

Arterial Stiffness, Brain Injury, and Clinical Cognitive Impairment: A Causal Mediation Analysis in NOMAS

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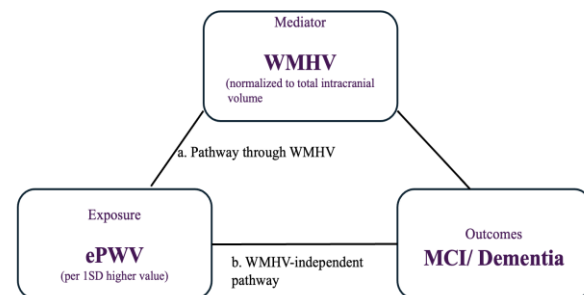
KEY TAKE AWAY: Cerebral small vessel injury partially explains the arterial stiffness-cognition pathway; additional WMHV-independent pathophysiological mechanisms likely contribute to late-life cognitive decline.

BACKGROUND

- Arterial stiffness is a marker of vascular aging,
- Estimated pulse wave velocity (ePWV) is a surrogate measure of arterial stiffness
- ePWV has been associated with cerebral small-vessel disease and white matter hyperintensity volume (WMHV), and cognitive impairment in previous Northern Manhattan Study (NOMAS) analyses.

Objective: Quantify the mediating effect of WMHV on the association between ePWV and cognitive decline in a multi-ethnic aging population.

Causal mediation framework



METHODS

- NOMAS: prospective population-based study, MRI subcohort, mean follow-up 12.2±1.3y
- Exposure: ePWV calculated from age and blood pressure and analyzed per 1SD higher value.
$$ePWV = 9.587 - (0.402 * age) + (4.560 * 0.001 * age^2) - (2.621 * 0.00001 * age^2 * MAP) + (3.176 * 0.001 * age * MAP) - (1.832 * 0.01 * MAP)$$
$$MAP = DBP + 0.4 * (SBP - DBP)$$
- Mediator: WMHV, normalized to total intracranial volume, natural log-transformed, and standardized.
- Outcomes: mild cognitive impairment (MCI) and dementia (reference outcome was cognitively normal/no MCI or dementia), adjudicated by clinical team based on comprehensive neuropsychological assessment. Causal mediation: counterfactual regression-based natural effects models; linear regression for the WMHV, logistic regression for cognitive outcomes

RESULTS

N=1,268, Age 71±9 years; 61% female; 68% HTN

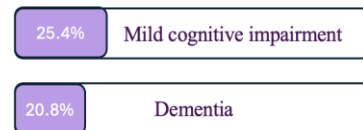
Mean ePWV: 11.7 ± 2.0 m/s

Higher ePWV → greater WMHV: $\beta=0.39$, 95%CI 0.33-0.45

Higher ePWV → MCI: OR=1.57, 95%CI 1.34-1.84

Higher ePWV → dementia: OR=1.98, 95%CI 1.61-2.43

Proportion of total association mediated by WMHV



- ✓ Model 1: unadjusted
- ✓ Model 2: adjusted for, sex, race and ethnicity, education
- ✓ Model 3: Model 2 + BMI, DM, hypercholesterolemia, antihypertensive medication, smoking status
- ✓ Model 4: Model 3 + ApoE4

Natural indirect effect through WMHV:		OR (95% CI)
Model1	MCI	1.16 (1.08, 1.25)
Model1	Dementia	1.22 (1.11, 1.34)
Model2	MCI	1.16 (1.08, 1.25)
Model2	Dementia	1.22 (1.11, 1.34)
Model3	MCI	1.13 (1.05, 1.21)
Model3	Dementia	1.15 (1.05, 1.27)
Model4	MCI	1.12 (1.04, 1.21)
Model4	Dementia	1.15 (1.04, 1.26)

Demographics, n=1,268

Age, years, mean (SD)	70.5 (9.0)	Diabetes, n (%)	245 (19.3%)
Male sex, n (%)	499 (39.4%)	Hypercholesterolemia, n (%)	822 (64.8%)
White, n (%)	189 (14.9%)	Antihypertensive meds, n (%)	381 (37.0%)
Black, n (%)	216 (17.0%)	Smoking status, n (%)	167 (13.2%)
Hispanic, n (%)	833 (65.7%)	APOE4 carrier, n (%)	294 (23.2%)
Other race/ethnicity, n (%)	30 (2.4%)	Raw ePWV, m/s, mean (SD)	11.7 (2.0)
Hypertension, n (%)	865 (68.2%)	WMHV/TCV, mean (SD)	-0.91 (0.95)
Education, years, mean (SD)	9.7 (5.1)	MCI, n (%)	316 (24.9%)
BMI, kg/m2, mean (SD)	28.5 (5.1)	Dementia, n (%)	161 (12.7%)

CONCLUSIONS

- In multi-ethnic aging NOMAS cohort, higher ePWV is associated with greater WMHV and higher odds of MCI and dementia.
- Cerebral small vessel disease is one pathway linking arterial stiffness with MCI and dementia.
- WMHV partially mediates these associations - most of the associations remain independent of WMHV.

CONTACT

