ACCSCIENCE PUBLISHING

Brain & Heart

ORIGINAL RESEARCH ARTICLE

Design and methodology of a multidimensional investigation of brain structure and function in women with suspected ischemia with no coronary artery disease

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Abstract

Ischemia with no obstructive coronary artery disease (INOCA), often due to coronary microvascular dysfunction (CMD), disproportionately affects women and may be linked to cognitive impairment and increased risk of dementia. While CMD and cerebral small vessel disease (CSVD) share similar risk factors and may contribute to cognitive decline, the mechanistic pathways connecting these conditions in women remain unclear. We conducted a cross-sectional observational study with a planned enrollment of 100 women aged 18 years and older with symptoms of INOCA and suspected CMD, recruited from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation–Pre-Heart Failure with Preserved Ejection Fraction study (ClinicalTrials.gov identifier: NCT03876223) and the Microvascular Aging and Eicosanoids–Women's Evaluation of Systemic Aging Tenacity (MAE-WEST) ("You are never too old to become younger!") Specialized Center for Research Excellence (SCORE) (U54AG065141) studies at Cedars–Sinai Medical

Center and the University of Florida. Each participant underwent a comprehensive assessment protocol, including advanced brain magnetic resonance imaging to quantify markers of CSVD, cardiac MRI to evaluate CMD, non-mydriatic retinal imaging, peripheral vascular function testing, and an extensive battery of cognitive assessments. Clinical, sociodemographic, and vascular risk factor data were collected. We analyzed cross-sectional associations between multimodal imaging biomarkers and cognitive performance. This protocol describes the first multidimensional, imaging-based investigation to integrate assessments of CMD, CSVD, retinal microvasculature, and cognitive function in women at risk for INOCA. Findings will enhance our understanding of the shared vascular mechanisms underlying cognitive decline and inform strategies for early intervention in at-risk women.

Keywords: Heart; Brain; Cerebral small vessel disease; Cognition; Coronary microvascular dysfunction; Ischemia with no obstructive coronary artery disease; Magnetic resonance imaging; Retina

1. Introduction

Ischemia with no obstructive coronary artery disease (INOCA) is a prevalent and underrecognized cause of ischemic symptoms in women and is most commonly attributed to coronary microvascular dysfunction (CMD).[1–3] Women with INOCA experience angina, reduced quality of life, and elevated risk of adverse cardiovascular outcomes, despite the absence of flow-limiting epicardial stenosis.[4,5]

Although CMD and cerebral small vessel disease (CSVD) share vascular risk factors, the mechanistic links between coronary microvascular physiology, brain microvascular dysfunction, and cognition remain insufficiently defined.[6–8] CSVD is a major contributor to cognitive impairment and dementia and is characterized by impaired cerebral perfusion regulation, white matter injury, and network disruption.[9,10] Few studies have directly connected coronary microvascular function to multimodal brain microvascular markers and cognitive performance within the same individuals, particularly in women, who exhibit sex-specific vascular biology and potentially distinct vulnerability trajectories.[11]

We hypothesize a unified heart–brain microvascular pathway in which CMD reflects systemic endothelial and microvascular dysfunction. This systemic phenotype manifests across multiple vascular beds, including the retina and peripheral circulation, and extends to the brain as impaired cerebral perfusion regulation and cerebrovascular reactivity. Over time, these functional disturbances may contribute to structural markers of CSVD—such as white matter hyperintensities (WMH) and microstructural white matter injury—and to domain-specific cognitive inefficiencies (Figure 1).

This women-only ancillary study is nested within two parent studies: the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE)–Pre-Heart Failure with Preserved Ejection Fraction study (NCT03876223) and the Microvascular Aging and Eicosanoids–Women's Evaluation of Systemic Aging Tenacity (MAE-WEST) ("You are never too old to become younger!") Specialized Center for Research Excellence (SCORE) (U54AG065141). The ancillary study integrates cardiac and coronary magnetic resonance imaging (MRI), advanced brain MRI, retinal imaging, peripheral vascular function testing, and standardized cognitive assessment to move beyond shared-risk-factor epidemiology toward a mechanistic evaluation of systemic microvascular disease. By aligning each measurement domain with pre-specified hypotheses and a coherent analysis plan, the study aims to clarify vascular pathways linking CMD, CSVD, and cognition and to inform future prevention and intervention strategies in at-risk women.

2. Methods

2.1. Study design and setting

Participants underwent standardized multimodal phenotyping, including coronary and cardiac assessment, advanced brain MRI, retinal imaging, peripheral vascular function testing, and cognitive testing at two centers of excellence, Cedars–Sinai Medical Center and the University of Florida, Gainesville. Study procedures were completed in a coordinated protocol (typically within one to two visits) to minimize temporal drift between cardiac,

