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Adverse Vascular Risk Relates to Cerebrospinal Fluid Biomarker Evidence of Axonal Injury in the Presence of Alzheimer's Disease Pathology

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Abstract.
Background: Vascular risk factors promote cerebral small vessel disease and neuropathological changes, particularly in white matter where large-caliber axons are located. How Alzheimer's disease pathology influences the brain's vulnerability in this regard is not well understood.
Objective: Systemic vascular risk was assessed in relation to cerebrospinal fluid concentrations of neurofilament light, a biomarker of large-caliber axonal injury, evaluating for interactions by clinical and protein markers of Alzheimer's disease.
Methods: Among Alzheimer's Disease Neuroimaging Initiative participants with normal cognition ($n = 117$), mild cognitive impairment ($n = 190$), and Alzheimer's disease ($n = 95$), linear regression related vascular risk (as measured by the modified Framingham Stroke Risk Profile) to neurofilament light, adjusting for age, sex, education, and cognitive diagnosis. Interactions were assessed by cognitive diagnosis, and by cerebrospinal fluid markers of $A\beta_{42}$, hyperphosphorylated tau, and total tau.

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Results: Vascular risk and neurofilament light were not related in the main effect model ($p = 0.08$). However, interactions emerged for total tau ($p = 0.01$) and hyperphosphorylated tau ($p = 0.002$) reflecting vascular risk becoming more associated with cerebrospinal fluid neurofilament light in the context of greater concentrations of tau biomarkers. An interaction also emerged for the Alzheimer's disease biomarker profiles ($p = 0.046$) where in comparison to the referent 'normal' biomarker group, individuals with abnormal levels of both $A\beta_{42}$ and total tau showed stronger associations between vascular risk and neurofilament light.

Conclusion: Older adults may be more vulnerable to axonal injury in response to higher vascular risk burdens in the context of concomitant Alzheimer's disease pathology.

Keywords: Alzheimer's disease, cerebrovascular, neurodegeneration, neurofilament light, vascular risk

INTRODUCTION

Modifiable vascular risk factors, such as systolic hypertension [1], diabetes mellitus [2], and smoking [3, 4] are associated with an increased incidence of cognitive impairment and dementia, likely due to effects on cerebral small vessel disease (SVD) contributing to abnormal cognitive aging [5]. Cerebral SVD exists in the majority of pathologically-confirmed dementia cases [6] and disrupts network connectivity [7, 8], conferring cognitive impairment and decline [9]. Longitudinal data from large-scale multicenter collaborations (i.e., the Leukoaraiosis and Disability (LADIS) Study) are increasingly substantiating the role of cerebral SVD and white matter changes in contributing to cognitive and motor declines, depressive symptomatology, and reduction of functional autonomy with aging [10], including clinical manifestation of vascular-related dementia [11].

Cerebral SVD is the most common pathology to co-occur with Alzheimer's disease (AD) [12, 13], lowers the threshold for clinical expression of AD pathology [14], and compromises the efficacy of anti-amyloid therapy [15]. Extant literature has yet to fully establish the extent to which AD and SVD confer disparate versus overlapping pathological cascades, constituting a critical knowledge gap with important implications for identifying effective prevention and treatment targets. Even if SVD and AD represent unique injury pathways, these two disease processes may exacerbate one another and compromise the aging brain in a synergistic manner [13].

Cerebral white matter is particularly vulnerable to ischemic injury from SVD in advanced age [16], but little is known about whether co-occurring AD pathology affects susceptibility to white matter damage, including axonal injury, in response to vascular risk factors. Animal models of compromised cerebrovascular function suggest ischemia promotes diffuse amyloid-β protein precursor expression [17] and increased amyloid-β (Aβ) deposition [18]. Given that Aβ clearance occurs through vascular-mediated pathways across the blood-brain barrier [19] and through interstitial fluid bulk flow between perivascular basement membranes [20, 21], cerebral SVD may propagate Aβ deposition by interfering with the integrity of clearance pathways [22], contributing to worse disease trajectory [23, 24]. Progressive degeneration of cholinergic cells in AD can also disrupt regional cerebral blood flow homeostasis [25, 26], increasing susceptibility of the cerebral vasculature to damage [27, 28]. Overall, vascular risk likely drives cognitive and neurodegenerative changes through non-AD pathways [29] but concomitantly exacerbates AD-related damage once neural injury exists [30].

