Proposal for construction of a dynamic multi-dimensional integrated assessment system for exercise and brain health

Initial framework for community

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A framework for the potential biomarkers

Cardiac health metrics

Central artery properties

Brain health metrics

Physical performance metrics

Life’s essential 8

HRV, BPV, hemodynamics?

Cardiac health metrics

- left ventricular mass index
- Left ventricular ejection fraction
- Cardiac output
- Cardiac index
- Coronary artery calcium score
- Total plaque burden and volume
- Coronary microvascular function

Vascular risk factors

- 24-hour BP profiles
- Heart rate variability
- Insulin resistance
- HbA1c
- LDL-c, HDL-c, total cholesterol
- Lipoprotein (a)
- BMI

Mental health:

depression, anxiety, neuropsychological battery

Cognition:

MMSE, MoCA, cognitive performance tests

Lifestyle

- Physical activity
- Diet
- Smoking
- Sleep

Brain imaging

- Cerebral microbleeds
- White matter integrity
- White matter hyperintensities
- Gray matter volume
- Regional brain structure and volume
- Total brain volume

Cerebral hemodynamics tests

- Cerebral blood flow (global and regional)
- Cerebrovascular reactivity
- Cerebral pulsatility index
- Pulse pressure
- Mean arterial pressure
- Cerebral autoregulation

Vascular properties

- Carotid-femoral pulse wave velocity
- Carotid β-stiffness
- Carotid intima-media thickness
- Cerebrovascular resistance

Vascular risk factors

- 24-hour BP profiles
- Heart rate variability
- Insulin resistance
- HbA1c
- LDL-c, HDL-c, total cholesterol
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Framework for exercise testing

Traditional metrics

- Aerobic fitness: VO_2peak,
- Muscle strength: handgrip strength, knee-extension strength
- Flexibility: sit-to-reach test
- Body composition
- Balance
- Muscle power

Physical functional performance metrics in the upper and lower extremities

- Walking test
- Gait performance
- Lower-extremity functional test: timed-up-and-go (TUG), Sit-to-Stand test
- Upper extremities tests

- Physical performances for vascular health, metabolic health, heart health, cardiac diseases (CAD, HF), brain health

Cardiac disease may contribute to the development of Cerebral microbleeds

- Risk for cortical infarcts tends to increase with atherosclerotic/coronary processes
- Cerebral microinfarcts had a significantly higher prevalence of atrial fibrillation, ischemic heart disease, and congestive heart failure
- Concentric LV hypertrophy was associated with cortical cerebral microinfarcts and dementia
- Cortical microinfarcts showed greater decline in MoCA and global cognition per year.

