

Supplementary Methods:

1. The definitions of different CSVD neuroimaging biomarkers

WMH volume was measured from T2-fluid-attenuated inversion recovery (FLAIR) sequences usually using a fully automated software. Lacunar stroke was defined as a subcortical infarct with a diameter ≤ 15 mm on diffusion-weighted imaging for acute infarcts and on fluid-attenuated inversion recovery or T1 sequences for non-acute infarcts. CMBs were defined as small, hypointense lesions on susceptibility-weighted imaging or T2*-weighted gradient echo sequences. Among participants who had CMBs, 61.3% were classified as having lobar CMB, while the remaining were classified as mixed CMBs, defined as deep or infratentorial CMBs with a possible combination of CMBs in the lobar region. Fractional anisotropy (FA) is a reliable measurement of brain structural connectivity and white matter microstructure, with higher FA values typically indicating better white matter integrity. PVS were quantified in the cerebral BG using visual semi-quantitative rating scales or automated computational methods. These were identified as round, ovoid, or linear shape fluid-filled spaces, mimicking the signal of cerebrospinal fluid, usually with a maximum diameter of < 3 mm. They exhibit no hyperintense rim on T2-weighted or fluid-attenuated inversion recovery sequences, and are located in areas supplied by perforating arteries.

2. Detailed information of cognitive function tests

Self-administered computerized cognitive function tests were developed for UKB to enable population-scale cognitive testing and have been described in detail

previously.

Mean time to correctly identify matches: Before the test began, participants were shown a video demonstration. For each trial, participants were shown two cards with a symbol on them, side-by-side on the screen. The two cards either had matching symbols, or different symbols on them. Participants were instructed that, when the cards matched, they were to push a button-box that was on the desk in front of them as quickly as possible. When the cards were different, the participant was to do nothing, and, after a short delay, the cards disappeared and a new pair would appear. There were 12 trials in total. The first 5 trials (rounds 0-4) were regarded as practice trials. Of the remaining 7 trials, 4 contained 4 matching cards. The score is the mean time, in milliseconds, to press the button-box for these four trials with matching cards.

Prospective memory test: At the start of the UK Biobank cognitive test battery, participants were shown a screen with the following instructions: “At the end of the games we will show you four coloured symbols and ask you to touch the Blue Square. However, to test your memory, we want you to actually touch the Orange Circle instead.” Participants then completed all other tests in the UK Biobank cognitive test battery. At the end of the UK Biobank tests, participants were shown a screen with four shapes (blue square, pink star, grey cross, orange circle) and were instructed to touch the Blue Square. If participants touched the Orange Circle (correct answer) the test ended. If the participant touched any other shape, they received the following prompt: “At the start of the games we asked you to remember to touch a different

symbol when this screen appeared. Please try to remember which symbol it was and touch it now.” If the participant touched the blue square, the prompt was repeated (ad infinitum). If the participant touched any other shape, the test ended. In this study, the score we used was a dichotomous variable, coded 1 if the participant correctly touched the orange circle on the first attempt, and 0 if they touched any other shape.

Number of fluid intelligence questions attempted within time limit: The UKB Fluid IQ test was designed to assess verbal and numerical reasoning. This task involved participants answering 13 multiple-choice questions. For each question, the question was presented at the top of the screen and between three and five multiple-choice options were presented underneath. The participant was to select which of the possible options they thought was the correct answer, or select “Do not know” or “Prefer not to answer”. The questions assessed verbal (e.g., “Bud is to flower as child is to...” Possible answers: Grow/Develop/Improve/Adult/Old) and numerical (e.g., 5 “150...137...125...114...104... What comes next?” Possible answers: 96/95/94/93/92) reasoning abilities. The score was the number of questions answered correctly in two minutes.

Numeric memory test: A backward digit span task was used to assess working memory. Participants watched an instructional video demonstration before they started the task. Participants were briefly shown a two-digit number on the screen. The number then disappeared and, after a short delay, the participants were asked to enter the number in the reverse order using a keypad on the screen. The

