

Background

- Coronary microvascular dysfunction (CMD) may signal a systemic microvascular phenotype that accelerates brain aging and increases vulnerability to Alzheimer's disease and related dementias (ADRD) [1-4] .
- However, neuroimaging signatures linking reduced coronary flow reserve (CFR) to early cerebral small vessel disease (CSVD), brain iron, network integrity, and brain structure—before cognitive deficits emerge—are poorly defined.

Objective

- We tested whether lower CFR is associated with a multimodal magnetic resonance imaging (MRI) biomarker profile and cognitive performance in women with suspected CMD.

Materials and Methods

- Participants:** Thirty-five women with suspected CMD, aged 21–75 years (median: 54), were included from the Women's Ischemia Syndrome Evaluation (WISE) study (NCT03876223) [5].
- Assessments:**
 - Questionnaires:** Seattle Angina Questionnaire
 - Cognitive testing:** NIH Toolbox Cognition Battery (NIHTB-CB) & Montreal Cognitive Assessment (MoCA)
 - CSVD burden:** Quantified using MRI markers defined by Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria.
- Imaging:** 3T MRI (Siemens Vida), including:
 - Resting-state fMRI
 - Submillimeter 3D-EPI for quantitative susceptibility mapping (QSM) reconstruction, iron measures, and perivascular space enlargement [6].
 - T1-MPRAGE for the parcellation and volumetric measures using Freesurfer
 - T2-FLAIR to assess white matter hyperintensities and lacunes.
 - Diffusion-weighted imaging to assess cerebral microbleeds.

Multimodal relationships were evaluated using canonical correlation and mediation modeling.

Results

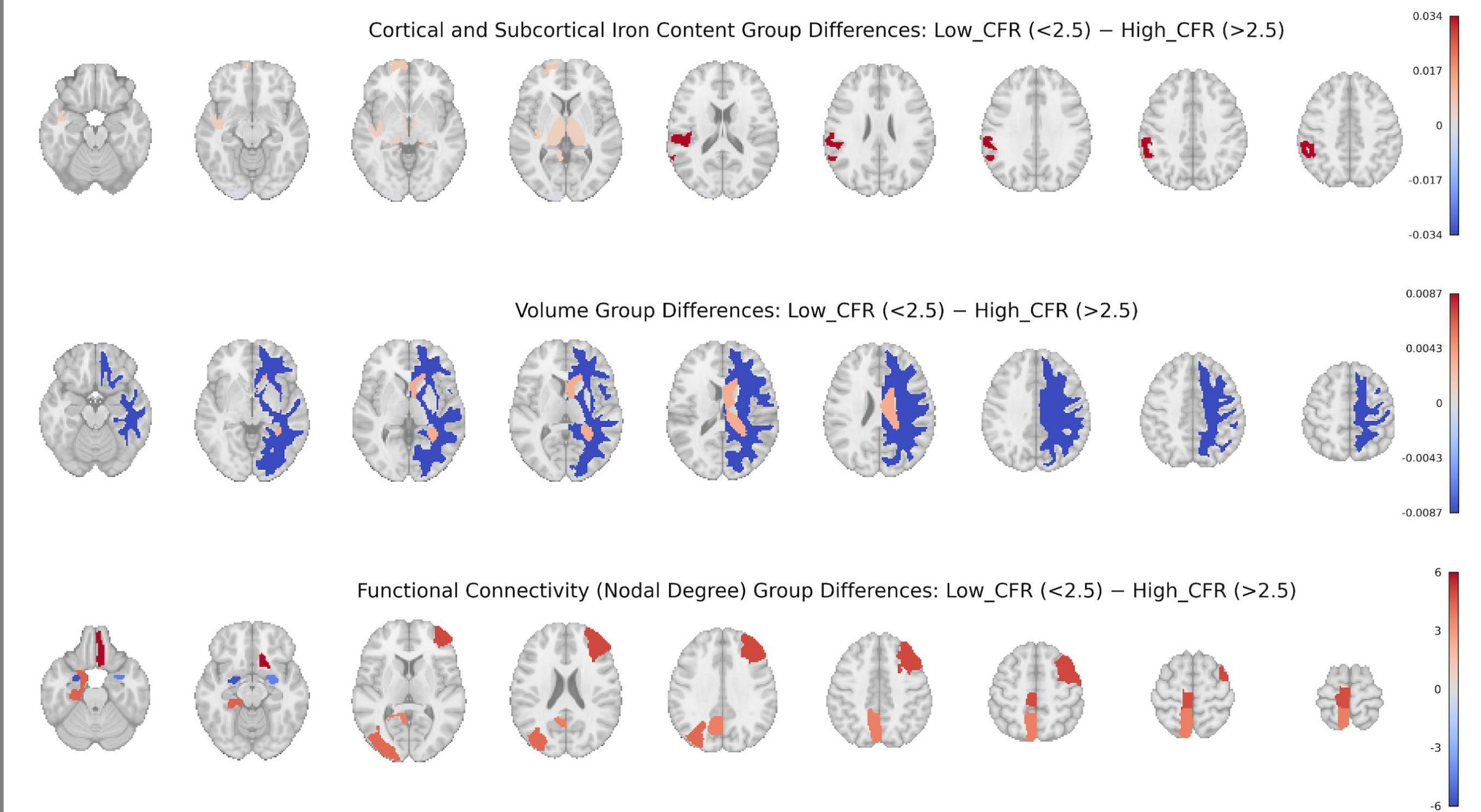
- Women with low CFR demonstrated higher CSVD occurrence than women with preserved CFR:**