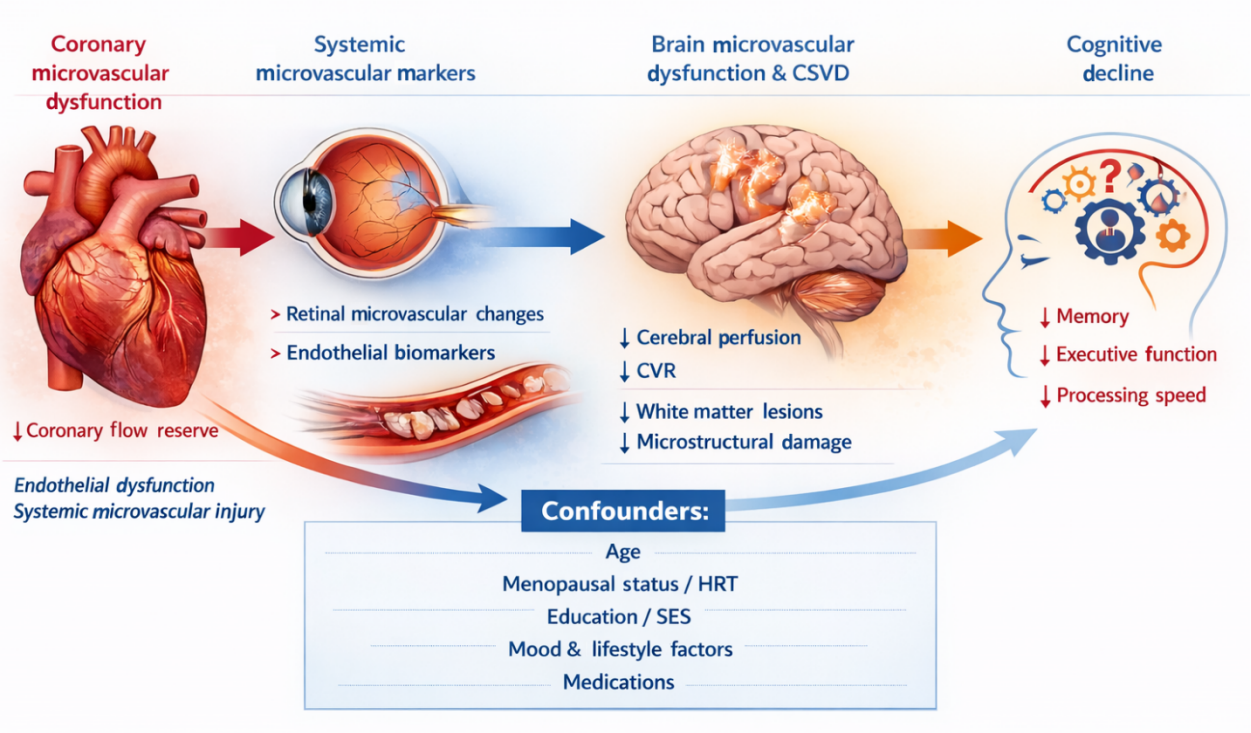

Figure 1. Hypothesized heart–brain microvascular pathway in women with INOCA. Coronary microvascular dysfunction may reflect a systemic microvascular phenotype manifesting as retinal and peripheral vascular abnormalities, impaired brain microvascular function, downstream CSVD markers, and cognitive inefficiencies. Analyses adjust for key confounders, including age, menopausal status/hormone replacement therapy (HRT), education/socio-economic status (SES), mood, lifestyle factors, medications, and site effects.
Abbreviations: CSVD: Cerebral small vessel disease; CVR: Cerebrovascular reactivity; INOCA: Ischemia with no obstructive coronary artery disease.

brain, and cognitive measures.

This study was designed as a cross-sectional observational study. Primary analyses focused on cross-sectional associations between coronary microvascular function metrics and brain MRI and cognitive endpoints.

2.2. Parent studies and study sample

The parent studies recruited adults with ischemic symptoms undergoing evaluation for suspected INOCA/CMD and collected standardized clinical, retinal imaging, and cognitive testing data. The present ancillary study leverages these infrastructure elements by adding brain MRI to enable integrated heart–brain analyses.

Although the parent studies include both women and men, the analytic sample for this study was restricted to women to address sex-specific mechanisms and the disproportionate burden of INOCA/CMD in women. All acquisition protocols and derived variables were identical across participants; only the analytic restriction differed.

We plan to enroll up to 100 women aged ≥ 18 years with ischemic symptoms and no obstructive coronary arteries (per parent study criteria) or clinical suspicion of INOCA/CMD. Baseline demographics, vascular risk factors, medication exposures, and reproductive history were collected using harmonized instruments to support analyses of confounding and effect modification.

2.3. Eligibility criteria

Parent and ancillary study key inclusion criteria were designed to identify women with suspected INOCA/CMD who can safely complete the multimodal protocol and cognitive assessment:

- Women aged ≥ 18 years.
- Ischemic symptoms consistent with INOCA and non-obstructive coronary arteries (e.g., <50% stenosis on invasive or computed tomography coronary angiography) or clinical suspicion of INOCA/CMD per parent study criteria.
- Eligible for cardiac and brain MRI (no contraindications; able to tolerate scanning) and willing to comply with protocol instructions.
- Able to complete cognitive testing in English and provide informed consent.

Key exclusion criteria were intended to avoid conditions that would preclude safe participation or materially confound brain microvascular or cognitive endpoints:

- Contraindication to MRI (e.g., non-MRI-compatible implanted device; severe claustrophobia not manageable per site protocol).
- Acute or unstable cardiovascular illness that precludes safe completion of study procedures.
- Major neurological disorder likely to confound CSVD/cognition endpoints (e.g., prior large territorial stroke; diagnosed neurodegenerative disorder).
- Other conditions that, in the investigator's judgment, would prevent valid data collection (e.g., inability to comply with procedures; anticipated excessive motion).

2.4. Imaging procedures and analysis

Imaging and physiologic protocols were designed to quantify complementary components of the hypothesized heart–brain microvascular pathway. Cardiac phenotyping includes invasive coronary microvascular function measures and noninvasive cardiac MRI-derived indices of myocardial perfusion, structure, and function. Brain MRI provides measures of CSVD burden (e.g., WMH, lacunes, cerebral microbleeds), microstructural integrity and structural connectivity, and brain microvascular function (cerebral blood flow and cerebrovascular reactivity). Retinal imaging (fundus photography, optical coherence tomography (OCT), and OCT angiography [OCT-A]) and peripheral vascular function testing provide systemic microvascular markers complementary to coronary physiology.

To improve readability, the main methods emphasized measurement domains and derived variables aligned to pre-specified hypotheses, while detailed acquisition parameters (sequence timing, voxel sizes, and vendor-specific settings) and software/version information are provided in Table S1.

Medication and behavioral preparation for imaging were standardized across sites when feasible to reduce acute physiologic variability (e.g., avoidance of nicotine and vasoactive substances before imaging).