A current limitation in understanding the implications of SVD is that the cerebral microvasculature is too small to be clearly visualized *in vivo*, thus interfering with prompt diagnosis and intervention [31]. Accordingly, there is a pressing need to better characterize underlying physiological changes related to cerebrovascular disease burden and unhealthy brain aging [31]. Neurofilament light (NFL) is a protein polymer found in large-caliber myelinated axons. Elevated cerebrospinal fluid (CSF) levels of NFL are posited to reflect axonal injury [32] and correlate with white matter damage and clinical severity across neurodegenerative diseases [33–35]. Unlike the mechanistically heterogeneous nature of white matter hyperintensities observed on magnetic resonance imaging (MRI) fluid-attenuated inversion recovery (FLAIR), which correspond to multiple structural changes and pathological processes [36], CSF concentrations of NFL allow for measurement of axonal injury. Accordingly, CSF NFL offers a means of measuring axonal damage in the aging brain. Given the high prevalence of vascular-related health problems among older adults at risk for AD [37], more research is warranted to elucidate how burgeoning AD pathology influences the aging brain's vulnerability to vascular-related damage, including axonal injury. This research topic is especially clinically relevant given the modifiable nature of most vascular risk factors and paucity of promising prevention and treatment targets for AD.

In the current study, we assess how vascular risk burden as measured by the Framingham Stroke Risk Profile (FSRP) relates to axonal injury as measured by CSF NFL in the context of varying degrees of concomitant AD pathology. The FSRP is a composite measure of vascular risk burden. Originally designed to predict incidents of clinical stroke, FSRP scores also correspond to neuroimaging evidence of cerebral SVD, including white matter hyperintensities [38, 39] silent cerebral infarcts [40, 41], and microbleeds [42]. We leveraged the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, which represents a spectrum from normal cognition (NC), mild cognitive impairment (MCI), and clinical AD. In doing so, we are able to 1) test interactions between FSRP and cognitive diagnosis to determine whether FSRP and NFL associations depend on the presence of clinical symptoms and 2) test interactions between FSRP and AD CSF biomarkers (i.e., $A\beta_{42}$, total tau [t-tau], and hyperphosphorylated tau [p-tau]) to determine how associations differ as a function of co-occurring evidence of AD. Since co-occurring cerebrovascular disease and AD synergistically confer worse clinical outcomes [43, 44], we hypothesize that the association between FSRP and CSF NFL will be strongest with increased AD pathology defined as presence of abnormal concentrations of AD CSF biomarkers (i.e., $A\beta_{42}$, t-tau, and p-tau) and clinical evidence (i.e., stronger associations across cognitive spectrum from NC to clinical AD).

MATERIALS AND METHODS

Participants

Participants were drawn from the ADNI, launched in 2003 (http://adni.loni.usc.edu). The original ADNI study enrolled approximately 800 participants, aged 55–90 years, excluding major neurological disease (other than AD), and history of brain lesion, head trauma, or psychoactive medication use (for full inclusion/exclusion criteria, please refer to http://www.adni-info.org). Participants were enrolled based on criteria outlined in the ADNI protocol (http://www.adni-info.org/Scientists). Specifically, NC participants showed no signs of depression, MCI, or dementia. Participants with MCI presented with subjective memory concerns and impaired performance on Wechsler Memory Scale Logical Memory II in the context of preserved daily living activities and no significant levels of impairment in other cognitive domains nor signs of dementia. Participants with AD met clinical criteria for dementia with a predominantly amnestic profile. Written informed consent was obtained from all participants prior to assessments at each site. Analysis of ADNI's publicly available database was approved by our local Institutional Review Board. We accessed publicly available data from ADNI on 06/09/2017. For the current study, we included participants from the ADNI1 cohort with available baseline CSF biomarker samples and vascular risk factor data necessary to calculate the FSRP.