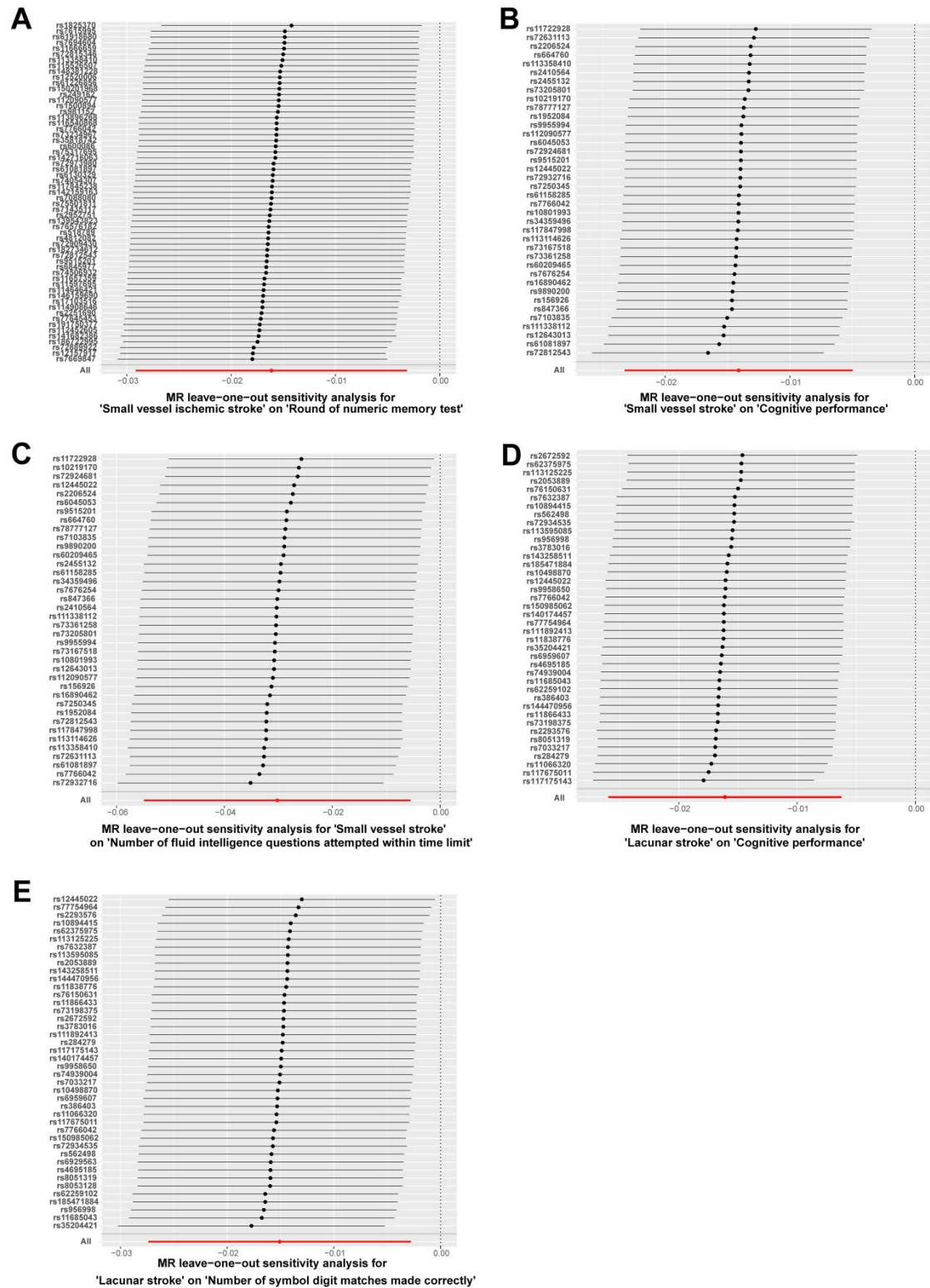
to-be-remembered digit sequence then became one digit longer each time the participant correctly remembered the digits in the reverse order. If the participant incorrectly remembered a sequence, they were then asked to recall a different number sequence of the same length. The test ended when the participant incorrectly recalled two trials of the same digit length, or once the participant correctly remembered a 12-digit number. The score was the maximum number of digits correctly remembered in the reverse order. We note that, for this test, all of the to-be-remembered digit-sequence appeared on the screen at once (e.g., participants saw “48951” on the screen). Therefore it was possible to get the correct answer either by carrying out a backward digit span (e.g., reading the numbers left-to-right and mentally reversing the digits) or a forward digit span (e.g., reading from right-to-left and remembering “15981”).

Number of symbol digit matches made correctly: This test for complex processing speed was completed at follow-up (~2014) on home computers and involves matching numbers to a set of symbols. Participants are presented with symbols paired with digits and are asked to enter the digits that are paired with the symbols in the empty spaces. We used the number of correct substitutions for our analyses. Potential outliers were truncated to 4 SD away from the mean.