2.4.1. Brain magnetic resonance imaging: Protocol and hypothesis-driven biomarkers

Participants underwent brain imaging on 3-Tesla MRI scanners at Cedars–Sinai Medical Center and University of Florida using harmonized protocols adapted from Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3). The brain MRI protocol includes structural, susceptibility-weighted, perfusion, diffusion, intracranial vessel wall, and resting-state functional acquisitions, as well as a standardized CO_2 challenge for cerebrovascular reactivity. Key acquisition parameters and timing details are provided in Tables S1 and S2.

Brain MRI endpoints were pre-specified to test the hypothesized heart–brain microvascular pathway. Primary outcomes include CSVD burden (white matter hyperintensity volume, lacunes, cerebral microbleeds, and perivascular space enlargement), diffusion-derived white matter microstructural integrity, structural connectivity metrics, and measures of brain microvascular function (baseline cerebral blood flow and cerebrovascular reactivity) (Figure 2). Resting-state functional magnetic resonance imaging was used to derive within- and between-network functional connectivity measures reflecting large-scale network organization potentially sensitive to microvascular dysfunction. Intracranial vessel wall biomarkers characterized large-artery remodeling that may influence cerebral hemodynamics (Figure 3). Detailed preprocessing, quality control, and software/version information are provided in Sections S1.1–S1.2.

2.4.2. Cardiac magnetic resonance imaging protocol

Cardiac MRI was previously performed as described in Takahashi *et al.*[12] Acquisition details are provided in Table S1.

2.4.3. Retinal imaging protocol and analysis procedure

Retinal microvascular phenotyping was performed using non-mydriatic color fundus photography, spectral-domain OCT, and OCT-A, as previously published.[13] Primary retinal endpoints include central retinal arteriolar and venular equivalents, vessel tortuosity/fractal dimension, retinal nerve fiber layer and macular thickness, and OCT-A vessel density/perfusion metrics. Image acquisition and grading follow standardized protocols with centralized quality control; detailed acquisition settings, scan patterns, and grading procedures are provided in Section S2 and Tables S1 and S3.

2.5. Cognitive assessment

Cognitive function was assessed using the Montreal cognitive assessment (MoCA) and the NIH toolbox cognition battery (NIHTB-CB). The NIHTB-CB provides standardized domain and composite scores for executive function/attention, processing speed, episodic memory, working memory, and language, as published.[14]

Montreal cognitive assessment total score and pre-

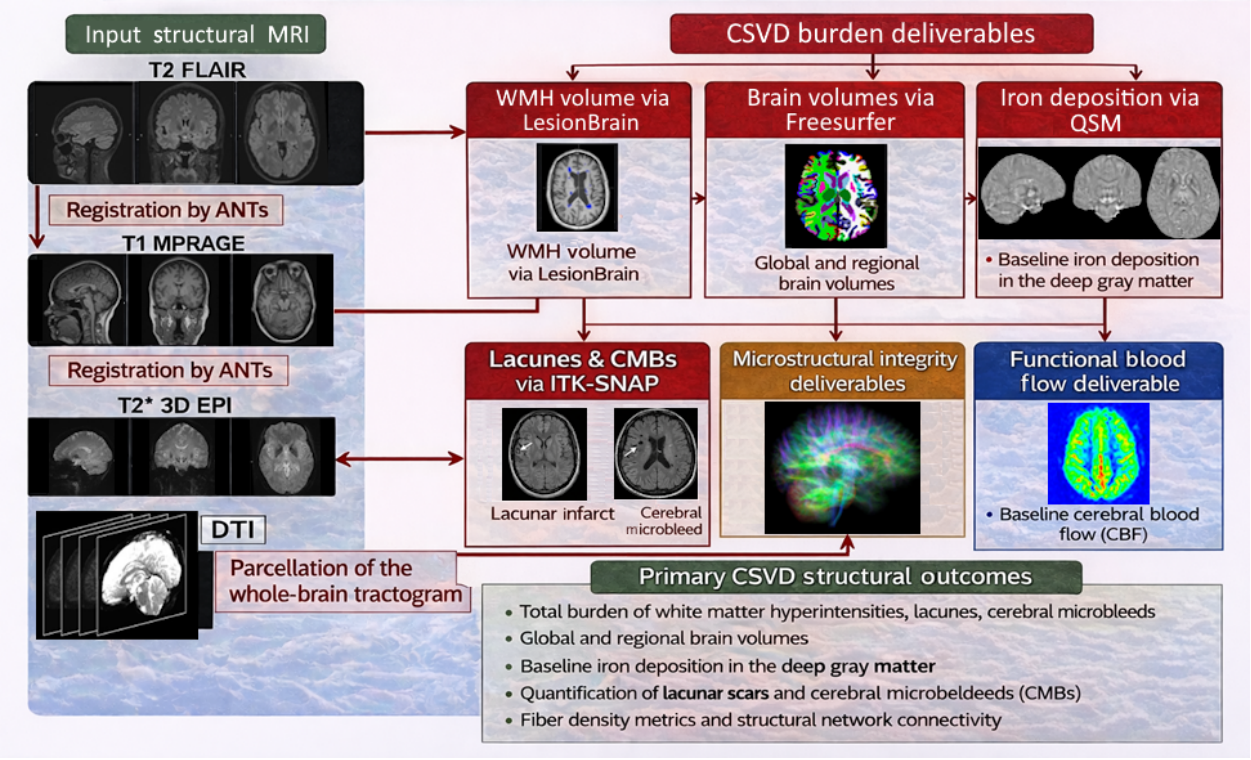

Figure 2. Structural MRI analysis pipeline and derived CSVD and tissue integrity biomarkers. T1-weighted MPRAGE and T2-FLAIR will be used for volumetry and WMH segmentation. T2*W 3D EPI will support QSM reconstruction for deep gray matter susceptibility (total generalized variation) and visual adjudication and quantification of cerebral microbleeds and lacunes using ITK-SNAP. Diffusion MRI will provide tensor-derived microstructural metrics and estimates of structural connectivity. pASL will provide cerebral blood flow maps.
Abbreviations: ANTs: Advanced normalization tools; CBF: Cerebral blood flow; CMBs: Cerebral microbleeds; CSVD: Cerebral small vessel disease; DTI: Diffusion tensor imaging; EPI: Echo planar imaging; FA: Fractional anisotropy; FLAIR: Fluid-attenuated inversion recovery; FOD: Fiber orientation distribution; MPRAGE: Magnetization-prepared rapid acquisition gradient-echo; MRI: Magnetic resonance imaging; pASL: Pulsed arterial spin labeling; QSM: Quantitative susceptibility mapping; WMH: White matter hyperintensities.

specified domain scores were used to characterize the cognitive profile at baseline and served as primary/secondary cognitive endpoints in heart–brain analyses.[15] Detailed scoring components and test administration procedures are provided in Section S2 and Table S3.