Vascular risk burden

To assess systemic vascular risk burden, we calculated a modified FSRP in the ADNI dataset based on baseline visit data. FSRP assigns points by sex for age, systolic blood pressure (accounting for antihypertensive medication usage), history of diabetes, current cigarette smoking, prevalent cardiovascular disease (i.e., history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or heart failure), left ventricular hypertrophy, and history of atrial fibrillation [45]. The FSRP calculation was modified for the current study by excluding left ventricular hypertrophy due to this information being unavailable in ADNI [29, 46].

Lumbar puncture and biochemical analyses

ADNI's CSF protocol, including collection, processing, and storage procedures, have been outlined in detail [47]. We leveraged the master CSF dataset compiled by the University of Pennsylvania (UPENNBIOMK_MASTER) and used the first measure of $A\beta_{42}$, t-tau, and p-tau for each participant. CSF NFL levels were quantified by the Blennow laboratory in Sweden using a sandwich ELISA method (UmanDiagnostics, Sweden) following established procedures [48].

AD biomarker profiles

Participants were classified into AD [49] and suspected non-AD pathology (SNAP) [50] biomarker profiles according to $A\beta$ and t-tau-defined neurodegeneration (ND) status, including biomarker negative (Aβ–/ND–), amyloid positive only (Aβ+/ND–), SNAP (i.e., Aβ–/ND+), and both biomarker positive (Aβ+/ND+). CSF $A\beta_{42}$ values $\leq$192 pg/mL reflected amyloid positivity, and t-tau values $\geq$93 pg/mL reflected presence of ND based on established cutoffs [51].

Experimental design and statistical analysis

Prior to analyses, six participants were excluded for outlying CSF NFL values (defined as >4 standard deviations). For hypothesis testing, linear regression cross-sectionally related modified FSRP (minus points assigned to age) to CSF NFL concentration (pg/mL), adjusting for age, sex, education, and cognitive diagnosis (NC, MCI, AD). Next, a series of interaction terms, including 1) *FSRP* × *cognitive diagnosis*, 2) *FSRP* × *CSF* $A\beta_{42}$, 3) *FSRP* × *CSF t-tau*, 4) *FSRP* × *CSF p-tau*, and 5) *FSRP* × *AD biomarker profile* were related to CSF NFL in separate models. For interpretive purposes, models were repeated stratifying by cognitive diagnosis, by CSF $A\beta_{42}$ and CSF t-tau using established cutoffs [51], and by AD biomarker profile. Models were not stratified by CSF p-tau due to its established cutoff having relatively poor sensitivity and specificity in distinguishing AD from NC in the ADNI cohort [51]. Significance was set *a priori* at $\alpha = 0.05$. Analyses were conducted with R version 3.3.1 (http://www.r-project.org).

RESULTS

Participant characteristics

The sample included 402 adults age 54–89 years (74 ± 7 years), including 117 participants with NC, 190 participants with MCI, and 95 participants with clinical AD. CSF NFL ranged from 405 to 5,315 pg/mL. CSF $A\beta_{42}$ ranged from 71 to 300 pg/mL. CSF t-tau ranged from 28 to 495 pg/mL. CSF p-tau ranged from 8 to 115 pg/mL. See Table 1 for participant characteristics by cognitive diagnosis. In this participant sample, CSF NFL weakly correlated with p-tau ($r = 0.14$, $p < 0.0001$) and total tau ($r = 0.23$, $p < 0.0001$). CSF NFL and $A\beta_{42}$ were not correlated ($p = 0.66$).

FSRP and CSF NFL

See Table 2 for detailed results of main effect, interaction, and stratified analyses. Among the whole sample, FSRP appeared modestly related to NFL, but the association did not meet the *a priori* statistical significance threshold ($\beta = 17.97$, $p = 0.08$). FSRP did not interact with cognitive diagnosis on NFL levels ($F(2,398) = 0.30$; $p = 0.74$). In stratified models, FSRP was unrelated to NFL in each of the three diagnostic groups (p-values>0.29).