Baseline Characteristic	CFR < 2.5 (n=10)	CFR ≥ 2.5 (n=25)	p-value
CSVD occurrence, n (%)	10 (100%)	17 (68%)	0.073
CSVD score	2 (1-3)	1 (0-2)	0.013*
Age, years	60 (46 – 75)	51.5 (21 – 75)	0.020*
Hypertension, n (%)	6 (66.7%)	7 (25.0%)	0.042*
Diabetes, n (%)	3 (33.3%)	2 (6.5%)	0.065
Dyslipidemia, n (%)	1 (14.3%)	9 (32.1%)	0.644
Smoking history (ever), n (%)	5 (55.6%)	4 (12.9%)	0.016*
Seattle Angina Questionnaire 7	51.5 ± 19.6	52.6 ± 20.8	0.87
Physical limitation score, 0-100 (0 worse score, 100 = no limitation)	62.16 ± 9.94	66.11 ± 22.56	0.799
Migraine history	4 (40%)	14 (56%)	0.471
Hemoglobin	12.18 ± 0.77	12.35 ± 0.94	0.58
Systolic blood pressure, mm Hg	138 (108 – 159)	117 (92 – 156)	0.067
Diastolic blood pressure, mm Hg	71 (57 – 101)	71 (47 – 90)	0.476

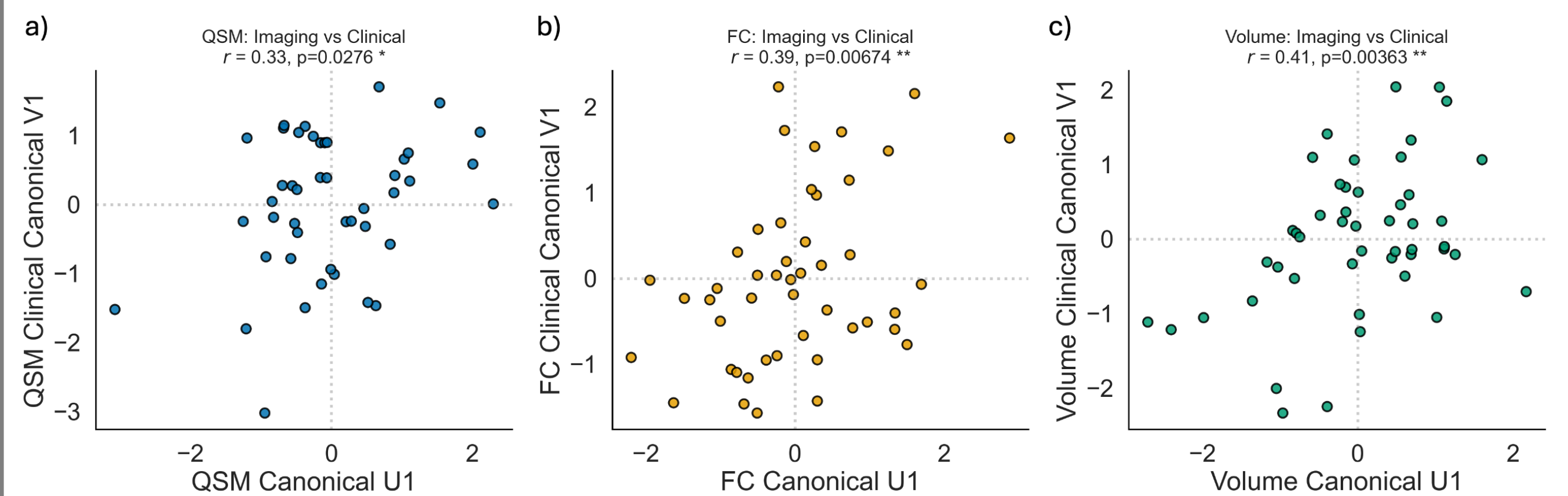
Conclusions

Multimodal neuroimaging reveals brain vulnerability linked to impaired CFR in women with suspected CMD with preserved cognition consistent with early network adaptation/compensation [7-9]. This biomarker profile supports a heart-brain microvascular axis relevant to vascular contributions to cognitive aging and ADRD vulnerability, supporting multimodal MRI as a tool for earlier risk stratification in women.

