

Latent Composites of Multimodal MRI, Plasma Biomarkers & Cardiovascular Risk are Sensitive to Cognition and Alzheimer's Disease Dementia

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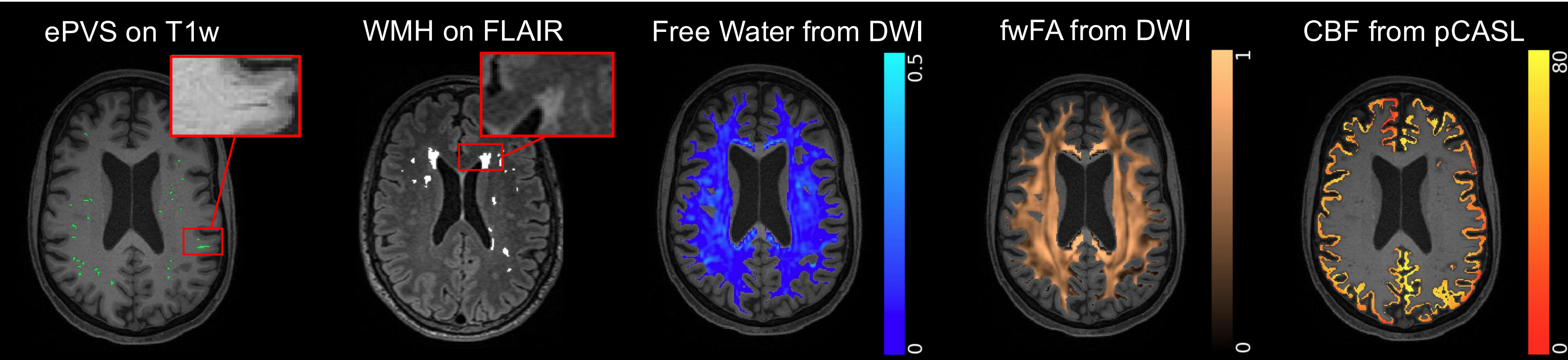
INTRODUCTION

Many interdependent systems maintain brain homeostasis, including the neurovascular unit and the fluid transport (glymphatic) system¹. These systems are dysfunctional long before overt cognitive impairment arises in many neurodegenerative diseases, including Alzheimer's disease (AD)². Despite their biological connection, markers of these systems are often considered in isolation, obscuring the broader system-level processes they reflect.

AIM: To identify latent constructs of brain health, validate these constructs in an independent cohort, and investigate their associations with cognition and AD dementia.

METHODS

An exploratory factor analysis (EFA) of MRI (examples of outcomes below), plasma and cardiovascular risk measures was conducted in **132 healthy adults from the BACH study** (mean age 67, 68% women)³, revealing **four latent constructs**:



MRI Measures

- enlarged perivascular spaces (ePVS)
- white matter hyperintensities (WMH)
- diffusion Free Water
- fractional anisotropy (fwFA)
- gray matter cerebral blood flow (CBF)

- ventricle volume (% of TIV)
- hippocampal volume (% of TIV)
- cortical thickness

Plasma Biomarkers (SIMOA Assays)

- amyloid-beta (Aβ) 42/40 ratio
- phosphorylated Tau (pTau)181
- glial fibrillary acidic protein (GFAP)
- neurofilament light chain (NfL)

Cardiovascular Risk Factors

- BMI
- systolic blood pressure
- LDL cholesterol
- HDL cholesterol

	Factor 1: Brain & Vascular Health	Factor 2: Structural Integrity	Factor 3: WM Fluid Dysregulation	Factor 4: Blood Biomarkers
HDL Cholesterol	0.41	-0.03	0.21	0.18
BMI	-0.41	0.14	0.05	-0.25
Hippocampal Volume	0.82	-0.07	-0.06	-0.04
Ventricle Volume	-0.70	-0.06	-0.11	-0.02
Gray Matter CBF	0.41	0.11	-0.03	0.03
Basal Ganglia ePVS	0.40	0.36	0.13	-0.14
fwFA	-0.09	0.63	-0.08	0.24
Cortical Thickness	0.03	0.59	0.12	-0.16
White Matter ePVS	0.05	0.03	0.98	0.02
Free Water	-0.26	-0.12	0.56	0.17
pTau181	-0.06	0.09	0.06	0.32
GFAP	0.08	0.03	0.05	0.64
NfL	-0.04	0.03	-0.02	0.66