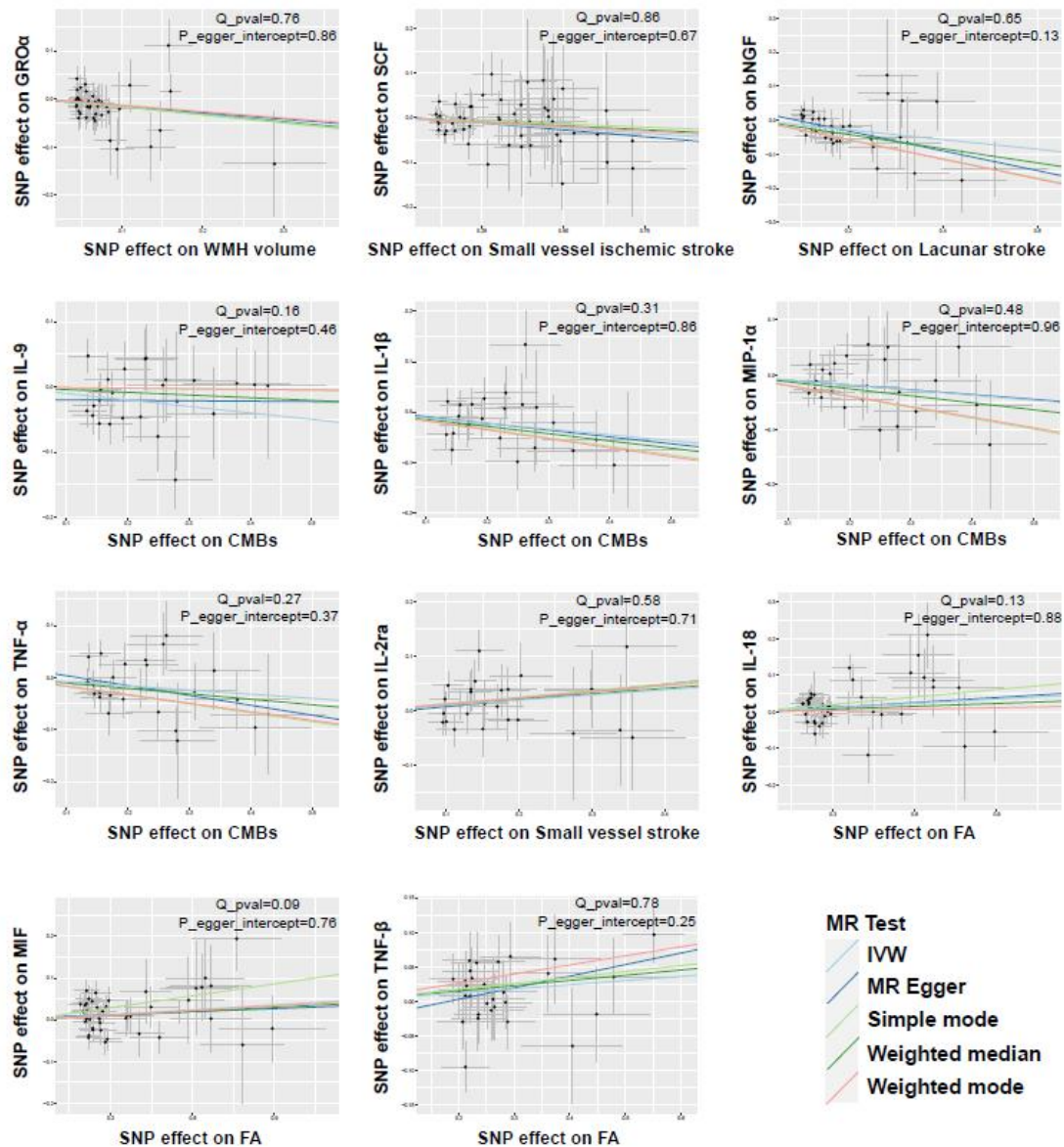
Supplementary Table S1. Detailed Information on 41 Circulating Inflammatory