2.6. Statistical methods and power calculations

2.6.1. Statistical analysis overview

Analyses were organized by pre-specified aims and hypotheses. Primary exposure variables include coronary microvascular function metrics derived from coronary and cardiac imaging (e.g., coronary flow reserve and myocardial perfusion reserve indices, where available). Primary outcomes include a limited set of pre-specified CSVD markers (white matter hyperintensity burden and diffusion-derived white matter integrity) and cognitive domain scores. Secondary outcomes include cerebrovascular reactivity, functional connectivity metrics, and additional brain vascular markers.

2.6.2. Covariates and potential confounders

All primary models were adjusted for age, race/ethnicity, education, and socio-economic status proxies, vascular risk factors (hypertension, diabetes, dyslipidemia, body mass index), menopausal status and hormone replacement therapy, and key medication classes (e.g., statins, beta blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, nitrates, vasoactive agents). Where available, mood symptoms (depression/anxiety) and lifestyle factors (smoking, physical activity, sleep) were included and evaluated in sensitivity analyses.

2.6.3. Multiplicity and dimensionality

To mitigate false-positive findings across multi-metric imaging, we designated a limited set of primary endpoints per domain. Secondary imaging analyses apply false discovery rate control. When appropriate, composite "microvascular burden" indices were constructed (e.g.,

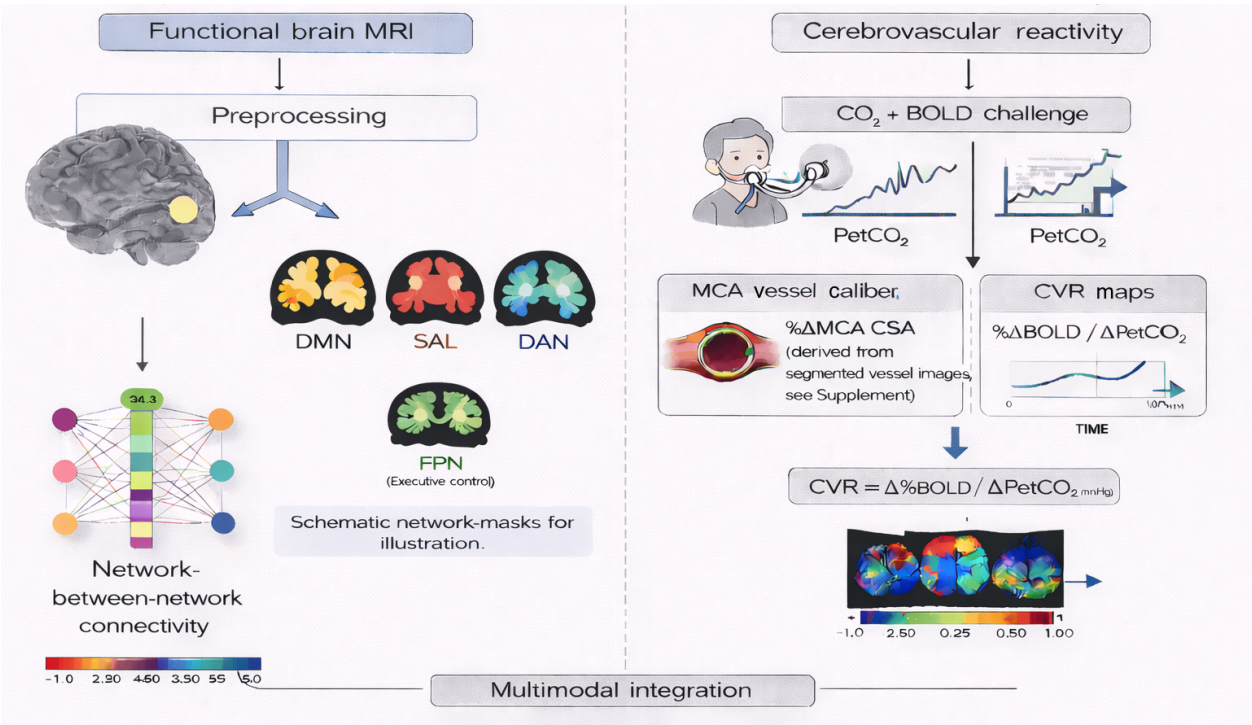

Figure 3. Parallel neural and cerebrovascular biomarkers derived from multimodal MRI. Schematic overview of the parallel extraction of neural network–based and cerebrovascular function biomarkers in the present study. Left panel: Functional brain MRI preprocessing and network-based analyses yield large-scale resting-state network measures, including the default mode network (DMN), salience network (SAL), dorsal attention network (DAN), and frontoparietal network (FPN; executive control). Within- and between-network connectivity metrics are derived to characterize large-scale neural organization. Network maps shown are schematic masks for illustration purposes. Right panel: Cerebrovascular reactivity (CVR) is assessed using a CO_2/blood–oxygen–level–dependent (BOLD) challenge paradigm, with end-tidal CO_2 ($PetCO_2$) as the physiological regressor. Vascular responsiveness is quantified via middle cerebral artery (MCA) caliber change (%Δ cross-sectional area [CSA]) and voxelwise CVR maps computed as %ΔBOLD per mmHg $\Delta PetCO_2$. Bottom: Multimodal integration of neural and vascular biomarkers enables investigation of heart–brain microvascular coupling and its relationship to cognition.

standardized *z*-score composites or principal components) to reduce dimensionality and improve interpretability.