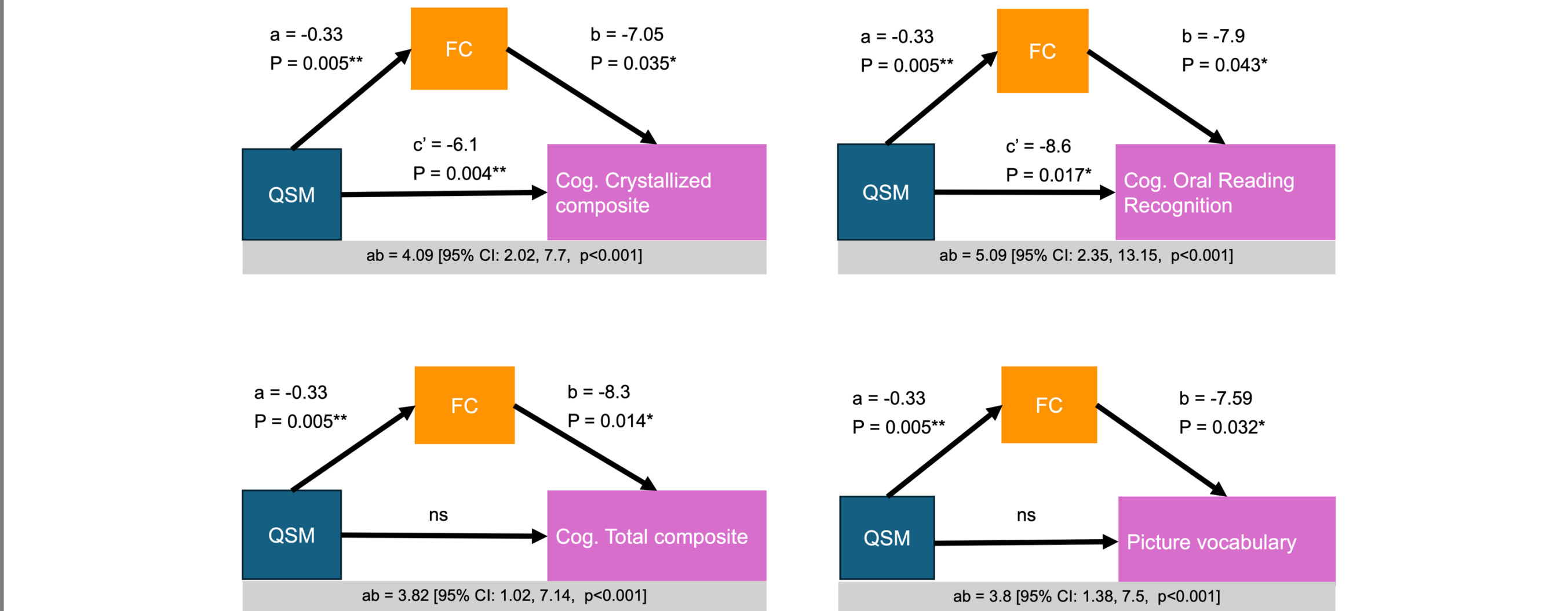
- Women with lower CFR also displayed a distinct brain phenotype including higher magnetic susceptibility in cortical and subcortical regions (including thalamus, insula, and posterior cingulate), subcortical atrophy, ventricular enlargement, and reorganization of FC networks:**



- Canonical correlation revealed significant multivariate associations between QSM/FC/volumetric markers as well as cognitive and cardiac outcomes (r=0.33-0.41, p<0.05):**



- Mediation analyses identified FC as a key intermediary linking iron measures to cognition, partially mediating crystallized and reading-related performance and fully mediating global/language-related cognitive outcomes (p<0.001):**



References

1) Camici PG, Crea F. New England Journal of Medicine. 2007. 2) Wardlaw JM , et al. The Lancet Neurology. 2013. 3) Mejia-Renteria H et al. Eur Heart J. 2023. 4) Feuer DS et al. The American Journal of Medicine. 2022. 5) Has Silemek et al. Brain & Heart, 2026. 6) Has Silemek et al. ISMRM 2023 & 2025 7). Davis SW et al. Cereb Cortex. 2008. 8) Reuter-Lorenz PA et al. Neuropsychology Review. 2014. 9) Schulz M et al. BMC Medicine. 2021.

Acknowledgements:

WISE Pre-Heart Failure With Preserved Ejection Fraction (Pre-HFpEF) (NCT03876223) study is supported by NIH R01-HL146158.