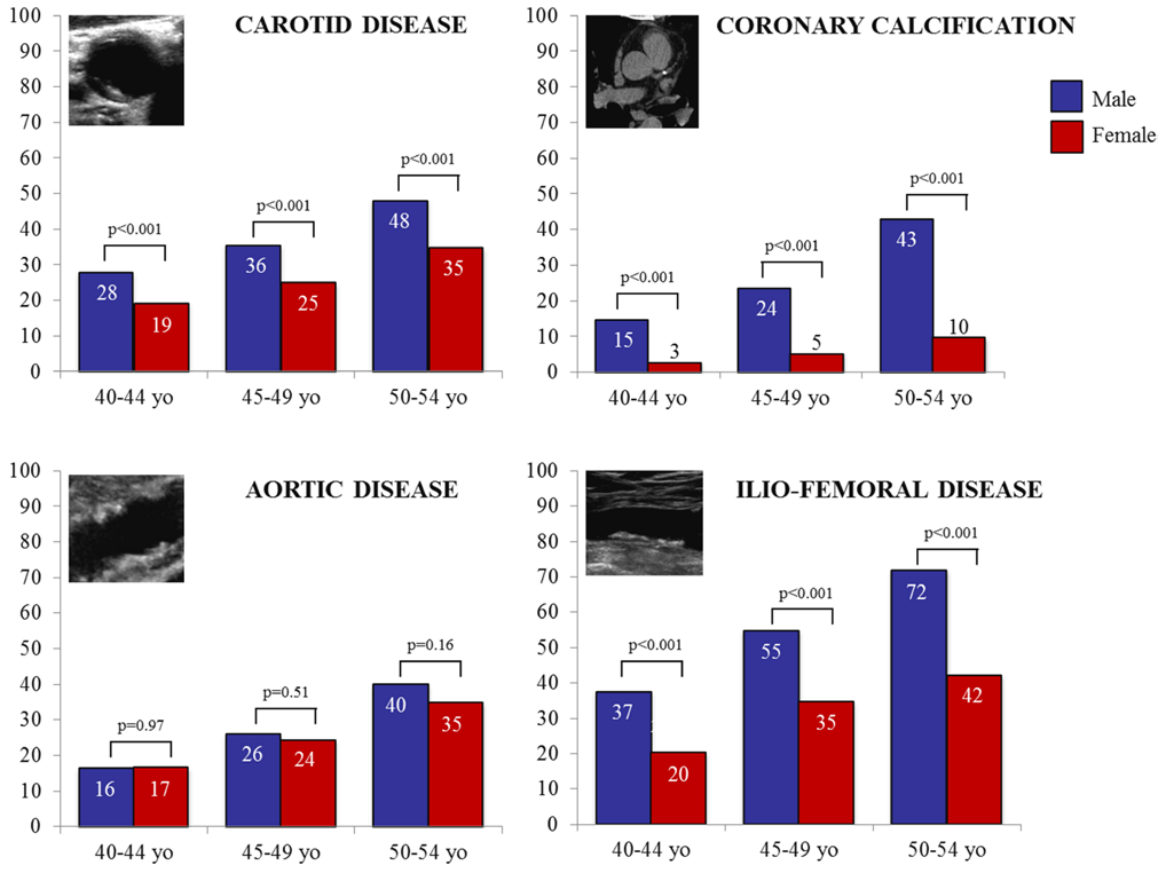
Both coronary microvascular dysfunction (CMD) and CSVD share common risk factors. These factors might have a common effect on the microvascular domain of cardiac and cerebral vascular beds

Major researchers: Christopher Chen, Saima hilal,
National University of Singapore

JAMA Neurol. 2017 Apr 1;74(4):403-410.

Findings from the Progression of Early Subclinical Atherosclerosis (PESA) study

- Over 6 years, subclinical atherosclerosis progressed in one-third of middle-age asymptomatic subjects.
- The impact of LDL-C and SBP on subclinical atherosclerosis progression was more pronounced in younger participants, suggesting that the prevention of atherosclerosis and its progression could be enhanced by tighter risk factor control at younger ages.