FSRP interacted with t-tau ($\beta = 0.40$, $p = 0.01$) and p-tau ($\beta = 1.67$, $p = 0.002$) on CSF NFL. In stratified models, FSRP was associated with NFL among t-tau positive ($\beta = 47.57$, $p = 0.002$) but not among t-tau negative participants ($\beta = –0.96$, $p = 0.94$). See Fig. 1A for illustration. Although the FSRP interaction with amyloid was nonsignificant ($\beta = –0.25$, $p = 0.18$), a similar pattern was observed in stratified analyses whereby FSRP was associated with NFL among amyloid positive ($\beta = 35.17$, $p = 0.006$) but not amyloid negative participants ($\beta = –19.35$, $p = 0.24$). See Fig. 1B for illustration.

Similar to the continuous biomarker interactions, FSRP interacted with AD biomarker profile ($F(3,389) = 2.68$; $p = 0.046$). Compared to the Aβ–/ND– referent group, the Aβ+/ND+ group differed in the association between FSRP and NFL ($\beta = 71.3$, $p = 0.005$). No differences were observed between the referent group and the Aβ+/ND– ($\beta = 42.4$, $p = 0.10$) or Aβ–/ND+($\beta = 55.3$, $p = 0.29$) groups. In stratified models, FSRP was associated with NFL in the Aβ+/ND+ group ($\beta = 58.74$, $p = 0.002$) but not in the Aβ–/ND– ($\beta = –32.20$, $p = 0.06$), Aβ+/ND– ($\beta = 14.18$, $p = 0.49$), or Aβ–/ND+ ($\beta = 30.18$, $p = 0.39$) groups. See Fig. 2 for illustration.

DISCUSSION

We evaluated associations between FSRP, a comprehensive index of vascular risk, and axonal injury among community-dwelling older adults ranging from cognitively normal to clinical dementia, assessing for interactions with cognitive diagnosis and CSF measurements of AD pathology. Axonal injury was quantified using CSF NFL, a biomarker posited to reflect large-caliber axon damage [52] that is elevated in MCI [48] and clinical AD [32] and may explain unique variance in clinical manifestation of AD beyond core AD pathology [32]. Within the ADNI cohort, we found the association between vascular risk burden and axonal damage appears amplified by the presence of AD pathology. Specifically, FSRP interacted with both p-tau and t-tau in

Table 1
Participant characteristics

	NC	MCI	AD	p
	$n = 117$	$n = 190$	$n = 95$	
Age, y	76 ± 5	75 ± 7	75 ± 8	0.28
Sex, % female	48	33	43	**0.03**[a]
Race, % White Non-Hispanic	91	94	98	0.09
Education, y	16 ± 3	16 ± 3	15 ± 3	0.06
APOE ε4, % carrier	25	55	69	**<0.001**[abc]
Modified FSRP, total*	12.8 ± 3.2	12.3 ± 4.0	12.8 ± 4.2	0.91
Systolic blood pressure, mmHg	133 ± 17	134 ± 18	135 ± 15	0.56
Anti-hypertensive medication usage, %	54	48	57	0.31
Diabetes mellitus, %	5	5	3	0.77
Current cigarette smoking, %	39	41	46	0.57
Prevalent CVD, %	3	6	4	0.41
Atrial fibrillation, %	1	1	0	0.68
CSF NFL, pg/mL	1120 ± 450	1405 ± 636	1631 ± 764	**<0.001**[abc]
CSF Aβ_{42}, pg/mL	206 ± 55	165 ± 54	144 ± 41	**<0.001**[abc]
CSF t-tau, pg/mL	70 ± 30	103 ± 61	122 ± 58	**<0.001**[abc]
CSF p-tau, pg/mL	25 ± 15	36 ± 18	41 ± 20	**<0.001**[abc]
Biomarker Group				
Aβ–/ND–, %	54	24	6	**<0.001**[abc]
Aβ+/ND–, %	27	31	29	0.79
Aβ+/ND+, %	10	43	61	**<0.001**[abc]
Aβ–/ND+, %	9	2	3	**0.02**[a]

