexed by CSF NfL (Osborn et al., 2019), and potentiates Aβ effects on lower cortical thickness in AD-vulnerable brain regions (Villeneuve et al., 2014). Here, we provided the first evidence of an interaction between vascular risk and AD pathophysiology on longitudinal plasma NfL, which can have relevant implications for the design of clinical trials.

We observed that VRF burden synergistically interacts with AD pathophysiology to accelerate subsequent longitudinal cognitive decline, particularly in memory function. The notion that vascular risk and AD pathophysiology jointly promote cognitive deterioration is also supported by evidence from the literature. In participants from the Harvard Aging Brain Study, a synergistic association of vascular risk and Aβ burden with cognitive decline was observed in CU older adults (Rabin et al., 2018). Similarly, another longitudinal study including CU older adults demonstrated that an increased Framingham Risk Score was associated with higher rates of cognitive decline only in the A+T + group, suggesting an interactive effect (Bos et al., 2019). In the present work, we expanded the aforementioned evidence by showing that the interplay between VRF burden and AD pathophysiology distinctly impacts cognition, predominantly affecting the memory cognitive domain. On the other hand, a recent investigation evaluating CU participants from the Biomarkers for Older Controls at Risk for Dementia study concluded that midlife vascular risk and AD pathophysiology have additive rather than synergistic effects on cognitive decline (Pettigrew et al., 2020). Besides assessing VRFs in midlife and having a longer follow-up (mean of 13.9 years), other factors could also account for the divergent results, such as vascular risk assessment (dichotomization by 0 or $\geq$ 1 evaluating the following conditions: hypertension, hypercholesterolemia, diabetes, smoking, and obesity) and cutpoints used for CSF AD biomarkers (based on tertiles calculated considering midlife biomarker concentrations). Using MRI-derived brain infarcts and WMH as markers of cerebrovascular disease, results from the Mayo Clinic Study of Aging cohort corroborated that brain vascular and Aβ pathologies have additive effects on cognitive decline in CU older adults (Vemuri et al., 2015). Even without a clear consensus in the literature, these findings reinforce that VRFs and AD pathophysiology often coexist and play pivotal roles in brain aging.

Our findings indicate that VRF burden does not directly impact AD pathophysiology. Previous studies have reported inconsistent relations between VRFs and AD pathophysiology. While some investigations found that VRFs were cross-sectionally associated either with higher Aβ or tau burden (Kobe et al., 2020; Vemuri et al., 2017), most evidence is against the presence of such relations (Bangen et al., 2015; Bilgel et al., 2021; Chui et al., 2012; Rabin et al., 2018). Our findings are in line with recent studies evaluating the associations between vascular risk scores and longitudinal changes in the CSF AD biomarkers (Bos et al., 2019; Lo et al., 2012; Pettigrew et al., 2020). In contrast, other investigations found that the number of midlife VRFs was associated with late-life Aβ deposition (Gottesman et al., 2017), as well as that high vascular risk and elevated Aβ burden were interactively associated with tau PET accumulation (Rabin et al., 2019; Yau et al., 2022), which was proposed to further mediate cognitive decline (Yau et al., 2022). Interestingly, a recent study in the Swedish BioFINDER-2 cohort found that vascular imaging features (but not VRFs) influence Aβ effects on longitudinal tau deposition in CU older adults (Coomans et al., 2023). Critical questions remain on the association between vascular burden and AD pathophysiology, and further work is warranted to elucidate the reasons for the discordant findings reported in the literature.

Not rarely do individuals without cognitive impairment present AD pathophysiology (Bennett et al., 2006; Perez-Nievas et al., 2013; Price and Morris, 1999), highlighting the role of both resilience mechanisms and concomitant pathological processes in the clinical expression of AD. It has been proposed that vascular dysfunction has an early role in AD progression (Iturria-Medina et al., 2016). There are different potential mechanisms by which vascular factors contribute to cognitive impairment and dementia, such as reduction in cerebral blood flow and hypoxia, blood-brain barrier (BBB) breakdown, endothelial dysfunction, systemic inflammation and oxidative stress, and disruption of trophic coupling (Zlokovic et al., 2020). Our results support the notion that CU individuals exposed to higher VRFs might have a decreased threshold for neurodegeneration and cognitive decline induced by AD pathophysiology. As previously suggested, a possible explanation is that VRFs

influence the progression of AD through the promotion of cerebrovascular injuries rather than through a direct effect on AD pathophysiology (Chui et al., 2012). Furthermore, BBB breakdown, an important feature in early AD (Montagne et al., 2015; van de Haar et al., 2016a; van de Haar et al., 2016b) and a potential biomarker of cognitive dysfunction (Nation et al., 2019), is associated with both AD pathophysiology and VRFs, but at different molecular levels (Lin et al., 2021), stressing the role of brain vasculature in cognitive impairment. Taken together, VRFs appear to impact brain resilience mechanisms against the deposition of Aβ-containing extracellular neuritic plaques and tau-containing neurofibrillary tangles.

At the moment, there is no pharmacological treatment that can unquestionably stop AD clinical deterioration. Since AD is a multifactorial disease, it is reasonable to consider that an effective therapy would need to have multiple targets, not only Aβ and tau accumulation. Also, given that AD pathophysiology starts to accumulate many years before the onset of clinical symptoms (Sperling et al., 2011), new clinical trials often focus on asymptomatic individuals presenting biomarker evidence of Aβ and tau pathologies (*i.e.*, preclinical stages of AD) (Cummings et al., 2021; Sperling et al., 2014). The findings from the present work corroborate that the development of therapies targeting both VRFs and AD pathophysiology in AD preclinical stages could potentiate treatment response.