Circulation. 2015 Jun 16;131(24):2104-2113

Coronary microvascular function and cardiovascular diseases

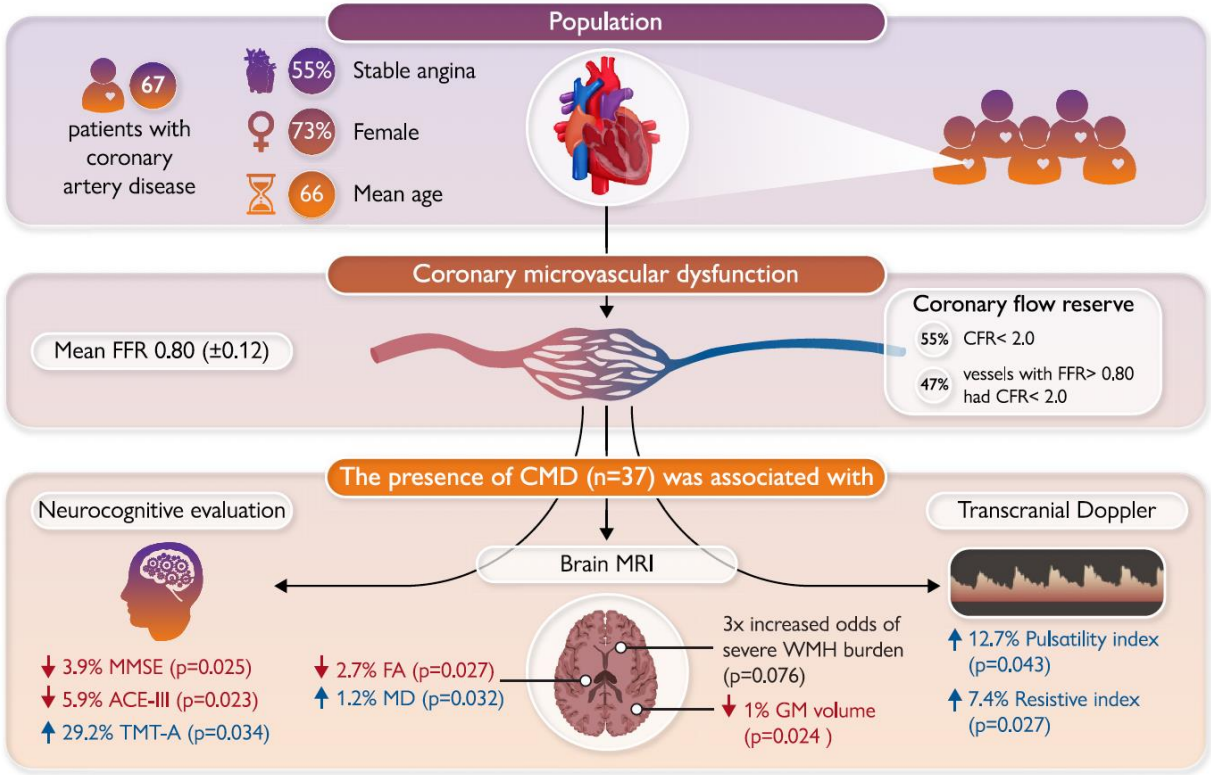
Coronary microvascular dysfunction (CMD) is emerging as a major cause of myocardial ischemia in patients with angina without obstructive coronary artery disease (CAD), obstructive CAD, primary cardiomyopathies, and heart failure

- To date, no specific therapeutic strategies targeting CMD validated by large scale randomized clinical trials
- Physical training, smoking cessation and weight management are necessary and beneficial

Coronary microvascular function and brain health

The Cerebral-Coronary Connection study (C3 study)

