**SUPPLEMENTAL MATERIAL**

**Supplemental Methods.**

I. Data collection of metabolic risk factors.

II. Magnetic resonance imaging protocols.

III. Illustrative case for the assessment of CSVD markers.

**Supplemental Results.**

IV. Baseline characteristics of the participants with and without MRI.



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**Supplemental Methods.**

## I. Data collection of metabolic risk factors.

Questionnaires were administered to investigate the demographic characteristics, family history, cardiovascular disease history, and current cigarette smoking status. Anthropometric measurements included body weight, body height, and waist circumference. Waist circumference was quantified in centimeters at the natural waist of a standing participate. Blood pressure was measured by an automated blood pressure monitor device and the averaged value of 3 times readings was used for our analysis. Venous blood samples, routinely drawn after an overnight fast, were used to determine plasma triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting glucose levels. A total of 5ml antecubital venous blood samples centrifuged at 3000r/min for 10 min in a microcentrifuge within 30 minutes after collection. Centralized blood assessments were used. Participants were self-reported whether they were on medications to treat hypertension, hyperglycemia, and dyslipidemia.

## II. Magnetic resonance imaging protocols.

MRI was performed with a single 3-T Skyra scanner (Siemens, Erlangen, Germany). Three-dimensional time-of-flight magnetic resonance angiography (TOF-MRA) was performed in axial planes with the following parameters: repetition time (TR) = 21 ms, echo time (TE) =3.43 ms, field of view (FOV)= 208 × 229 $mm^2$, voxel size = 0.3 × 0.3 × 0.6 $mm^3$, and flip angle=18°, with a total of 136 axial slices. 3D T1-weighted images using magnetization-prepared rapid gradient-echo sequence (TR =

2530 ms, TE = 3.43 ms, voxel size = 1 × 1 × 1.3 $mm^3$, flip angle = 8°, 144 sagittal slices), T2-weighted images (TR = 6000 ms, TE = 125 ms, slice thickness = 5 mm, gap = 1 mm, 20 axial slices), fluid-attenuated inversion recovery images (TR = 8500 ms, TE = 81 ms, slice thickness = 5 mm, gap = 1 mm, 20 axial slices) and susceptibility-weighted images (SWI, TR = 20 ms, TE = 27 ms, slice thickness =1.5 mm, flip angle =15°, 80 axial slices) were also acquired.

## III. Illustrative case for the assessment of CSVD markers.

- **White matter hyperintensities (WMHs)**: WMH were automatically segmented by the lesion growth algorithm as implemented in the lesion segmentation tool toolbox (http://statistical-modelling.de/lst.html) for Statistical Parametric Mapping 12 (SPM 12, http://www.fil.ion.ucl.ac.uk/spm/).

- **Lacunes**: Lacunes were defined as focal fluid-filled cavities 3–15 mm in diameter situated in the basal ganglia, subcortical white matter, or brain stem.

- **Cerebral microbleeds (CMBs)**: CMBs were defined as round or ovoid black lesions (signal void) that were smaller than 10 mm in size, and at least half of the lesion was surrounded by brain parenchyma on SWI.

- **Enlarged perivascular spaces (EPVS)**: EPVS were defined as cerebrospinal fluid-like signal lesions that were round, ovoid, or linear with a diameter generally smaller than 3 mm. The severity of EPVS in the basal ganglia (EPVS-BG) and in the white matter (EPVS-WM) were rated using a previously-established 4-level severity score on 3D T1-weighted images.