Cytokines

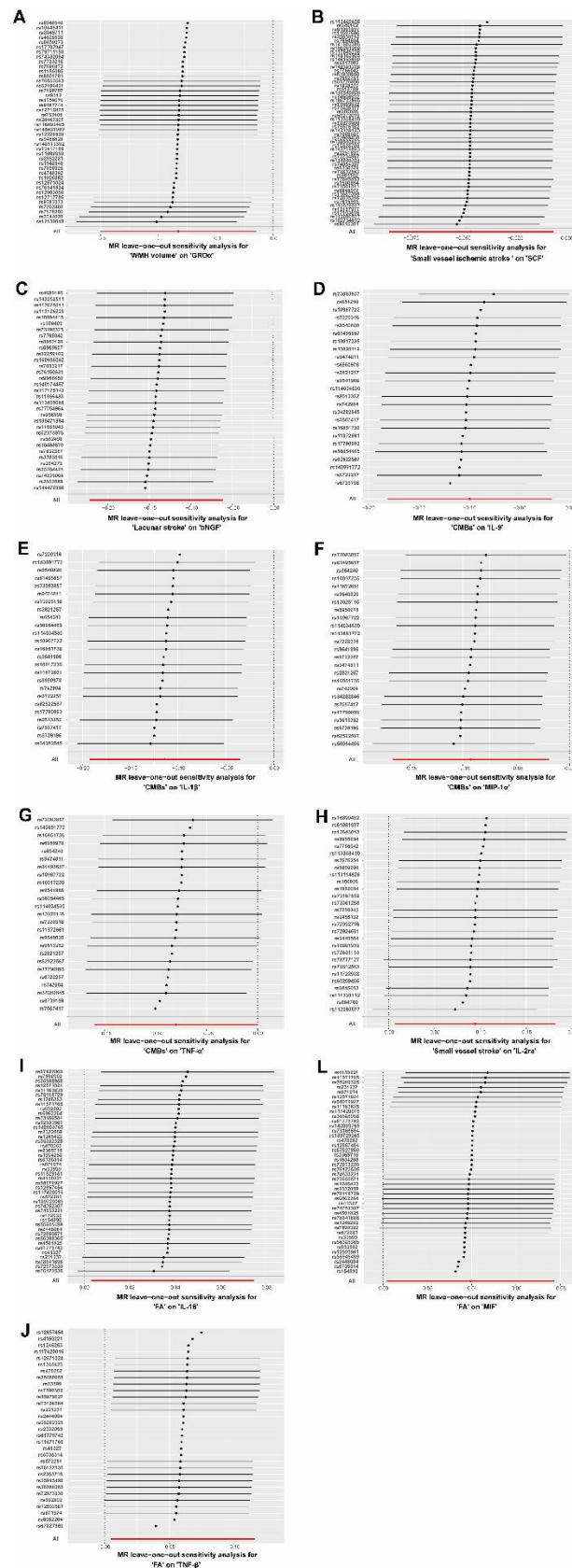
Inflammatory cytokines	Sample size	Inflammatory cytokines	Sample size
VEGF	7118	MIP-1 α	3522
TRAIL	8186	MIG	3685
SDF-1 α	7787	MIF	3494
SCF	8290	MCP-3	1085
PDGFbb	8293	MCSF	2472
MIP-1 β	8243	IP-10	3685
MCP-1	8293	IL-9	3634
IL-6	8189	IL-8	3526
IL-4	8124	IL-7	3409
IL-17	7760	IL-5	3364
IL-12p70	8270	IL-2ra	3677
IL-10	7681	IL-2	3475
IFN- γ	7701	IL-1ra	3638
HGF	8292	IL-1 β	3309
GCSF	7904	IL-18	3636
FGFBasic	7565	IL-16	3483
Eotaxin	8153	IL-13	3557
TNF- β	1559	GRO α	3505
TNF- α	3454	CTACK	3631
SCGF β	3682	bNGF	3531
RANTES	3421		