Values denoted as mean ± standard deviation or percentage. *Modified FSRP excludes points assigned for left ventricular hypertrophy. Modified FSRP minus age points for each diagnostic group were NC 5.9 ± 2.8, MCI 5.9 ± 2.9, and AD 6.2 ± 2.7. [a]NC differed from MCI, $p < 0.05$; [b]MCI differed from AD, $p < 0.05$; [c]NC differed from AD, $p < 0.05$. AD, Alzheimer's disease; APOE, apolipoprotein E; CSF, cerebrospinal fluid; CVD, cardiovascular disease; FSRP, Framingham Stroke Risk Profile; MCI, mild cognitive impairment; NC, normal cognition; ND, neurodegeneration; NFL, neurofilament light; p-tau, hyperphosphorylated tau; t-tau, total tau.

Table 2
Main effect, interaction, and sub-group analyses of FSRP on NFL

	Aβ	95% Confidence Interval	t-value	F-value	p
***Covariates+**					
FSRP	17.97	–1.93, 37.87	1.78	–	0.08
FSRP x diagnosis†	–	–	–	0.30	0.74
NC	13.58	–12.97, 40.12	1.01	–	0.31
MCI	14.85	–14.54, 44.23	1.00	–	0.32
AD	28.97	–26.13, 84.07	1.04	–	0.30
FSRP x Aβ_{42}	–0.25	–0.62, 0.12	–1.35	–	0.18
Aβ_{42} positive	35.17	10.42, 59.93	2.80	–	0.006
Aβ_{42} negative	–19.35	–51.98, 13.27	–1.17	–	0.24
FSRP x T-tau	0.40	0.09, 0.71	2.53	–	0.01
T-tau positive	47.57	17.23, 77.91	3.10	–	0.002
T-tau negative	–0.96	–27.87, 25.95	–0.07	–	0.94
FSRP x P-tau	1.67	0.59, 2.74	3.05	–	0.002
FSRP x Biomarker Group†	–	–	–	2.68	0.046
Aβ–/ND–	–32.20	–65.11, 0.72	–1.94	–	0.06
Aβ+/ND–	14.18	–26.72, 55.08	0.69	–	0.49
Aβ+/ND+	58.74	21.30, 96.17	3.12	–	0.002
Aβ–/ND+(SNAP)	30.18	–45.28, 105.65	0.91	–	0.39

*Covariates include age, sex, education, and cognitive diagnosis. †ANOVA; all other models presented are linear regression analyses. CSF, cerebrospinal fluid; FSRP, Framingham Stroke Risk Profile; MCI, mild cognitive impairment; NC, normal cognition; ND, neurodegeneration; NFL, neurofilament light; P-tau, hyperphosphorylated tau; SNAP, suspected non-AD pathology; T-tau, total tau.

