

Association of CSF vascular biomarkers with cerebrovascular and cardiovascular health, and cognition in cognitively unimpaired Veterans



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BACKGROUND: Despite the importance of vascular health to cognitive function, fluid biomarkers for vascular dysfunction are lacking. White matter hyperintensity lesions index cerebrovascular disease burden (CVD) and increase with both typical aging and CVD progression and are associated with cognitive impairment. We evaluated novel vascular related CSF biomarkers identified by Alomar Biosciences for possible associations with cerebrovascular and cardiovascular health and cognitive decline.

OBJECTIVE: To explore the association between twelve putative CSF biomarkers for vascular dysfunction (Alamar Biosciences USA) with white matter hyperintensity lesion volume, cardiovascular health, and global cognitive function in a sample of VA eligible Veterans.

METHODS:

Participants

The sample included $N = 114$ Veterans Affairs (VA) eligible Veterans enrolled into an 18-month randomized, clinical trial of Vascepa® IPE (NCT01492361). White matter hyperintensity and global cognition were measured at baseline, month 9 and month 18.

Baseline Measures

Cognition: Alzheimer’s Disease Cooperative Study Preclinical Alzheimer’s Cognitive Composite (**ADCS-PACC**) battery consisted of

- Mini mental state exam (MMSE)
- Free recall from Free & Cued Selective Reminding Test
- Digit Symbol Substitution
- Logical Memory delayed Recall

Cardiovascular health: We used AHA/ACC’s atherosclerotic cardiovascular disease (**ASCVD**)-10 year risk score (measured at baseline only)

Cerebral vascular health: Global white matter hyperintensity (**WMH**) lesion volume (mL) was calculated from T2-weighted FLAIR scans using the automated lesion prediction algorithm from the Lesion Segmentation Tool version 3.0.0 for SPM12, and normalized to total intracranial volume. WMH was adjusted for total intracranial volume.

WMH groups: Participants were classified into abnormal WMH groups: V+ (≥ 2.06 mL) and V- (< 2.06 mL) (see Du et al 2025).

CSF biomarkers: Baseline CSF vascular biomarkers from the NULISaseq CNS120 panel (Alamar Biosciences USA) included.

- FLT1 = FMS related receptor tyrosine kinase 1
- HBA1 = hemoglobin subunit 1
- KDR = kinase insert domain receptor
- MME = membran metalloendopeptidase
- PDGFRB = platelet derived growth factor receptor beta
- PGF = placental growth factor
- PGK1 = phosphoglycerate kinase 1
- POSTN = periostin, PTN = pleiotrophin
- SAA1 = serum amyloid A1
- VEGFA = Vascular endothelial growth factor A; VEGFD = Vascular endothelial growth factor

Key result: Placental Growth Factor (PGF) derived from cerebral spinal fluid (CSF) showed promise in identifying peripheral and central vascular risk.

Table 1. Association of PGF with cerebrovascular health, cardiovascular health, and global cognition adjusting for age.

	WMH			PACC			ASCVD		
Predictors	Estimate	95%CI	p	Estimate	95%CI	p	Estimate	95%CI	p
(Intercept)	0.86	-1.90 – 3.62	.002	0.42	-1.42 – 2.26	<.001	53.1	-7.7 – 113	<.001
Bse age	1.67	0.71 – 2.64	.001	-0.50	-0.66 – -0.34	<.001	11.0	8.59 – 13.4	<.001
PGF	0.08	-0.10 – 0.25	.39	-0.02	-0.14 – 0.10	.74	-2.26	-6.33 – 1.81	.27
Months since bse	0.02	0.01 – 0.03	<.001	0.03	0.02 – 0.04	<.001			

Abbreviations: WMH = white matter hyperintensity lesion volume (mL) ; ASCVD = atherosclerotic cardiovascular disease 10-year risk percentile; PACC = ADCS Preclinical Alzheimer’s Cognitive Composite score; Bse = baseline; PGF = placental growth factor.

Note: Linear mixed effects models were fit to WMH and PACC measured at baseline, 9 and 18 months with months since baseline as the measure of time and participant-level random intercepts. PACC scores were z-scored prior to analyses. Participant baseline age was z-scored prior to analyses.

Table 2. Baseline sample characteristics (N=114)

Age, M (SD)	65.4 (7.00)
APOE4 carrier, n(%)	31 (27.4%)
Male, n(%)	97 (85.8%)
Non-Hispanic, White, n (%)	112 (98.2%)
Education	
Did not graduate high school	2 (1.8%)
High school graduate	16 (14.2%)
Attended college	52 (45.6%)
College graduate	44 (38.9%)
adjusted WMH mL, M (SD)	2.11 (5.00)
ASCVD 10 year risk %, M (SD)	19.2 (14.8)
P score, M (SD)	0.04 (0.63)
V+ group, n(%)	31 (27.2%)

Abbreviations: WMH = white matter hyperintensity lesion volume (mL) ; ASCVD = atherosclerotic cardiovascular disease 10-year risk percentile; PACC = ADCS Preclinical Alzheimer’s Cognitive Composite score; **Note:** WMH group (V+/-) was based on a cut-off of 2.06 m.. See Methods for list of CSF biomarkers.