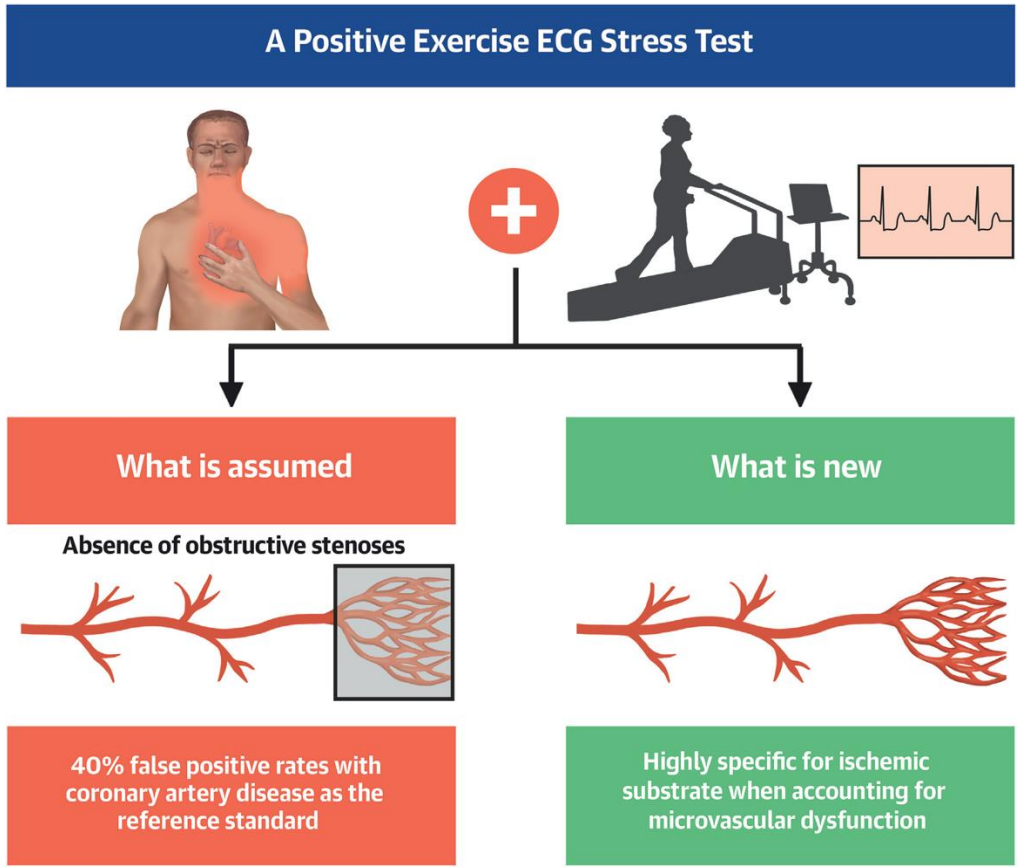
Conclusion: In patients with atherosclerotic CAD, the presence of CMD, as determined by low CFR, is associated with CSVD, abnormal cerebral flow haemodynamics, and subtle but significant impairment of cognitive function.



Eur Heart J, 2023 Jan 7;44(2):113-125.

Coronary microvascular function and exercise stress testing

Ischemic ECG changes during treadmill exercise stress testing have 100% specificity and positive predictive value for the detection of abnormal coronary microvascular function



Sinha A, et al. J Am Coll Cardiol. 2024;83(2):291–299.

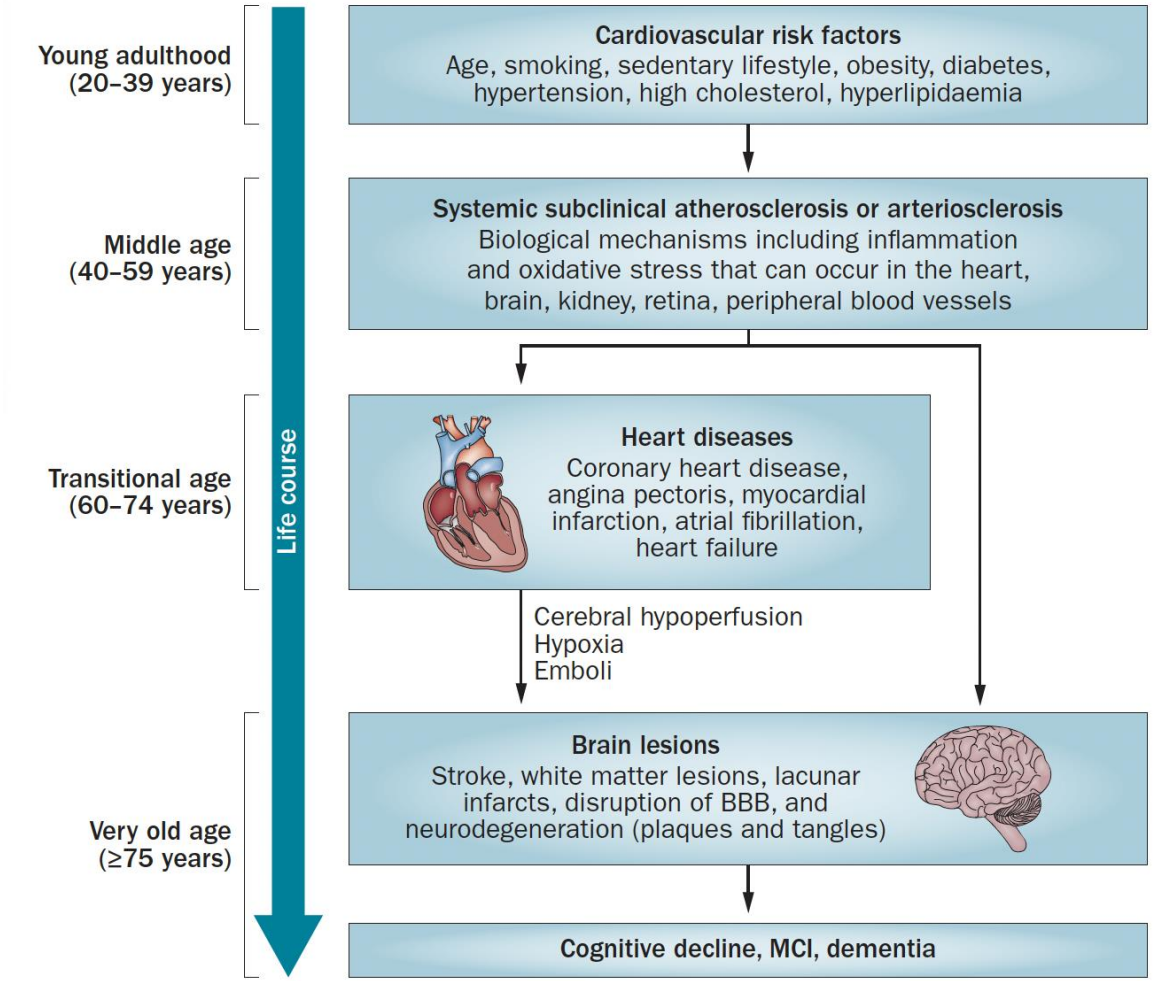
Reduction of cerebral blood flow and chronic diseases

