SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods – Brain MRI protocol

Participants underwent a 1.5-hour multi-modal MRI scan. Brain MRI scans were acquired at the Clinical Imaging Research Centre, on 3-Tesla MRI scanners with a state-of-the-art 32-channel head coil. Structural images were obtained with the following protocol and sequences:

- **T1-weighted MRI:** High-resolution T1-weighted Magnetization Prepared Rapid Gradient Recalled Echo (MPRAGE) or similar versions were acquired for the whole brain or specific regions of interest.

- **T2-weighted MRI:** T2-weighted images were also acquired using a double spin echo.

- **Fluid Attenuated Inversion Recovery (FLAIR):** FLAIR data were acquired using FSE- IR sequence.

- **Susceptibility weighted imaging (SWI):** SWI data were acquired during GRE sequence.

- **Quality Assurance (QA):** Quality assurance scans were performed on the day when the patient scan is scheduled. The QA scan is acquired using a gradient echo pulse sequence. The QA images were analyzed in regards to signal to noise ratio (SNR), spatial resolution, slice thickness and location.

The standardized protocol for the scanner acquisition parameters is as follows (51);

3D T1-weighted imaging (1.0x1.0x1.0 mm3 voxels, repetition time, TR=2300 ms, time to echo, TE=1.9 ms, inversion time (TI), 900 ms, flip angle 9°, matrix=256×256×180 mm3). 2D multislice T2-weighted (1.0x1.0x3.0 mm3 voxels, TR=3000 ms, TE=10.1 ms, matrix=247x256). 2D multislice fluid-attenuated inversion recovery (FLAIR) images

(1.0x1.0x3.0 mm3; TR=9000 ms; TE=82 ms; TI 2500 ms, matrix=232 x 256). SWI (echo time = 20 ms; repetition time = 27 ms; flip angle = 15 degrees; field of view= 256 mm; field of view= 75%; image matrix = 192×256; slice thickness = 1.50 mm).

Table S1. Characteristics of study population.

	All (N=272)	NCI (n=74)	CIND (n=99)	AD (n=78)	VaD (n=21)
Vascular stiffness					
β-index	12.14 (5.91)	10.73 (4.42)	12.03 (5.90)	12.77 (6.11)	15.01 (8.43)
Elastic modulus	167.06 (90.55)	144.18 (65.67)	161.67 (86.17)	180.13 (94.7)	221.44 (137.12)
Pulse wave velocity-β	7.39 (1.77)	6.91 (1.41)	7.30 (1.67)	7.64 (1.84)	8.50 (2.46)
CSVD markers					
White matter hyperintensities (WMH)	7.09 (3.77)	5.74 (3.68)	6.57 (3.41)	8.17 (3.66)	10.29 (3.49)
Presence of lacunes, n (%)	69 (25.37)	9 (12.16)	24 (24.24)	19 (24.36)	17 (80.95)
Presence of CMBs, n (%)	115 (42.28)	25 (33.78)	43 (43.43)	38 (48.72)	9 (42.86)
Cognition					
Global z-scores	-2.49 (2.55)	-0.11 (1.02)	-1.92 (1.47)	-4.79 (2.24)	-4.98 (2.09)
Attention	7.11 (2.39)	8.47 (2.07)	7.42 (2.21)	5.98 (2.08)	5.36 (1.84)
Executive function	100.39 (42.47)	61.22 (16.77)	95.37 (35.65)	134.29 (32.49)	140.75 (26.18)
Language	13.44 (2.37)	14.74 (0.60)	14.12 (1.03)	11.70 (3.15)	12.05 (2.97)
Visuomotor speed	20.61 (14.54)	35.42 (10.58)	21.72 (10.51)	8.55 (8.38)	7.57 (9.37)
Visuospatial function	20.33 (10.74)	29.01 (5.12)	22.64 (7.99)	12.01 (10.02)	9.55 (8.31)
Memory	7.54 (5.44)	13.60 (4.010	7.69 (4.19)	2.98 (1.75)	2.83 (1.63)

1A.

0.07* — CSVD — -0.91**

β-index — Global cognition

-0.29* (-0.23)

Indirect effect
β (95% CI) = -0.06 (-0.14, -0.01)
p= 0.02, proportion mediated = 22.0%

1B.

0.09** — CSVD — -0.88**

Elastic modulus (Ep) — Global cognition

-0.34*** (-0.26)*

Indirect effect
β (95% CI) = -0.08 (-0.15, -0.03)
p= 0.004, proportion mediated = 22.4%

1C.