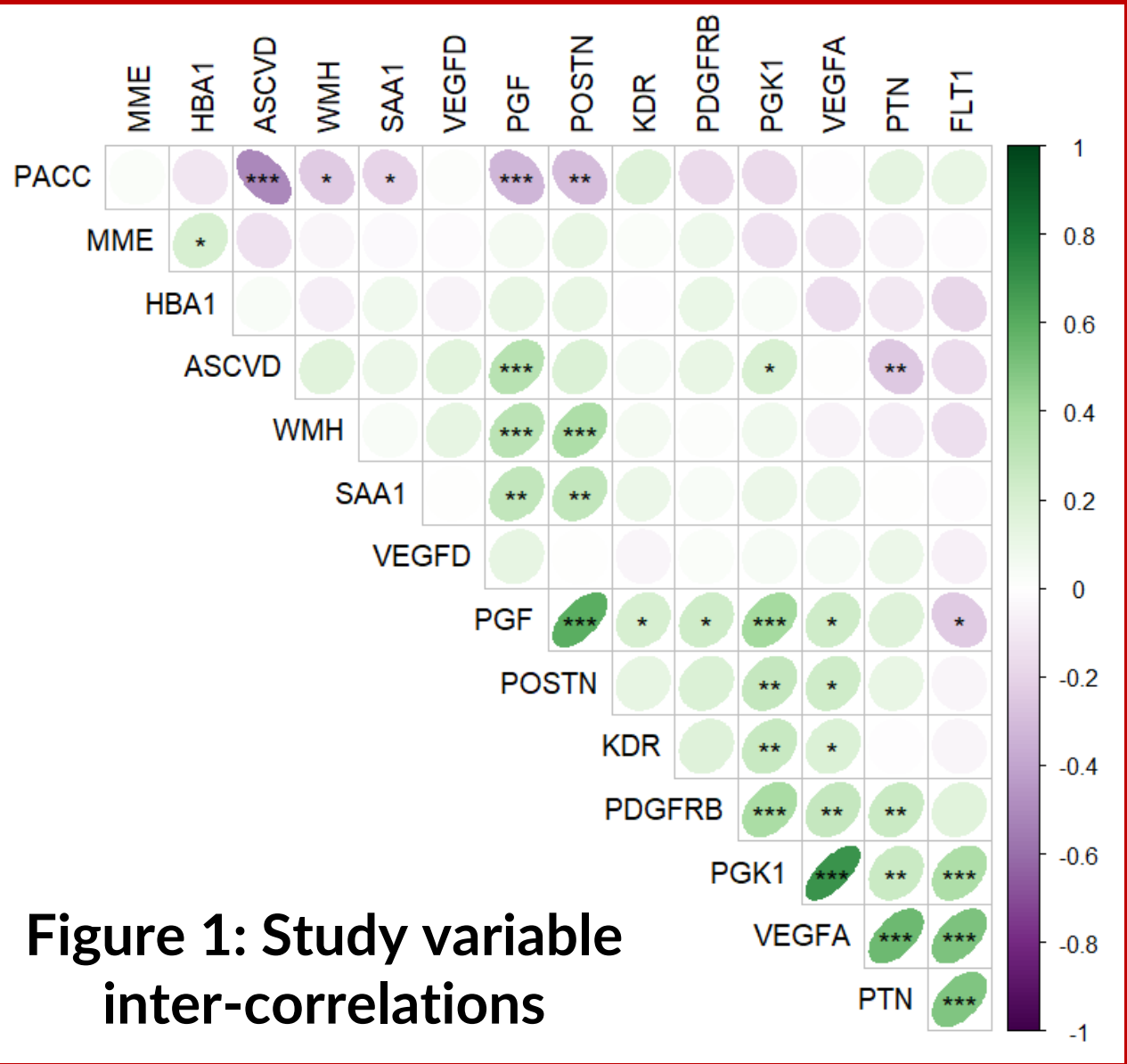


Figure 1: Study variable inter-correlations

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RESULTS:

- The sample was mostly male (86%), and non-Hispanic, White; 15% of the sample did not attend higher education (see Table 2).
- Older participants had higher WMH than younger participants, $t(161.7) = 7.12, p < .001$.
- There is a cluster of positively inter-related CSF vascular biomarkers (see Fig 1)
- Placental growth factor was the only biomarker correlated with white matter hyperintensity, cardiovascular health (ASCVD risk score), and global cognition (PACC score).
- After controlling for baseline age, linear regression (ASCVD) and linear mixed effects models (WMH, PACC) indicated the association between PGF and study outcomes was non-significant.
- PGF was associated high level of white matter abnormality (V+ group; OR=1.87, 95%CI:1.09-3.45).

CONCLUSION:

PGF measured in CSF identified cognitively unimpaired individuals with significant WMH burden. Replicating these analyses in blood samples would further enhance accessibility in research and clinical settings.

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