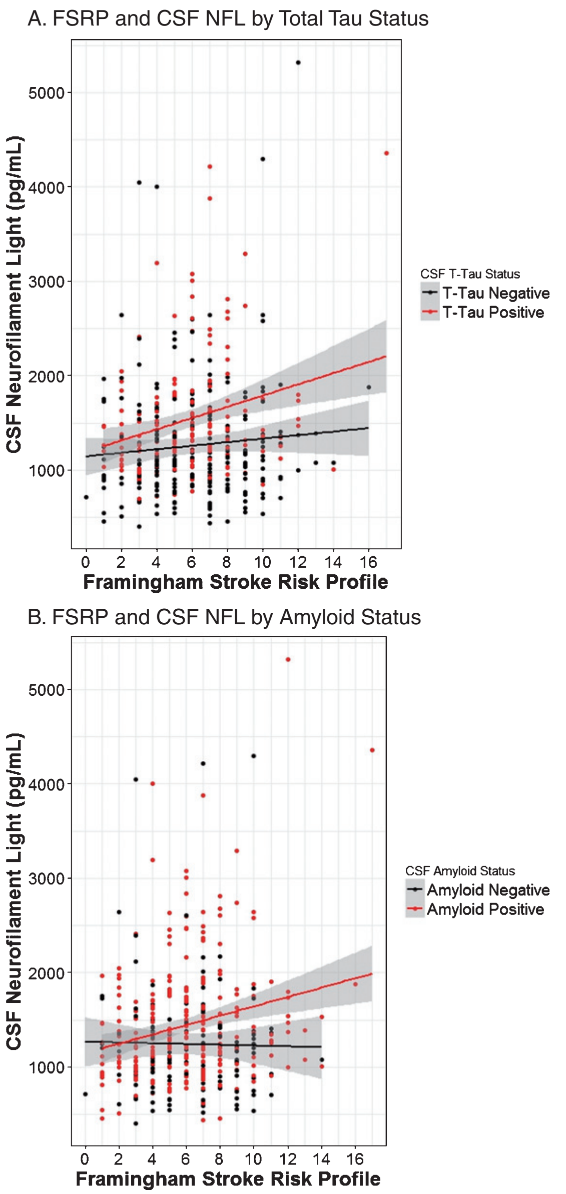

Fig. 1. FSRP and CSF NFL Stratified by Biomarker Status. Solid lines reflect unadjusted values of CSF NFL concentration (Y axis, pg/mL) corresponding to modified FSRP score excluding points assigned for age (X axis). Shading reflects 95% confidence interval. Amyloid positive, CSF $A\beta_{42}$ <193 pg/mL; amyloid negative, CSF $A\beta_{42}$ $\geq$193 pg/mL; t-tau positive, t-tau $\geq$93 pg/mL; t-tau negative, t-tau<93 pg/mL; CSF, cerebrospinal fluid; FSRP, Framingham Stroke Risk Profile; NFL, neurofilament light; t-tau, total tau.

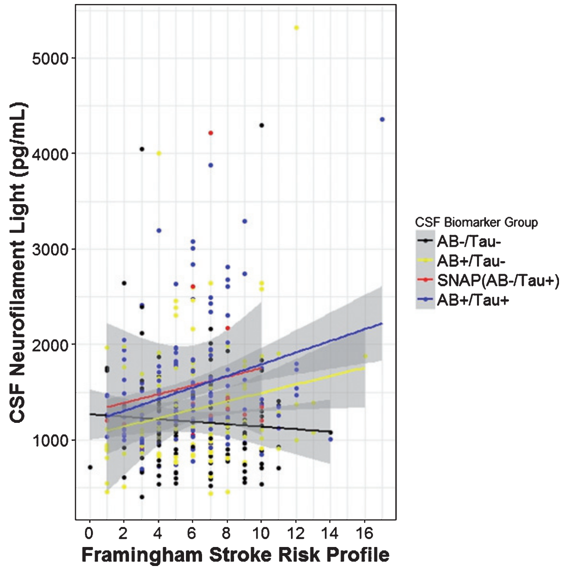

Fig. 2. FSRP and CSF NFL by Alzheimer's Disease and Suspected Non-AD Pathophysiology (SNAP) Profile. Solid lines reflect unadjusted values of CSF NFL concentration (Y axis, pg/mL) corresponding to modified FSRP score excluding points assigned for age (X axis). Shading reflects 95% confidence interval; CSF, cerebrospinal fluid; FSRP, Framingham Stroke Risk Profile; NFL, neurofilament light.

a manner suggesting that associations with axonal injury became stronger in participants commensurate with their extent of neurofibrillary tangle pathology (p-tau) and neurodegeneration (t-tau). A similar interaction also emerged for AD biomarker profile wherein compared to the referent 'normal' biomarker group, individuals with abnormal levels of both $A\beta_{42}$ (indicating cerebral amyloid deposition) and total tau (indicating neurodegeneration) showed stronger associations between vascular risk and axonal injury. While FSRP did not interact with $A\beta_{42}$ on NFL, stratified analyses indicated a modest association was present within the amyloid positive group. However, these stratified results should be interpreted with caution given the lack of a significant interaction effect.