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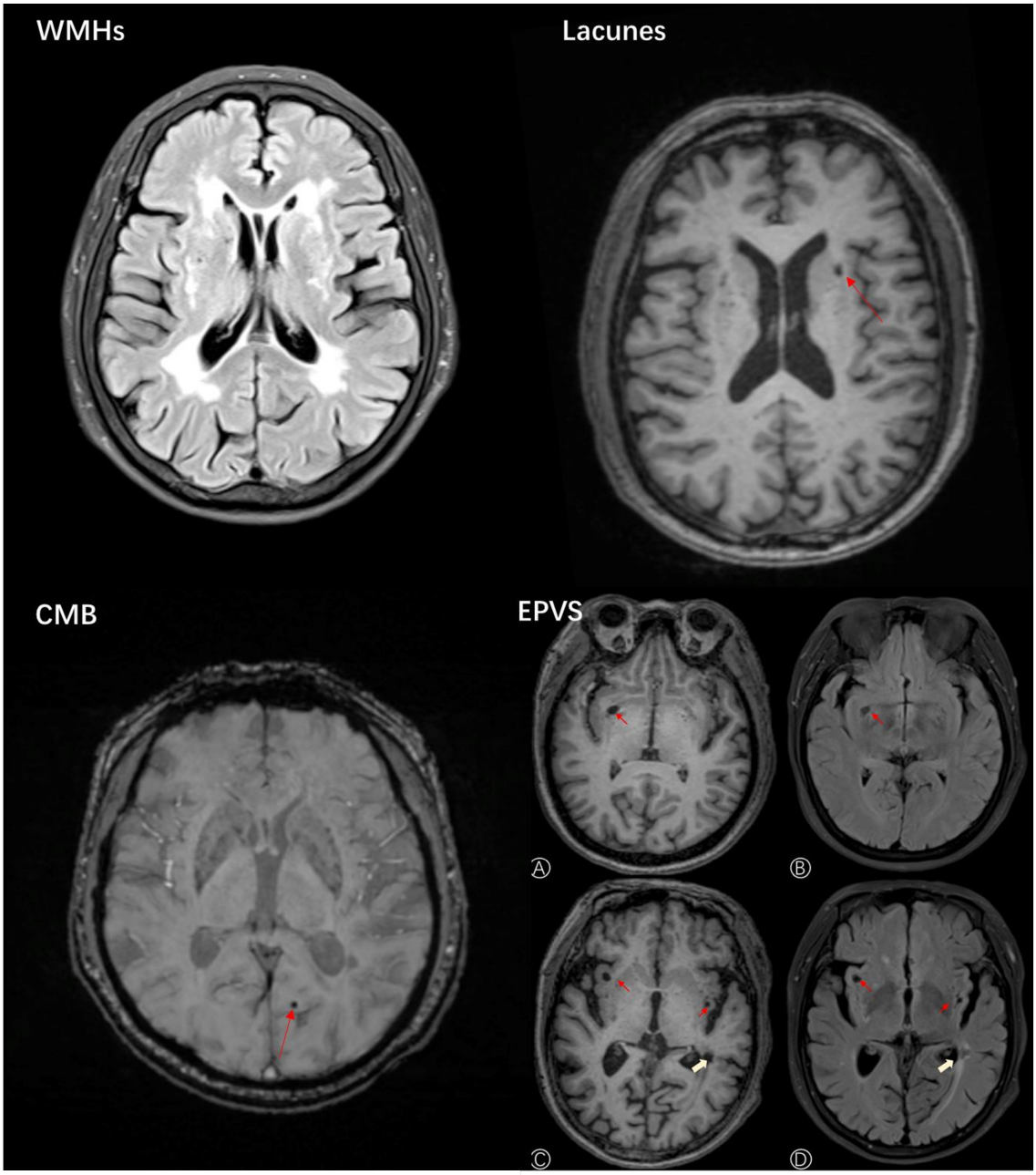


**Figure Legend.** WMHs, White matter hyperintensities; Lacunes; CMBs, Cerebral microbleeds; EPVS, Enlarged perivascular spacee;
EPVSs in different locations. (T1WI) (a), (FLAIR) (b): EPVSs (red arrows) were clustered around the anterior commissure and inferior one-third of BG. (T1WI) (c), (FLAIR) (d): EPVSs (bilateral subinsular WM, red arrows), mostly well defined, round, oval, tubular, or shuttle shaped, and often follow the orientation of perforating vessels, were along the path of perforating arteries as they enter the cortical gray matter and extend into WM, contrasted to lacune (white arrow). FLAIR, fluid-attenuated inversion recovery; BG, basal ganglia; WM, white matter.

## IV. Baseline characteristics of the participants with and without MRI.

| Demographic and clinical characteristics | Overall (n=1586) | Participants with MRI (n=1257) | Participants without MRI (n=329) | p-value* |
|---|---|---|---|---|
| Age, mean (SD), y | 56.7 (10.1) | 55.9(9.3) | 59.7(12.1) | **< 0.001** |
| Male, n (%) | 634(40.0) | 472(37.5) | 162(49.2) | **< 0.001** |
| Current smoker, n (%) | 381(24.8) | 285(23.4) | 96(30.0) | **0.015** |
| Body mass index, mean (SD) | 26.4(3.8) | 26.5(3.8) | 26.0(4.0) | 0.147 |
| waist circumference, mean (SD), cm | 89.6(10.7) | 89.6(10.5) | 89.5(11.4) | 0.171 |
| HDL-C, mean (SD), mmol/L | 1.3(0.3) | 1.3(0.3) | 1.2(0.3) | 0.944 |
| Triglyceride, median (IQR), mmol/L | 1.3(0.9, 1.9) | 1.3(0.9, 1.9) | 1.2 (0.8, 1.7) | 0.057 |
| SBP, mean (SD), mmHg | 133.6(19.6) | 133.2(19.1) | 135.2(21.6) | **0.003** |
| DBP, mean (SD), mmHg | 78.7(11.1) | 78.7(10.8) | 78.6(12.2) | **0.033** |
| Fasting blood glucose, mean (SD), mmol/L | 6.1(1.8) | 6.1(1.9) | 6.1(1.8) | 0.391 |

Abbreviation: MRI = magnetic resonance imaging; HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure; DBP = diastolic blood pressure.

* Differences ($p < 0.05$) between groups were compared using the t-test (for means), Mann-Whitney U test (for medians), and $\chi 2$ test (for percentages).