2.6.4. Power and scope

The planned sample size (n = 100) was designed to support primary mechanistic hypotheses relating coronary microvascular function to pre-specified CSVD and cognitive outcomes. Given the breadth of secondary imaging phenotypes, analyses beyond primary endpoints were explicitly exploratory and hypothesis-generating, with multiplicity control and dimensionality reduction strategies applied as above. Power calculations for key primary endpoints are provided in Tables 1–3.

2.6.5. Power assumptions and effect-size justification

Standard deviations and baseline rates used in the power calculations were drawn from prior literature and our available pilot data, as cited in Tables 1–3. We selected minimum-detectable differences corresponding to small-to-moderate effects that would be clinically meaningful for microvascular and cognitive endpoints (e.g., differences on the order of ~0.4–0.6 SD or moderate associations between coronary microvascular function and primary brain outcomes). Because this study integrates multiple imaging and cognitive domains, we pre-specified a limited set of primary endpoints for confirmatory inference and designated secondary/high-dimensional imaging features as exploratory, with multiplicity control and dimensionality reduction as described above. Since this was a cross-sectional study, sample size calculations were based on baseline cross-sectional endpoints rather than longitudinal follow-up.

2.6.6. Sample size inflation for non-completion and missing data

This ancillary study was cross-sectional in design; there was no longitudinal follow-up, and analyses were based on baseline multimodal phenotyping completed within one to two coordinated visits. Accordingly, the relevant analog of "loss to follow-up" for this protocol is non-completion

of one or more components of the baseline multimodal assessment (e.g., a participant enrolled and consented but unable to complete cardiac MRI, brain MRI, retinal imaging, or cognitive testing, or an acquisition that fails central quality control [QC]). The targeted enrollment of $n = 100$ women was prospectively inflated to account for this partial non-completion and for technical data loss. Based on prior experience in the parent WISE and MAE-WEST studies and comparable multimodal imaging studies, we assumed a conservative combined non-completion plus unusable-data rate of approximately 20–25% per primary-endpoint domain. Under these assumptions, we expect at least 75–80 participants with complete primary-endpoint data, which will preserve ≥ 80% power to detect the minimum-detectable differences in Tables 1–3 for the pre-specified CSVD and cognitive endpoints at $\alpha = 0.05$ (two-sided). If observed non-completion exceeds 25% in any primary domain at the interim review, the steering committee will consider expanding enrollment and/or extending the recruitment window with institutional review board (IRB) concurrence to maintain analytic power. For the cross-sectional primary analyses, multiple imputation by chained equations will be used to address item-level missingness under a missing-at-random assumption, with pattern-mixture and complete-case sensitivity analyses to evaluate robustness. Participants missing an entire primary endpoint domain (e.g., unusable brain MRI) will be excluded from the corresponding domain-specific analysis but retained for analyses in other domains.

2.6.7. Strategies to minimize protocol non-completion

Since this was a cross-sectional study with no longitudinal follow-up, the potential limitation is that enrolled participants may not complete the full multimodal baseline assessment. A proactive, participant-centered plan was implemented at both sites to minimize partial non-completion and unusable data. Core elements include: (i) designated study coordinators who serve as single points of contact and build rapport through personalized outreach; (ii) coordinated scheduling that consolidates cardiac, brain MRI, retinal, and cognitive assessments into one to two visits to reduce participant burden; (iii) pre-visit reminder calls, text messages, and e-mails at 1 week and 24–48 hours before each visit, with automated research electronic data capture (REDCap) reminders for questionnaires; (iv) travel and parking reimbursement and flexible scheduling (including evenings and weekends where feasible) to reduce barriers to participation; (v) participant appreciation measures including modest compensation and, where appropriate, educational feedback on imaging and cognitive results; (vi) structured tracking of missed or incomplete visits in REDCap with escalating outreach (up to three contact attempts across phone, text, and e-mail) to schedule make-up sessions for incomplete modalities where feasible; (vii) collection of alternate contact information (secondary phone, e-mail, next-of-kin) at enrollment to reduce unreachable participants; and (viii) formal adjudication of non-completion versus withdrawal, with reasons captured to inform sensitivity analyses and consolidated standards of reporting trials-style flow reporting. Completion metrics (visit completion rates, time-to-completion, and domain-specific data capture) are monitored monthly by the steering committee. Pre-specified thresholds trigger corrective action: if the cumulative non-completion rate for any primary-endpoint domain exceeds 15% at a site, site-level audits, coordinator retraining, and targeted re-contact campaigns were initiated; if it exceeds 25%, protocol amendments to expand recruitment, extend the timeline, or further simplify procedures were considered. Potential selection effects arising from differential non-completion were examined using inverse probability weighting in sensitivity analyses.

2.7. Quality control

Given the breadth of measurement domains and the multi-site design, a structured QC framework was embedded across every procedural step to ensure data accuracy, scientific validity, and reproducibility. QC procedures are pre-specified, documented in a study-wide manual of operations and procedures, and overseen by a central data and quality committee that meets monthly to review site- and domain-specific metrics. Each imaging and cognitive domain has a designated domain lead who is responsible for certifying procedures, reviewing QC metrics, and adjudicating exceptions. Site initiation visits, annual refresher trainings, and documented certification of all personnel performing study procedures are required before and during data collection.

2.7.1. Screening, recruitment, and clinical data capture

Eligibility is independently verified by two trained coordinators using a standardized checklist, with discrepancies adjudicated by the site principal investigator. Sociodemographic, vascular risk factor, medication, and reproductive history data were collected using harmonized case report forms in REDCap, with built-in range checks, required-field logic, branching logic, and automated data-validation rules. Double data entry is performed for source documents captured on paper, and weekly automated data-quality reports flag missing, out-of-range, or internally inconsistent values for coordinator review.