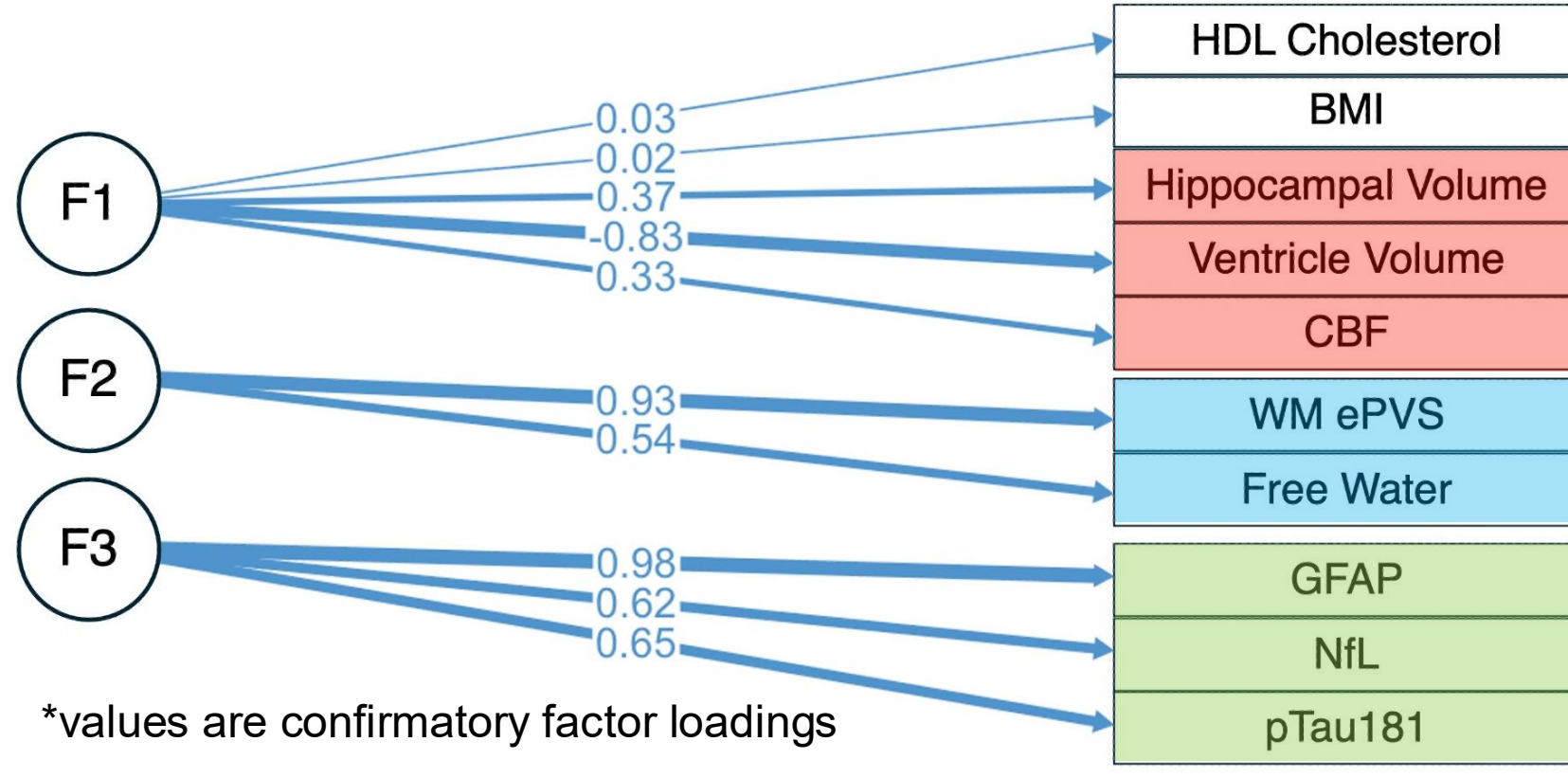
Factor loadings are reported; variables $\geq \pm 0.30$ are considered to meaningfully contribute.