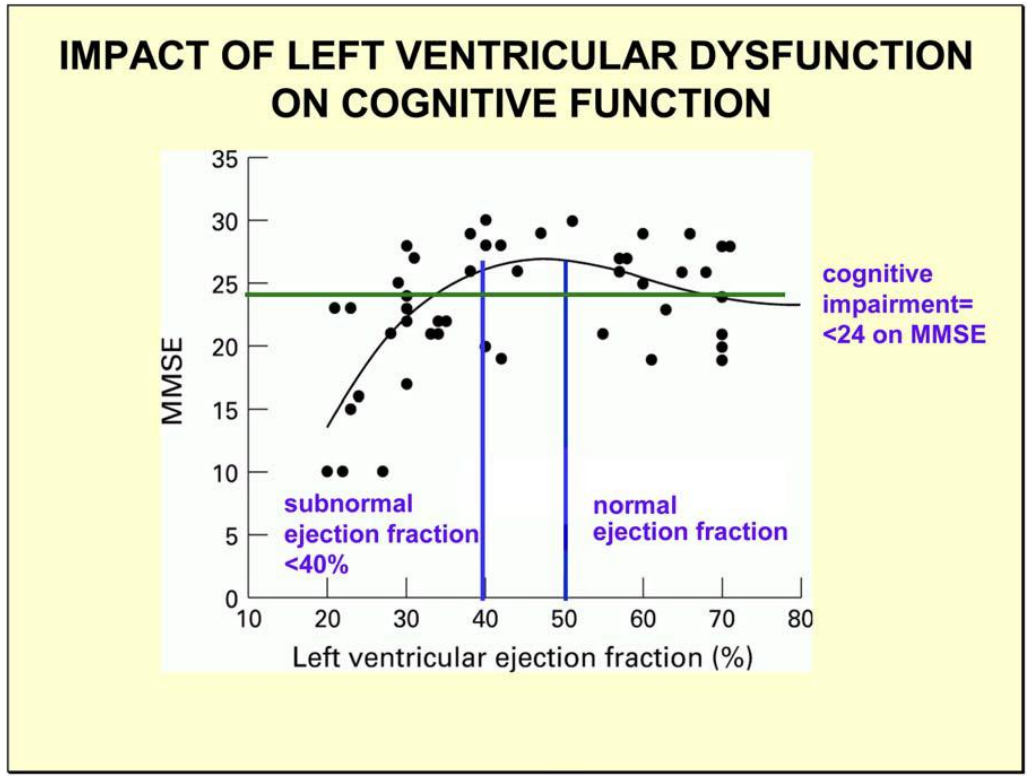
Hypertension	Global reduction in cerebral blood flow (CBF)
MCI and AD	• Lower CBF can be detected in cognitive normal subjects in the early AD continuum. • CBF is linked to biomarkers of AD, synaptic dysfunction, and neurodegeneration.
CVSD	• CBF reduction relates to WMH progression • In cognitively normal elderly individuals, incidental cerebral microbleeds in cortical locations are associated with widespread reductions in resting-state CBF.
Atherosclerosis	• Presence of cerebrovascular plaque was significantly associated with CBF reduction • progression of subclinical carotid atherosclerosis was associated with an additional decline in brain metabolic decline in Alzheimer's disease brain regions • The presence and volume of coronary artery calcium are associated with white matter lesion, cerebral microbleeds, larger WMH volumes
CAD	CAD is associated with altered cerebral hemodynamics in proportion to both cardiometabolic risk factors and cognitive function
AF	Global reduction in CBF
Heart failure	Regional reduction in CBF
T2DM	Regional reduction in CBF
Obesity	Global and regional reduction in CBF
Depression	Major depressive disorder is associated with CBF redistribution