All protocol deviations were logged and reviewed by the steering committee.

2.7.2. Brain magnetic resonance imaging

Harmonized 3T acquisition protocols, adapted from ADNI3, are deployed at both sites with matched pulse sequences, coil configurations, and physiologic monitoring. Scanner stability was verified through weekly ACR phantom scans and ADNI-style traveling-phantom acquisitions at study initiation and annually thereafter, with signal-to-noise ratio, geometric distortion, and B0/B1 homogeneity monitored against pre-specified tolerances. Every scan underwent standardized real-time QC at the scanner console (series completeness, motion screening, and coverage) and centralized post-acquisition QC within 72 h, including automated motion metrics (e.g., framewise displacement for functional magnetic resonance imaging and diffusion), signal-to-noise ratio (SNR), ghosting, and artifact screening. Scans that fail QC thresholds were flagged for re-acquisition, where feasible. Structural segmentation (e.g., FreeSurfer), WMH segmentation, diffusion, perfusion (pulsed arterial spin labeling), quantitative susceptibility mapping, and cerebrovascular reactivity pipelines include automated QC outputs plus blinded visual review by two trained readers, with a third senior neuroradiologist/neuroscientist adjudicating discrepancies. Inter- and intra-rater reliability is assessed on a 10% random subsample using intraclass correlation coefficients (ICC) and dice similarity indices, with a pre-specified acceptable ICC ≥ 0.80. End-tidal CO_2 recordings for cerebrovascular reactivity were inspected for signal quality and acceptable end-tidal carbon dioxide excursions; substandard recordings were excluded. All software versions and pipeline parameters are version-controlled, and multi-site effects are evaluated using ComBat-style harmonization in sensitivity analyses.

2.7.3. Cardiac magnetic resonance imaging and coronary microvascular function

Cardiac MRI acquisitions follow the standardized WISE heart failure with preserved ejection fraction (Pre-HFpEF) protocol with centralized analysis at the Cedars–Sinai Biomedical Imaging Research Institute core laboratory. Sequence fidelity, adherence to the pharmacologic stress protocol (adenosine/regadenoson dosing and hemodynamic response), electrocardiogram (ECG) gating quality, and breath-hold performance are verified in real time by trained cardiac MRI technologists. Myocardial perfusion reserve index and coronary flow reserve were computed using pre-specified software with blinded reads by two core-laboratory analysts; a 10% duplicate-read subset is used to quantify inter-reader reproducibility (target ICC ≥ 0.85). Invasive coronary reactivity testing follows standardized WISE protocols with medication washout, continuous hemodynamic monitoring, and laboratory-based pressure/flow-wire calibration before each case. Studies that do not meet the technical adequacy criteria were excluded from the primary analyses, with reasons documented.

2.7.4. Retinal imaging

Non-mydriatic fundus photography, spectral-domain OCT, and OCT-A were performed by certified photographers using identical device models and acquisition settings across sites. Device calibration was verified daily, and signal-strength indices, segmentation fidelity, and motion/centration artifacts were screened at acquisition; images not meeting pre-specified quality thresholds (e.g., OCT signal strength ≥ 7, gradable fundus photograph per standardized criteria) were re-acquired when possible. All images were uploaded to a centralized grading platform and independently graded by two masked readers at a reading center, with standardized quantification of arteriolar and venular calibers, fractal dimension, retinal nerve fiber layer, macular thickness, and OCT-A vessel density. Discrepancies beyond pre-specified tolerances were adjudicated by a senior grader. Intra- and inter-grader reliability were monitored on a rolling 10% subset (target ICC ≥ 0.85 for continuous metrics; kappa ≥ 0.80 for categorical features).

2.7.5. Peripheral vascular function testing

Peripheral vascular measures were obtained under standardized fasting, temperature-controlled, and medication-washout conditions (where clinically permissible), with pre-specified participant preparation (avoidance of caffeine, nicotine, and vasoactive substances for ≥ 6 h) documented on a checklist. Devices underwent daily calibration; operators completed initial certification and annual recertification. Waveforms and raw tracings were reviewed by a blinded analyst for signal quality and motion artifact before inclusion, with a 10% duplicate-read sample to assess reproducibility.

2.7.6. Cognitive assessment

The MoCA and NIHTB-CB were administered by certified examiners who completed formal training, supervised practice, and initial/annual recertification. Testing was conducted in a quiet, standardized environment at a consistent time of day where feasible, using identical iPad/software configurations across sites. Administration fidelity was supported by structured scripts, pre-test equipment checks, and post-test integrity checklists. A 10% random sample of sessions was audio-recorded

(with consent) and reviewed by a cognitive-assessment domain lead for administration and scoring fidelity; deviations trigger targeted retraining. Scored data were transferred directly from the toolbox platform into the study database to eliminate transcription errors, and MoCA forms underwent double entry with reconciliation of discrepancies.

2.7.7. Data management, monitoring, and governance

All study data were stored in the U.S. Health Insurance Portability and Accountability Act (HIPAA)-compliant REDCap instance hosted on the Cedars–Sinai secure network with role-based access control, encrypted transmission, and full audit trails. Imaging data were transferred to a central repository using de-identified digital imaging and communications in medicine with a brain imaging data structure-compliant organization; transfers were verified via checksum. Automated data-quality dashboards tracked completeness, timeliness, out-of-range values, and protocol-deviation rates by site and domain. The monthly steering committee and data and quality committee reviewed the evaluated QC metrics and triggered corrective action (e.g., site retraining, equipment servicing) when pre-specified thresholds were exceeded. Annual independent audits of a random 10% sample of case report forms against source documents were conducted, and any systematic discrepancies were addressed through protocol clarification and coordinator retraining. Analysis code, pipeline versions, and derived variable definitions are version-controlled and archived to support reproducibility.