0.08** — CSVD — -0.86**

PWV-β — Global cognition

-0.40*** (-0.32)**

Indirect effect
β (95% CI) = -0.07 (-0.14, -0.02)
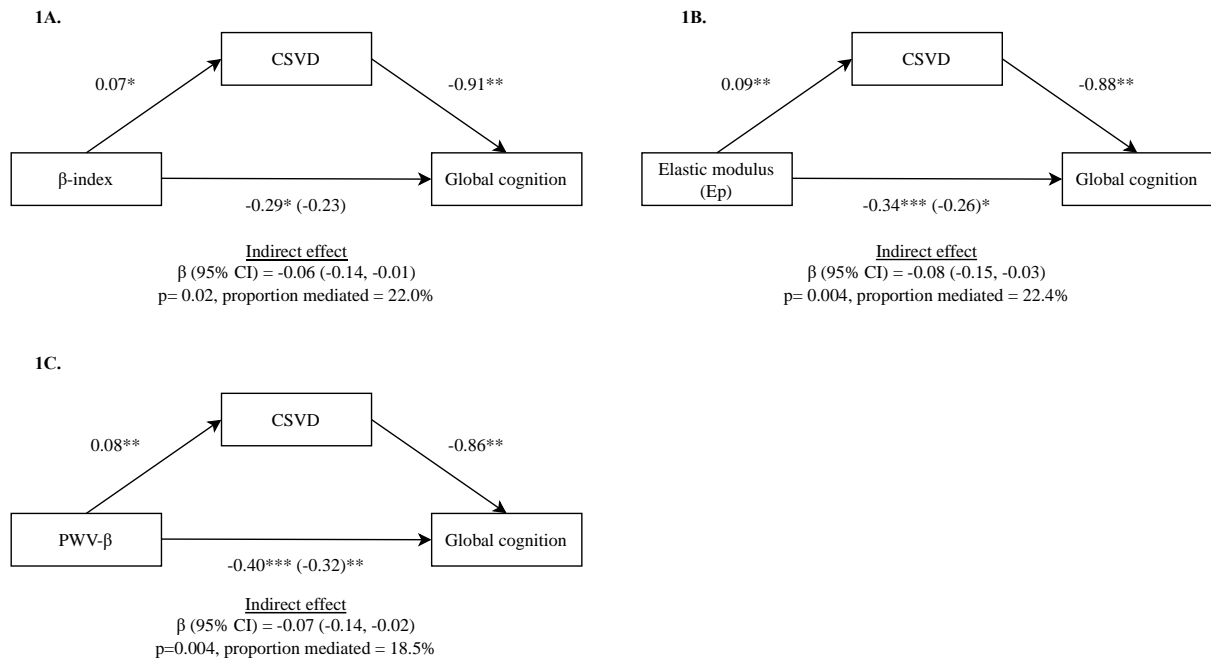p=0.004, proportion mediated = 18.5%

Figure S1. Mediation effect of CSVD on the association between carotid artery stiffness and global cognition. N=272; all models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidaemia, CVD, smoking; *$p<0.05$, **$p<0.01$, ***$p<0.001$.

0.08** — CSVD — -0.85***

PWV-β — Executive function

-0.31** (-0.24)*

Indirect effect
β (95% CI) = -0.07 (-0.13, -0.02)
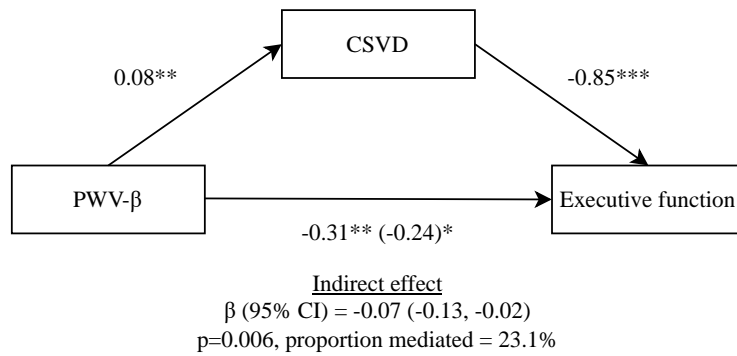p=0.006, proportion mediated = 23.1%

Figure S2. Mediation effect of CSVD on the association between PWV-ß and executive function. N=272; all models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidaemia, CVD, smoking; *$p<0.05$, **$p<0.01$, ***$p<0.001$.

3A.

CSVD

$0.07*$ $-0.52***$

β-index   Visuomotor speed

$-0.17***\ (-0.13)**$

Indirect effect
β (95% CI) = -0.03 (-0.07, -0.01)
p=0.016, proportion mediated = 21.4%

3B.

CSVD

$0.09**$ $-0.51***$

Elastic modulus (Ep)   Visuomotor speed

$-0.18***\ (-0.14)**$

Indirect effect
β (95% CI) = -0.04 (-0.08, -0.01)
p=0.014, proportion mediated = 23.7%

3C.