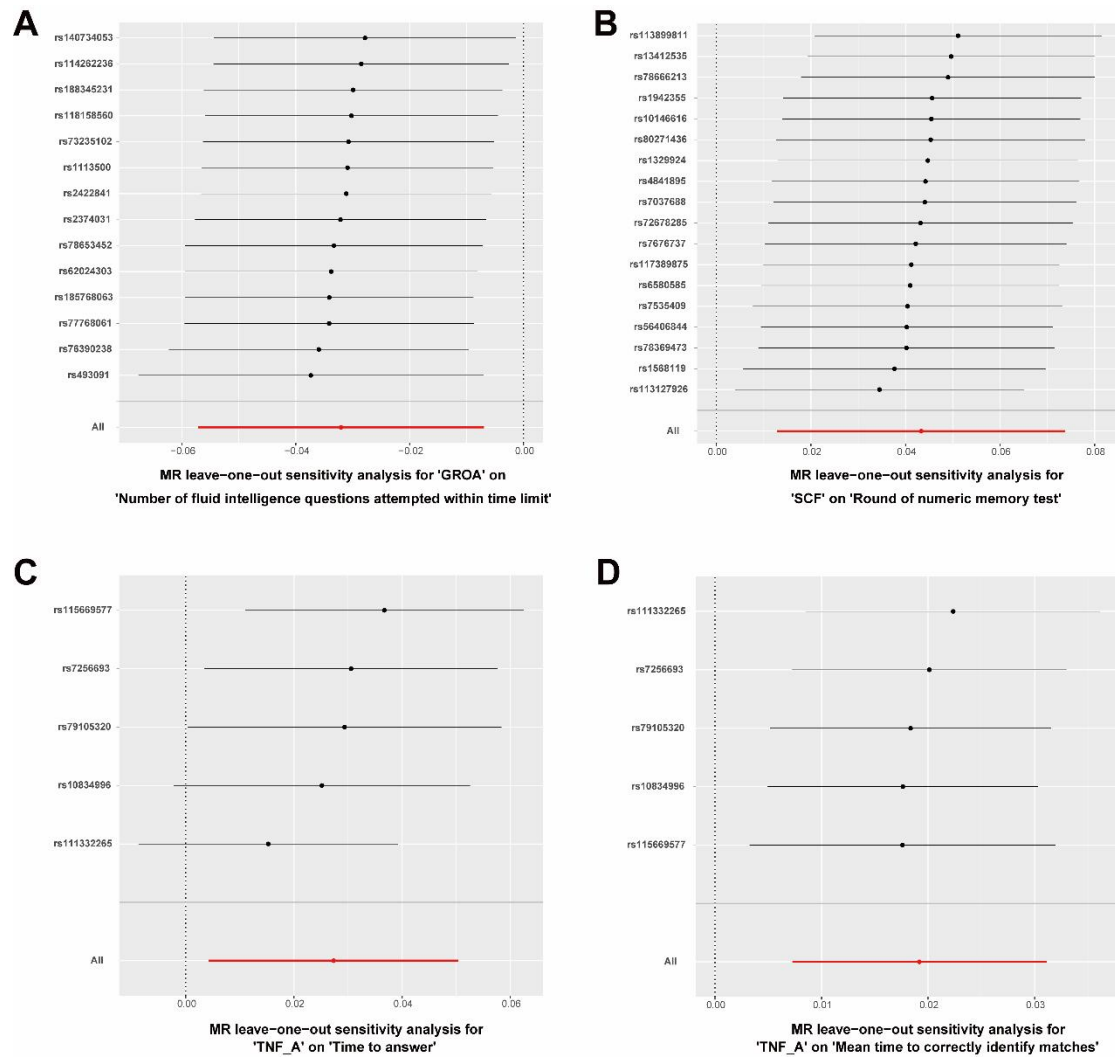
Supplementary Figure S1. Leave-one-out plot for the effects of CSVD exposure on cognition.



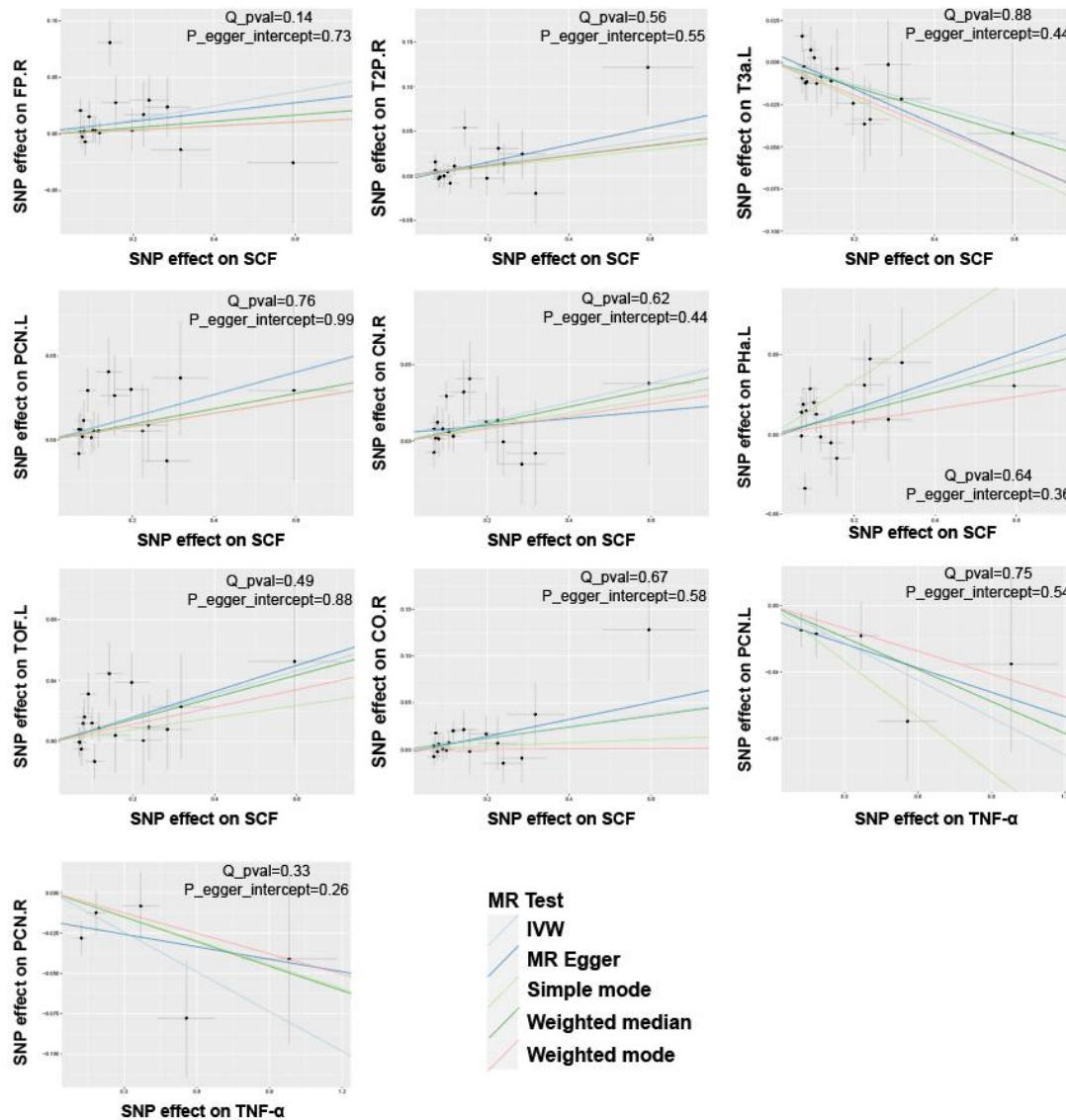
Supplementary Figure S2. Scatter plots of MR analysis for casual associations between CSVD and inflammatory cytokines. The SNP effects are plotted into lines for IVW (light blue line), MR-Egger (dark blue line), Simple mode (light green line), weighted median (dark green line), Weighted mode (red line). The slope of the line corresponds to the causal estimation. Q_pval: P value of Cochran's Q values; P_egger_intercept: P value of MR Egger intercept test.