3. Results

To date, participants with suspected CMD have been enrolled from the parent studies. Baseline demographic information and clinical characteristics of women enrolled to date are summarized in Table 4.

Table 1. Power calculations for primary cerebral small vessel disease imaging endpoints (minimum detectable differences)

CSVD variable	SD	MDD 80%/20%	MDD 50%/50%
Global CBF (mL/100 g/min)[16]	10.48	7.413	5.930
Total white matter (mL)[17]	4.87	3.445	2.756
Total brain volume without ventricles normalized[18]	2.33	1.648	1.319
WMH volume (mL)[19]	0.005	0.004	0.003
Brain iron right putamen (ppb)[20]	3.98	2.815	2.252
Intracranial vessel lumen volume (mm^3)[21]	16.7	11.813	9.45
Intracranial vessel wall index[21]	0.06	0.042	0.034
Intracranial vessel wall thickness (mm)[21]	0.14	0.099	0.079

Abbreviations: CBF: Cerebral blood flow; CSVD: Cerebral small vessel disease; MDD: Minimum detectable differences; SD: Standard deviation; WMH: White matter hyperintensities.

Table 2. Power calculations for associations between coronary microvascular function (MPRI, CFR) and global cerebral blood flow

Variable	SD	Outcome	SD	MD slope
MPRI[2]	0.43	Global CBF	10.48	6.635
CFR[22]	0.7	Global CBF	10.48	4.076

Abbreviations: CBF: Cerebral blood flow; CFR: Coronary flow reserve; MD: Minimum detectable; MPRI: Myocardial perfusion reserve index. SD: Standard deviation.

Table 3. Power calculations for cognitive endpoints (minimum detectable differences)

Outcome	SD	MDD 80%/20%	MDD 50%/50%
Fluid cognition composite[23]	14.4	10.186	8.149
Crystallized cognition composite[23]	14.0	9.903	7.922
Flanker inhibitory control and attention[23]	14.6	10.327	8.262
Pattern comparison processing speed[23]	14.9	10.54	8.432

Abbreviations: MDD: minimum detectable differences; SD: Standard deviation.

Table 4. Baseline demographics and clinical characteristics of women enrolled to date (*n* = 44)

Baseline demographics and clinical characteristics	Total sample enrolled to date
Age (mean ± SD)	53.4 ± 11.9
Race *n* (%)	
White/Not Hispanic	34 (77.3%)
Black/African American	3 (6.8%)
Hispanic/Latin	2 (4.5%)
Asian/Pacific Islander	3 (6.8%)
Other	2 (4.5%)
Annual income *n* (%)	
$0–$49,999	4 (9.1%)
$50,000–$99,000	10 (22.7%)
$100,000+	30 (68.2%)
Highest level of education *n* (%)	
Grade and high school	0 (0.0%)
High school diploma	1 (2.3%)
Associate's degree to doctorate	43 (97.7%)
Body mass index (kg/m^2; mean ± SD)	27.2 ± 5.9
Hypertension *n* (%)	15 (34.1%)
Dyslipidemia *n* (%)	10 (22.7 %)
Diabetes Mellitus *n* (%)	4 (9.1%)
Cerebrovascular disease (stroke, transient ischemic attack, carotid revascularization) *n* (%)	2 (4.5%)
Smoking Status *n* (%)	
Former	9 (20.5%)
Current	0 (0.0%)
Post-menopausal *n* (%)	20 (45.5%)
History of Pregnancy *n* (%)	31 (70.5%)
Adverse Pregnancy Outcome *n* (%)	14 (31.8%)
Medications *n* (%)	
Statins	24 (54.5%)
Angiotensin-converting enzyme inhibitor	4 (9.1%)
Angiotensin II receptor blocker	11 (25%)
Beta blockers	17 (38.6%)
Calcium channel blockers	25 (56.8%)
Diuretics	6 (13.6%)
Vasodilators	1 (2.3%)
Nitrates	25 (56.8%)
Hormone replacement therapy	14 (31.8%)

(*Cont'd...*)

Table 4. ***(Continued)***

Baseline demographics and clinical characteristics	Total sample enrolled to date
Seattle angina questionnaire (mean ± SD)	
Angina limitation	64.4 ± 21.1
Angina frequency	46.1 ± 26.1
Angina stability	47.2 ± 27.2
Angina treatment satisfaction	71.1 ± 16.7
Angina quality of life	37.8 ± 24.7
Seattle angina questionnaire-7 (mean ± SD)	51.7 ± 20.9
Angiographic coronary severity score (median [range])	5 (5-15)
Angiographic findings *n* (%)	
No coronary artery disease (< 20% stenosis)	25 (56.8%)
No obstructive coronary artery disease (20–50% stenosis)	19 (43.2%)

Baseline characteristics indicate that the study sample is enriched for clinically relevant microvascular risk modifiers, including vascular comorbidities, medication exposures, and reproductive factors. The distribution of menopausal status and hormone therapy use underscores the importance of modeling reproductive status as a confounder or effect modifier in primary heart–brain analyses. These baseline data support the feasibility of integrated multimodal phenotyping and inform the covariate structure of planned models.

As this is a protocol manuscript and recruitment is ongoing, no hypothesis-testing analyses have been performed at this stage.