Validation was conducted in an independent cohort of **197 PISA⁴ study participants** (mean age 62, 80% women): **157 healthy controls, 18 MCI and 22 AD**. Data analysis closely replicated the EFA. Confirmatory factor analysis was conducted in healthy controls, and **weighted composite scores were derived** from the confirmed factor loadings.

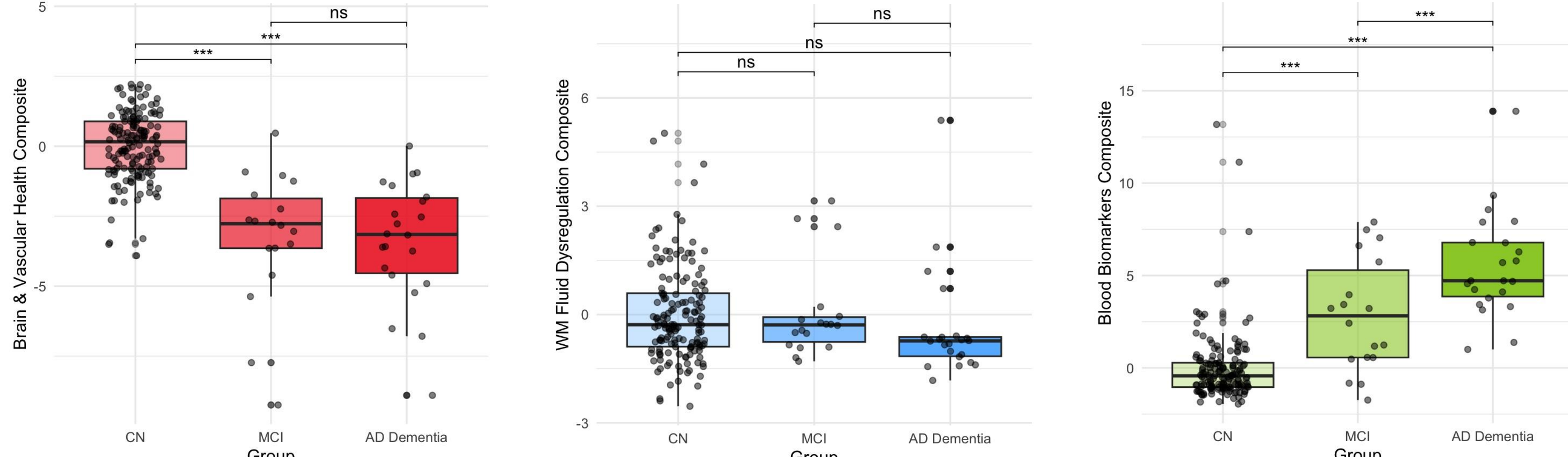
Adjusting for age, sex, and education, we evaluated: **1) group differences in composites** with ANCOVAs; **2) composite sensitivity to MCI/AD** with binomial logistic regressions, repeated for comparison with individual biomarkers; and **3) composite associations with cognition** (Similarities, RAVLT-A, Topographical Test, FAS) with linear regression.

RESULTS

Three reproducible factors emerged: The **Brain & Vascular Health** replicated, except for BMI and HDL Cholesterol (factor loading $< .30$). The **WM Fluid Dysregulation** and **Blood Biomarkers** constructs faithfully replicated the EFA. Due to a change in direction (BG ePVS now negative), the Structural Integrity construct did not replicate.