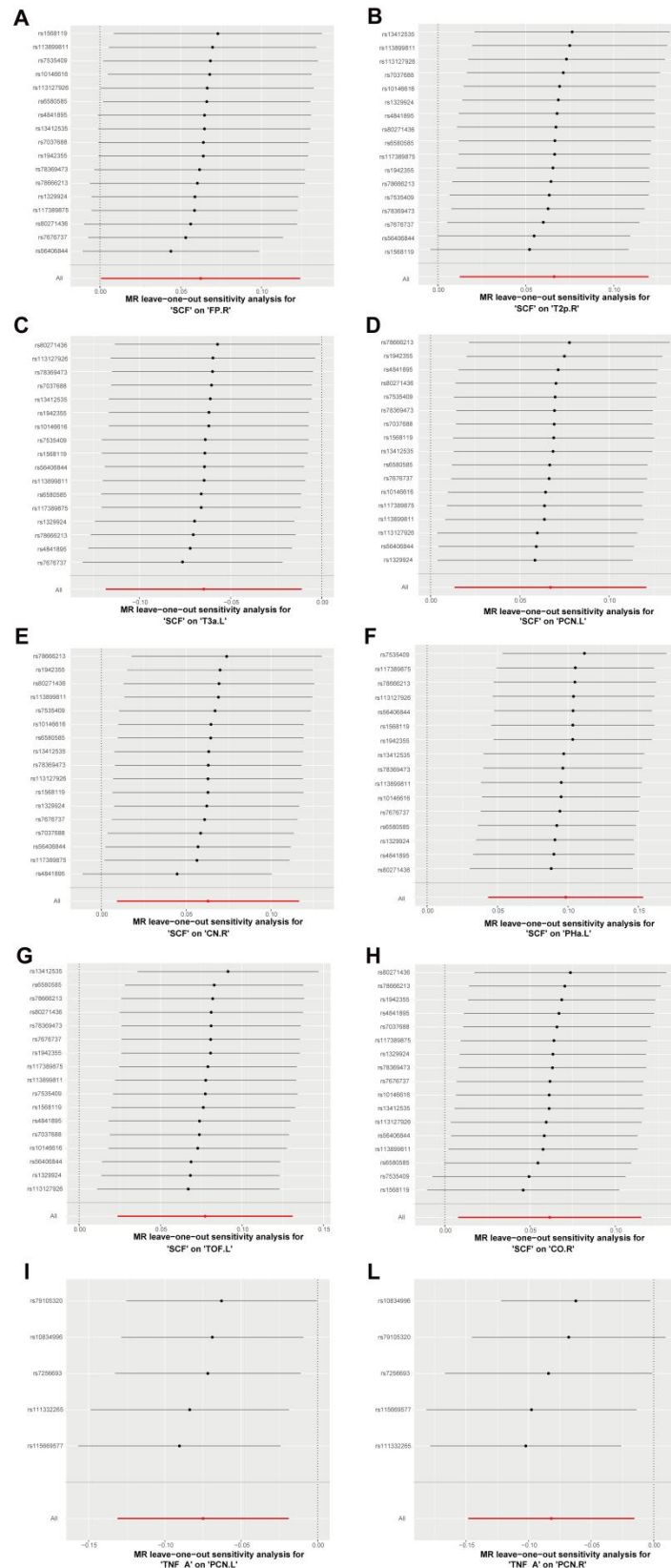
Supplementary Figure S3. Leave-one-out plot for the effects of CSVD exposure on inflammatory cytokines.