Here, we used medical records to calculate a VRF burden score developed to assess cerebrovascular pathologies (Bangen et al., 2015; Nation et al., 2012). We employed this composite vascular risk score due to its value in (i) studying AD progression, as it was validated in autopsy-confirmed AD patients; (ii) predicting mild cerebrovascular changes, which is particularly important as the ADNI study does not include individuals with significant cerebrovascular lesions; and (iii) assessing a sample with an age range from 55 to 90 years, which is a limitation for using other vascular risk scores, such as the Framingham Risk Score that was initially validated in a sample with 30 to 74 years (D'Agostino et al., 2008). Given that the VRF burden was assessed as the sum of individual risk factors, future studies should address potential weighted contributions, as well as differential mechanisms potentially underlying the influence of each VRF on AD pathogenesis. Neuroimaging studies suggested specific pathways connecting cerebrovascular lesions and AD pathogenesis development (Chirinos et al., 2019; Coomans et al., 2023; Gottesman et al., 2020; Moore et al., 2021; Pasha et al., 2020). Thus, imaging vascular disease markers may provide a unique opportunity to elucidate the links between individual VRFs and AD progression.

Cognition is the primary outcome of interest in disease-modifying drug trials; however, individuals with preclinical AD can stay cognitively stable over many years (Dubois et al., 2021). Therefore, an important limitation for the performance of these trials is the need for high sample sizes and extended follow-ups. In this context, the use of surrogate markers of disease progression can be a useful alternative. Although imaging and CSF biomarkers for AD are highly correlated with brain AD pathophysiology, their cost and invasiveness, respectively, restrict their applicability within trial settings. Recently, blood-based biomarkers have emerged as a simple and cost-effective alternative to facilitate clinical trials. In this scenario, a growing body of evidence suggests that plasma NfL is a robust neurodegeneration marker to monitor AD progression (Benedet et al., 2020; Mattsson et al., 2019). Additionally, a recent study by our group demonstrated that plasma NfL is a useful and cost-effective biomarker to monitor neurodegeneration in large-scale trials focusing on CU individuals (Ferreira et al., 2023). Plasma NfL is less invasive and expensive than imaging and CSF neurodegeneration markers (*e.g.*, MRI and CSF NfL). Nevertheless, no previous study has longitudinally appraised the associations of VRF burden and AD pathophysiology with plasma NfL trajectories. Hence, we selected plasma NfL as the marker to track longitudinal neurodegeneration, considering its potential utility in clinical trials. Similar to the pattern observed for cognition, our results showed that the synergy between VRF burden and AD pathophysiology led to longitudinal increases in plasma NfL. Together, these findings suggest that plasma NfL may be used as a surrogate marker to track therapeutic response in trials targeting VRFs and AD pathophysiology.

Some limitations need to be highlighted to interpret our results. The ADNI study involves a selective population of mostly white participants without substantial cerebrovascular lesions, which might further jeopardize the generalizability of our results, especially considering that different ethnic groups are heterogeneously affected by VRFs (Kibria et al., 2021; Kurian and Cardarelli, 2007; Yusuf et al., 2001). We had a restricted number of study participants with preclinical AD [(AT)+]. This could increase the risk of type I and type II errors in our interaction models. Besides, although estimations indicated that we had adequate power for testing our primary objectives, we may have been underpowered to detect smaller effects that were unrelated to the interaction between VRF burden and AD pathophysiology. Thus, we cannot rule out potential independent impacts of VRF burden and AD pathophysiology on neurodegeneration and cognition, because their more modest effects could have not been proven *via* $P < 0.05$. Our findings need to be replicated in subsequent studies across multiple representative cohorts with larger sample sizes, a wide range of cardiovascular disorders, and diverse ethnic groups. Midlife and late-life exposures to VRFs may be differentially related to AD risk (Tolppanen et al., 2012). The late-life assessment performed in the present study does not reflect the duration of exposure to VRFs and is confounded by late-life physiological changes related to frailty. Thus, we cannot determine whether our findings would differ considering the age of onset of VRFs. In addition, the presence of VRFs was determined based on previous diagnosis and use of medications information collected in clinical interviews rather than diagnosis performed at study entry with objective measurements, potentially being a source of bias. It is also important to recognize that we could not address whether individuals with treated VRFs have a similar risk in comparison to those with untreated VRFs. Lastly, cutpoints are always subject to conceptual and analytical idiosyncrasies, and the results could change whether we used different approaches to define cutpoints for AD pathophysiology and VRF burden.

5. Conclusions

In conclusion, we observed that VRF burden and biomarker evidence of AD pathophysiology are synergistically associated with neurodegeneration and cognitive decline in CU individuals. By contrast, VRF burden does not influence Aβ and tau pathologies. Our results provide additional evidence for the performance of clinical trials targeting VRFs and AD pathophysiology. Additionally, these trials could have advantages from using plasma NfL as a surrogate to track therapeutic response in these trials. Importantly, further community-based studies are warranted to confirm our findings.

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CRediT authorship contribution statement

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Competing interests

NJA has given lectures in symposia sponsored by Lilly and Quanterix. HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Pinteon Therapeutics, Red Abbey Labs, reMYND, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, all unrelated to the work presented in this paper. SOM reports receiving speaker fees from Medtronic, Novartis, Novo Nordisk, Pfizer, Bayer and advisory board fees from Boehringer Ingelheim. PR-N has served on scientific advisory boards and/or as a consultant for Eisai, Novo Nordisk and Roche. ERZ serves on the scientific advisory board of Next Innovative Therapeutics. All other authors declare no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.12.008.

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