Older adults may be more vulnerable to axonal injury in response to vascular risk burden when neural integrity is already compromised by the cumulative effects of mounting AD pathology. It is unlikely that tau pathology on its own directly accounts for the stronger association between vascular risk factors and axonal injury since prior work has not consistently supported a link between CSF tau and white matter damage [53], including work from our group investigating white matter macrostructure [36] and microstructure damage [54]. Like NFL, tau is a cytoskeleton protein, but tau differs from NFL in that it promotes microtubule stability and is more abundant in smaller, unmyelinated axons localized predominantly in cortical tissue. In contrast, NFL primarily serves to increase diameter and conduction velocity of large-caliber, myelinated subcortical axons [55, 56]. Compared to tau, NFL appears to have more clinical staging and prognostic utility across brain diseases involving prominent degradation of white matter tracks. For example, CSF concentrations of NFL but not tau differentiate between relapsing-remitting and primary progressive types of multiple sclerosis [57]. CSF concentrations of NFL but not tau also distinguish clinical Huntington's disease patients from preclinical gene expansion carrier controls and correlate with 5-year probability of disease onset among the gene expansion carriers [58]. While NFL does not appear to have disease specificity as a marker of axonal injury, its utility in reflecting clinical staging across diseases may convey value as a concomitant biomarker to be studied in conjunction with more disease-specific markers of AD.

The dominant theory of AD pathophysiology posits that biomarkers become abnormal in an ordered but temporally overlapping manner. A long asymptomatic phase of amyloid aggregation eventually reaches a threshold with subsequent progressive neuronal dysfunction and death corresponding to CSF t-tau elevations [59]. Accordingly, elevated t-tau and p-tau coupled with increased evidence of amyloid aggregation may reflect more advanced AD pathology and neurodegeneration, which could compromise neural resilience to vascular risk burden, resulting in greater vulnerability to axonal injury.

It is noteworthy that cognitive diagnosis did not modify the association between FSRP and NFL, suggesting the link between vascular risk burden and axonal injury occurs in both asymptomatic and symptomatic individuals. This finding has important therapeutic implications, as vascular-related axonal damage in AD may be detectable both prior to and throughout the clinical manifestation of symptoms. Future research should incorporate longitudinal models to further elucidate how vascular-related axonal injury temporally relates to the emergence and progression of AD symptoms.

Collectively, findings from this study suggest presence of vascular risk factors confers a greater likelihood of axonal damage in the context of mounting AD pathology and neurodegeneration, regardless of clinical status. These findings should be interpreted in the context of certain study limitations. The cross-sectional nature of our design limits our ability to draw causal inferences or speculate about temporal ordering of pathological changes or whether specific substrates of the AD pathophysiological cascade drive the observed associations. Unfortunately, gold-standard MRI FLAIR data are unavailable in this particular subset of the ADNI cohort, so white matter hyperintensities and other markers of cerebral SVD could not be examined. Other limitations to consider when interpreting results include that ADNI participants are predominantly non-Hispanic white and well-educated, so findings may not be generalizable to more diverse populations. Furthermore, ADNI eligibility criteria excluded for overt cerebrovascular disease (i.e., Hachinski score $\leq$4), so stroke risk and cerebrovascular pathology are likely underrepresented in the ADNI sample compared to the general population. Even with this study exclusion, we still observed associations between vascular risk burden and axonal injury. We speculate that in a cohort with greater vascular risk factors and cerebral SVD, the associations reported here would be stronger.

Despite these limitations, our study has several strengths, including the large, well-characterized dataset representing the entire cognitive aging spectrum from clinically normal to dementia. This range permitted evaluation of vascular risk and axonal injury in the context of preclinical and clinical AD. Additionally, the FSRP incorporates multiple vascular risk factors, offering a more comprehensive and integrated risk index, as opposed to examining risk factors individually.

Vascular-related axonal injury represents an important potential target for primary prevention and clinical intervention among individuals at high risk for developing AD or in the preclinical stages of AD. Whereas there are no current treatments or preventative therapies for AD, most vascular health problems are preventable or modifiable in nature. Primary prevention and close medical management of vascular health conditions should be emphasized to mitigate the clinical progression of AD in older adults. Further investigation into mechanisms linking vascular risk factors and axonal damage in AD and in non-AD-related abnormal cognitive aging is warranted to examine longitudinal associations and identify possible therapeutic targets.

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