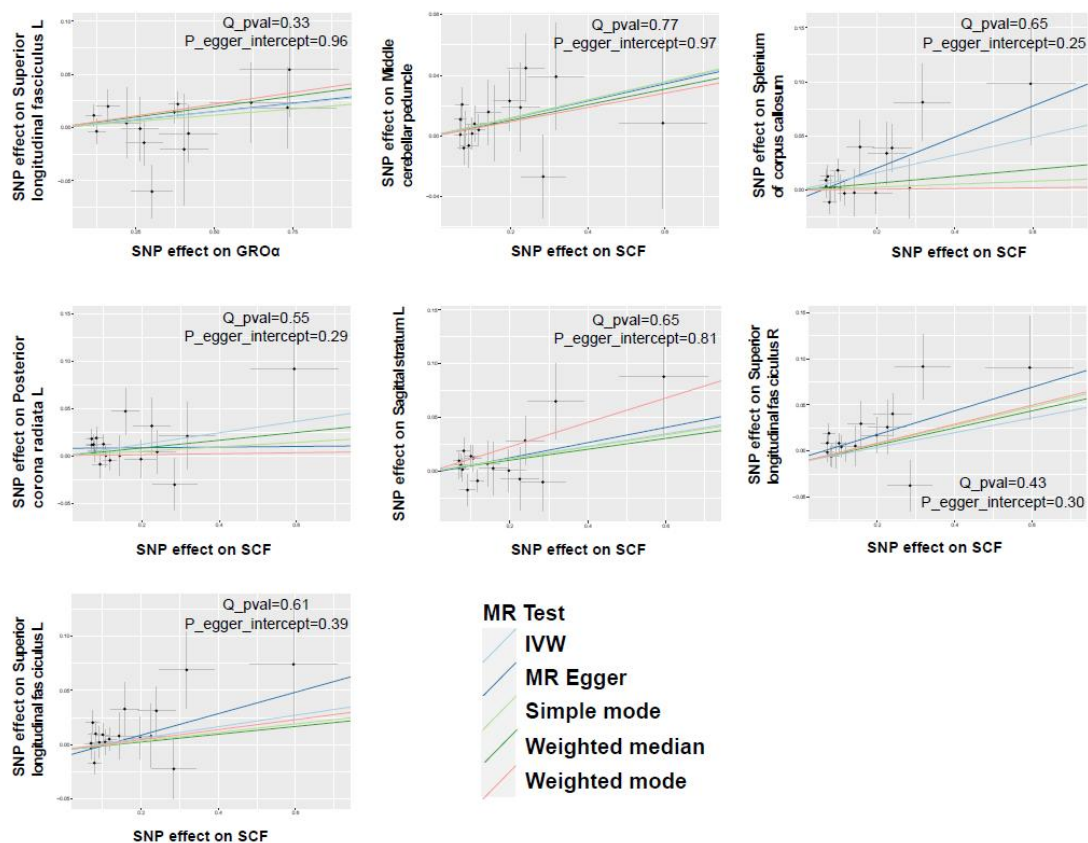
Supplementary Figure S4. Leave-one-out plot for the effects of CSVD-driven inflammatory cytokines exposure on cognition.