CSVD

$0.08**$ $-0.50***$

PWV-β   Visuomotor speed

$-0.21***\ (-0.17)**$

Indirect effect
β (95% CI) = -0.04 (-0.08, -0.01)
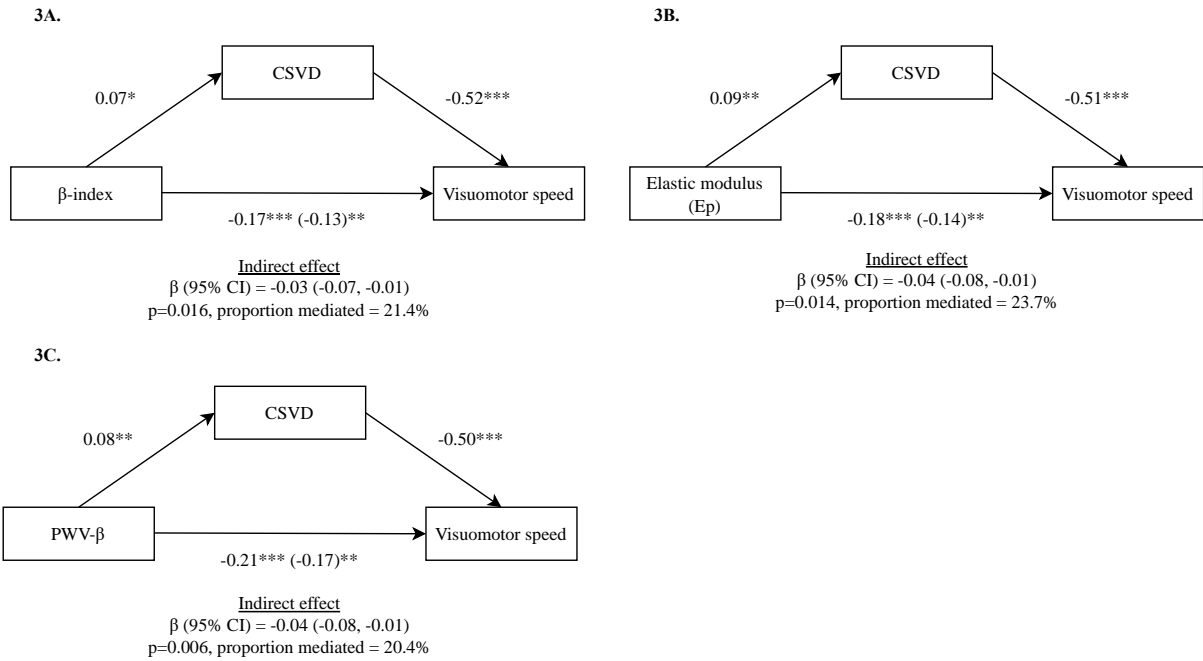p=0.006, proportion mediated = 20.4%

Figure S3. Mediation effect of CSVD on the association between carotid artery stiffness and visuomotor speed. N=272; all models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidaemia, CVD, smoking; $*p<0.05$, $**p<0.01$, $***p<0.001$.

CSVD

$0.08**$ $-0.54*$

PWV-β   Visuospatial function

$-0.32**\ (-0.27)*$

Indirect effect
β (95% CI) = -0.05 (-0.13, -0.02)
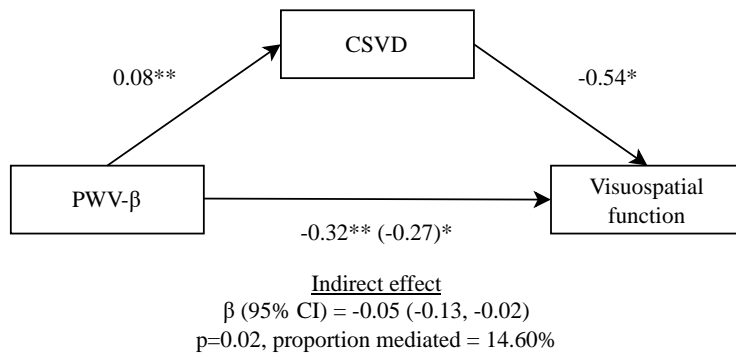p=0.02, proportion mediated = 14.60%

Figure S4. Mediation effect of CSVD on the association between carotid artery stiffness and visuospatial function. N=272; all models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidaemia, CVD, smoking; $*p<0.05$, $**p<0.01$, $***p<0.001$.

CSVD

$0.08**$ $-0.72***$

PWV-β   Memory

$-0.21**\ (-0.15)*$

Indirect effect
β (95% CI) = -0.06 (-0.12, -0.02)
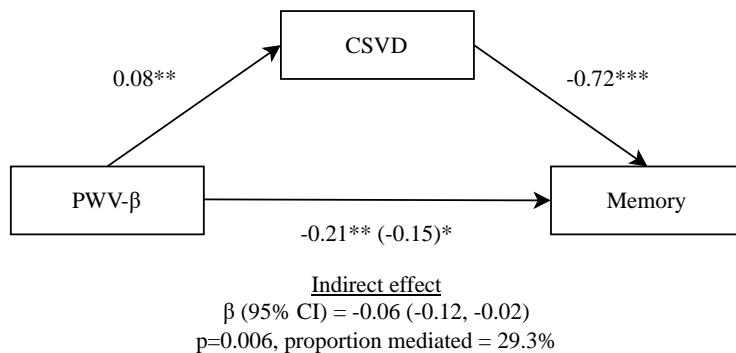p=0.006, proportion mediated = 29.3%

Figure S5. Mediation effect of CSVD on the association between carotid artery stiffness and memory. N=272; all models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidaemia, CVD, smoking; $*p<0.05$, $**p<0.01$, $***p<0.001$.