4. Discussion

Our protocol is motivated by converging evidence that microvascular dysfunction can represent a systemic small-vessel phenotype with clinically meaningful consequences for both the heart and brain. Cardiac and cerebral small-vessel disease share overlapping mechanisms, and recent syntheses emphasize the need for integrated, multi-organ phenotyping rather than organ-specific inference.[24,25] Emerging human data further support measurable heart–brain coupling: in the prospective Cerebral–Coronary Connection (C3) study, impaired coronary flow reserve was associated with greater white matter hyperintensity burden, lower grey matter volume, diffusion-based white matter injury, abnormal cerebral hemodynamics, and worse cognitive performance—findings consistent with a shared heart–brain microvascular process.[7] Complementary retinal literature—where microvessels can be directly visualized—has linked retinal microvascular abnormalities to silent brain infarcts and white matter lesions and, in some cohorts, to progression of cerebral microvascular disease, reinforcing the concept that microvascular injury may track across vascular beds rather than remaining confined to a single organ.[26,27]

Against this backdrop, our women-only INOCA-focused protocol extends prior work in ways that are directly relevant to clinical practice and mechanistic discovery. First, by studying women with suspected INOCA/CMD—rather than cohorts defined primarily by obstructive coronary disease—we target a population in which microvascular dysfunction is common, symptom-relevant, and frequently under-recognized, yet the pathways linking coronary microvascular physiology to brain outcomes remain insufficiently defined. Second, we integrate coronary/cardiac MRI phenotyping with advanced brain MRI markers of CSVD burden and brain microvascular function and standardized cognitive assessment within the same participants, enabling aligned, hypothesis-driven testing rather than parallel single-organ analyses. Third, the inclusion of retinal imaging and peripheral vascular function testing strengthens the ability to evaluate whether CMD reflects a broader systemic microvascular phenotype and provides complementary vascular-bed "readouts" that may improve interpretability when heart and brain measures are discordant.

Several feasibility and interpretive considerations are inherent to intensive multimodal phenotyping. The sample size is intentionally structured for hypothesis-driven primary analyses, while secondary high-dimensional imaging features require careful control of multiplicity and overfitting. We address this by pre-specifying primary endpoints, using a staged analysis plan, applying multiplicity control for secondary analyses, and employing parsimonious composite measures or dimension-reduction strategies where appropriate.

Multi-site acquisition introduces potential scanner and site effects; therefore, harmonized protocols, centralized quality control, and statistical adjustment for site/scanner are incorporated into the analytic framework. In addition, selection bias is possible because participants who are able to complete extended imaging and cognitive procedures may differ from broader clinical INOCA populations; we will characterize recruitment and retention patterns and interpret results within the context of protocol tolerability.

A major strength of the protocol is the explicit treatment of confounding and effect modification, which is essential when examining CMD, CSVD, and cognition in women. Menopausal status and hormone therapy exposure, education and socio-economic gradients, mood symptoms (depression/anxiety), lifestyle factors, and medication exposures can influence both vascular physiology and cognitive performance and may also correlate with symptom burden and healthcare access. Accordingly, these factors are incorporated as pre-specified covariates and, where feasible, evaluated as effect modifiers through stratified and sensitivity analyses to strengthen causal interpretability and reduce the likelihood that observed associations reflect correlated exposures rather than microvascular biology.

Clinically, a reproducible heart–brain microvascular signature could help identify women with INOCA who are vulnerable to brain microvascular injury and cognitive inefficiencies and may help explain heterogeneity in symptoms and functional outcomes. If coronary microvascular dysfunction aligns with brain microvascular dysfunction and CSVD-related injury markers, findings would support systemic microvascular risk phenotyping and inform future prevention and intervention strategies targeting endothelial and microvascular mechanisms rather than focusing exclusively on obstructive epicardial anatomy. More broadly, this integrated protocol provides a framework for future studies examining heart-brain microvascular mechanisms in women with suspected INOCA/CMD.

Finally, dissemination will prioritize transparency and reproducibility. In addition to peer-reviewed publications and presentations, we will share harmonized variable definitions, derived endpoints, and quality-control specifications to facilitate replication and accelerate multicenter collaboration in heart–brain microvascular research.

5. Conclusion

This protocol establishes a comprehensive framework for examining the potential heart–brain microvascular links in women with suspected INOCA/CMD. Through coordinated multimodal phenotyping of coronary and cardiac function, brain structure and microvascular physiology, retinal vascular status, peripheral vascular function, and cognition, the study is positioned to provide a uniquely detailed characterization of systemic microvascular health in a population in whom INOCA is common yet incompletely understood.

By focusing on women with suspected INOCA/CMD, this study addresses an important gap in knowledge regarding whether coronary microvascular dysfunction is associated with parallel abnormalities in cerebral small vessel disease markers and cognitive performance. The resulting data will help define the cross-sectional vascular and cognitive profile of this population, identify patterns relevant to risk stratification, and generate a stronger empirical basis for future longitudinal and mechanistic studies. By doing so, this work may contribute to a broader shift toward integrated, multi-organ assessment of microvascular disease and support more informed strategies for early recognition and prevention of adverse cardiovascular and neurological outcomes in women.

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Conflict of interests

Cathleen Noel Bairey Merz serves as a director and received stock in iRhythm. Janet Wei participates on the Advisory Board for Abbott Vascular Coronary Microvascular Dysfunction Advisory Board (paid to institution). Michael D. Nelson receives funding from an extramural grant organization for his research. These grants cover part of his time and effort, and payments are made to his institution. Mitzi M. Gonzales is supported by R01AG085571, R01AG089711, and R01AG077472. The remaining authors have no conflicts to disclose.

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Ethics approval and consent to participate

The study protocol received approval from the Cedars–Sinai Medical Center Institutional Review Board (IRB). The trial was registered at ClinicalTrials.gov (NCT03876223). All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Amendments to the protocol will be submitted to the CSMC IRB for approval. The study was conducted under IRB approval Pro00054999, which includes the WISE Pre-HFpEF protocol and the approved neurocognition/brain MRI substudy addendum, including the approval letter for the study. All participants provided written informed consent prior to participation. The consent form specified that participation was voluntary and that participants could withdraw at any time without penalty or loss of benefits.

Consent for publication

All participants provided written informed consent for publication in the study after being informed of the objectives, procedures, potential risks, and benefits. Consent was obtained in accordance with the requirements of the Cedars–Sinai Medical Center Institutional Review Board and the participating institutions. The personal information of these individuals was collected through hard-copy case report forms and electronic capture in REDCap, and stored securely on Cedars–Sinai Medical Center's network via VPN, in compliance with federal HIPAA laws.

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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