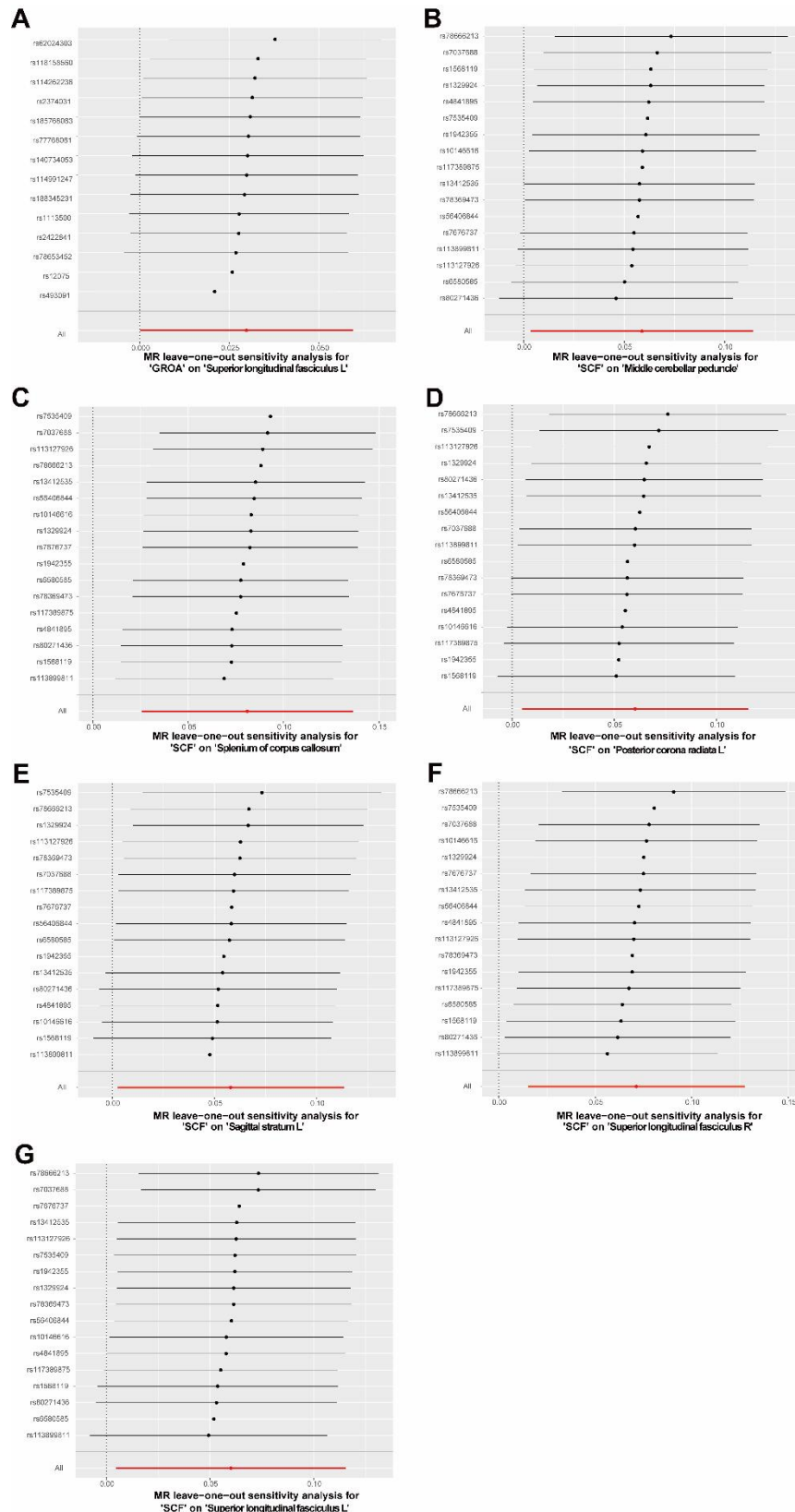
Supplementary Figure S5. Scatter plots of MR analysis for casual associations between mediating inflammatory cytokines and volumes of brain regions. The SNP effects are plotted into lines for IVW (light blue line), MR-Egger (dark blue line), Simple mode (light green line), weighted median (dark green line), Weighted mode (red line). The slope of the line corresponds to the causal estimation. Q_pval: P value of Cochran's Q values; P_egger_intercept: P value of MR Egger intercept test.



Supplementary Figure S6. Leave-one-out plot for the effects of mediating inflammatory cytokines exposure on volumes of brain regions.



Supplementary Figure S7. Scatter plots of MR analysis for casual associations between mediating inflammatory cytokines and FA values of white matter tracts. The SNP effects are plotted into lines for IVW (light blue line), MR-Egger (dark blue line), Simple mode (light green line), weighted median (dark green line), Weighted mode (red line). The slope of the line corresponds to the causal estimation. Q_pval: P value of Cochran's Q values; P_egger_intercept: P value of MR Egger intercept test.



Supplementary Figure S8. Leave-one-out plot for the effects of mediating inflammatory cytokines exposure on FA values of white matter tracts.