Studies recommending CBF screening in Alzheimer's disease prevention and treatment

Study name	Major findings
Harvard Aging Brain Study	Systemic vascular risk, white matter injury, and relative CBF independently explain cognitive decline beyond amyloid and tau.
Heart-Brain Connection consortium	Lower CBF at baseline was associated with faster cognitive decline at 2-year follow up in VCI patients.
Penn ADRC	• Regional CBF changes likely reflect effects of both neurodegeneration and microvascular impairment. • Spatial patterns of hypoperfusion may differentiate between AD and vascular risk factor-related effects
The Age, Gene/Environment Susceptibility-Reykjavik Study	• A lower CBF is consistently related to worse cognitive outcomes. • Higher CBF was related to higher cognitive functioning and lower odd of mild cognitive impairment or dementia, irrespective of BP level.

Assessment of CBF in cardiovascular diseases and heart failure to prevent and treat cognitive dysfunction





Knowledge gap in exercise training and CBF

- Literature review does not show a direct link between exercise-induced augmentation of brain perfusion and better cognitive functioning.
- Exercise training showed heterogeneous effects on regional but little effect on global cerebral blood flow as measured by MRI.
- In healthy older adults, cardiorespiratory fitness has little effect on CBF.

Cerebrovascular reactivity

Evidence	• Non-modifiable risk (older age and apolipoprotein ε4), modifiable factors (diabetes, traumatic brain injury, hypertension), clinical factors (stroke, carotid artery occlusion, stenosis) were consistently associated with reduced CVR. • In conditions of T2MD, hypertension, TBI, the affected brain regions varied between studies.
Increased risk of recurrent stroke	Among patients with symptomatic cerebrovascular large vessel disease, those exhibiting impaired BOLD-CVR in the affected hemisphere had a 10.7-fold higher risk of recurrent ischemic stroke events compared with individuals with nonimpaired BOLD-CVR.
Global cognition	CVR was positively associated with global cognition in older adults
WMH progression	Lower baseline cerebrovascular reactivity predicted an increase in WMH and perivascular space volumes after 1 year
VO2peak	In the cross-sectional analysis, there was a quadratic relation between $\dot{V}o_{2peak}$, but not linear. The nonlinear trend was consistent across all networks.
Knowledge gap	• Most studies found that physical activity was not associated or even inversely associated with CVR in older adults. • New evidence suggests regional CVR response from physical activity, in both female and male. • Hemodynamic response function is largely independent of CVR.