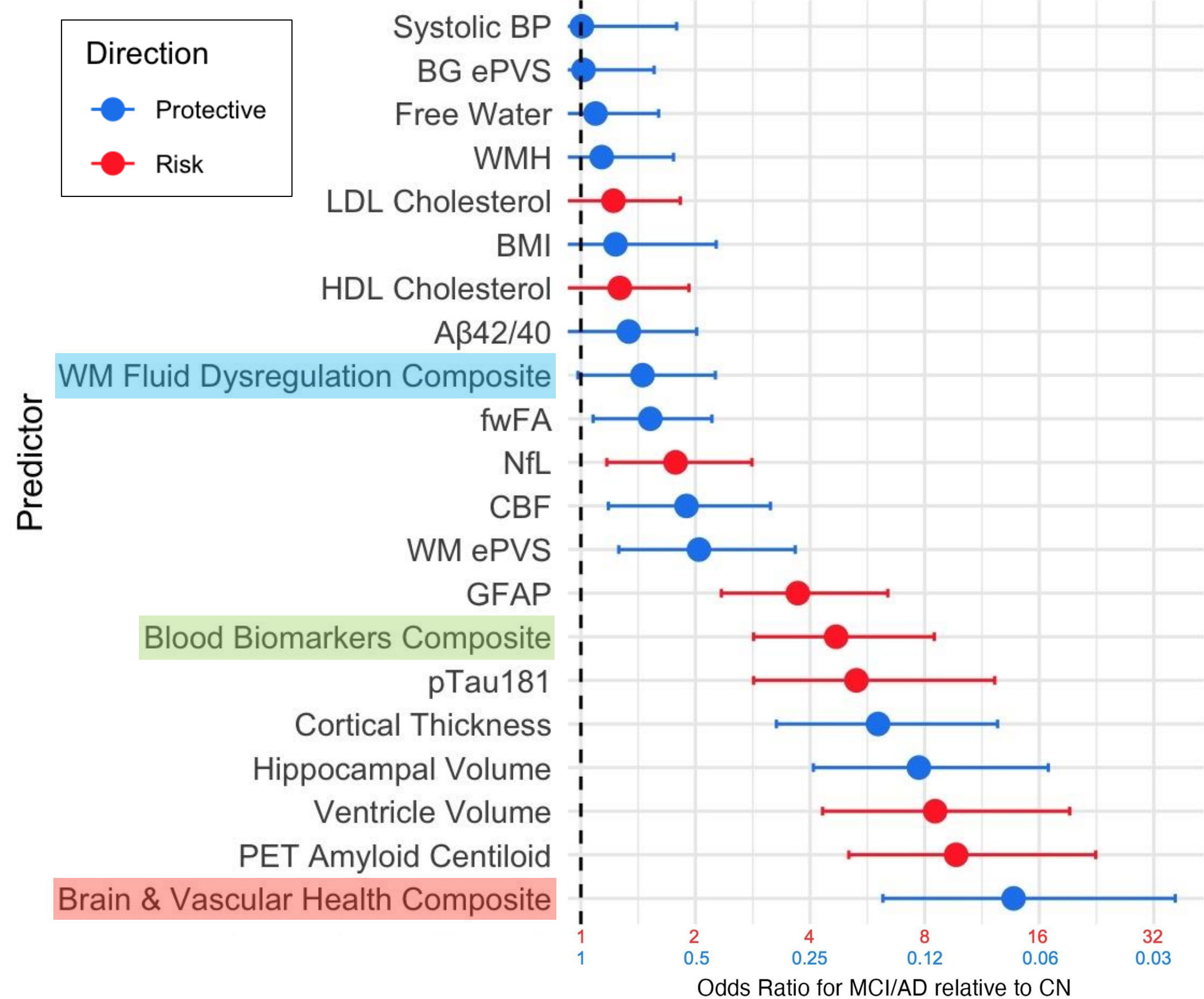


Participants with **MCI and AD dementia had significantly lower Brain & Vascular Health composite scores** ($F_{(2,192)}=92.97$, $p<.001$) and **higher Blood Biomarkers composite scores** than healthy control participants ($F_{(2,192)}=76.02$, $p<.001$). There was no significant difference in **WM Fluid Dysregulation** scores across groups ($F_{(2,192)}=0.89$, $p=.411$).



The **Brain & Vascular Health composite** had the **strongest association with MCI/AD** ($OR=0.07$, $95\%CI=[0.03, 0.16]$), even compared to other markers of AD, such as PET amyloid Centiloid ($OR=10.12$, $95\%CI=[5.35, 23.2]$).

Across all participants, the **Brain & Vascular Health composite** was **positively associated**, and the **Blood Biomarkers composite** was **negatively associated, with cognition** (all $p<.008$). The **WM Fluid Dysregulation composite** did not show a significant association (all $p>.121$).



CONCLUSIONS

Composites captured **distinct yet complementary dimensions** of brain health, offering an alternative to single-measure or classification-based biomarker frameworks. Derived from healthy aging, these reproducible and **disease-agnostic** factors can help advance our understanding of mechanisms underlying cognitive decline. With further validation, they may **aid early detection and tracking in neurodegenerative disease** research and clinical trials.