

SUPPLEMENTAL MATERIAL

Supplement 1 Figure I Exposures suggestively associated with lobar hemorrhage 3

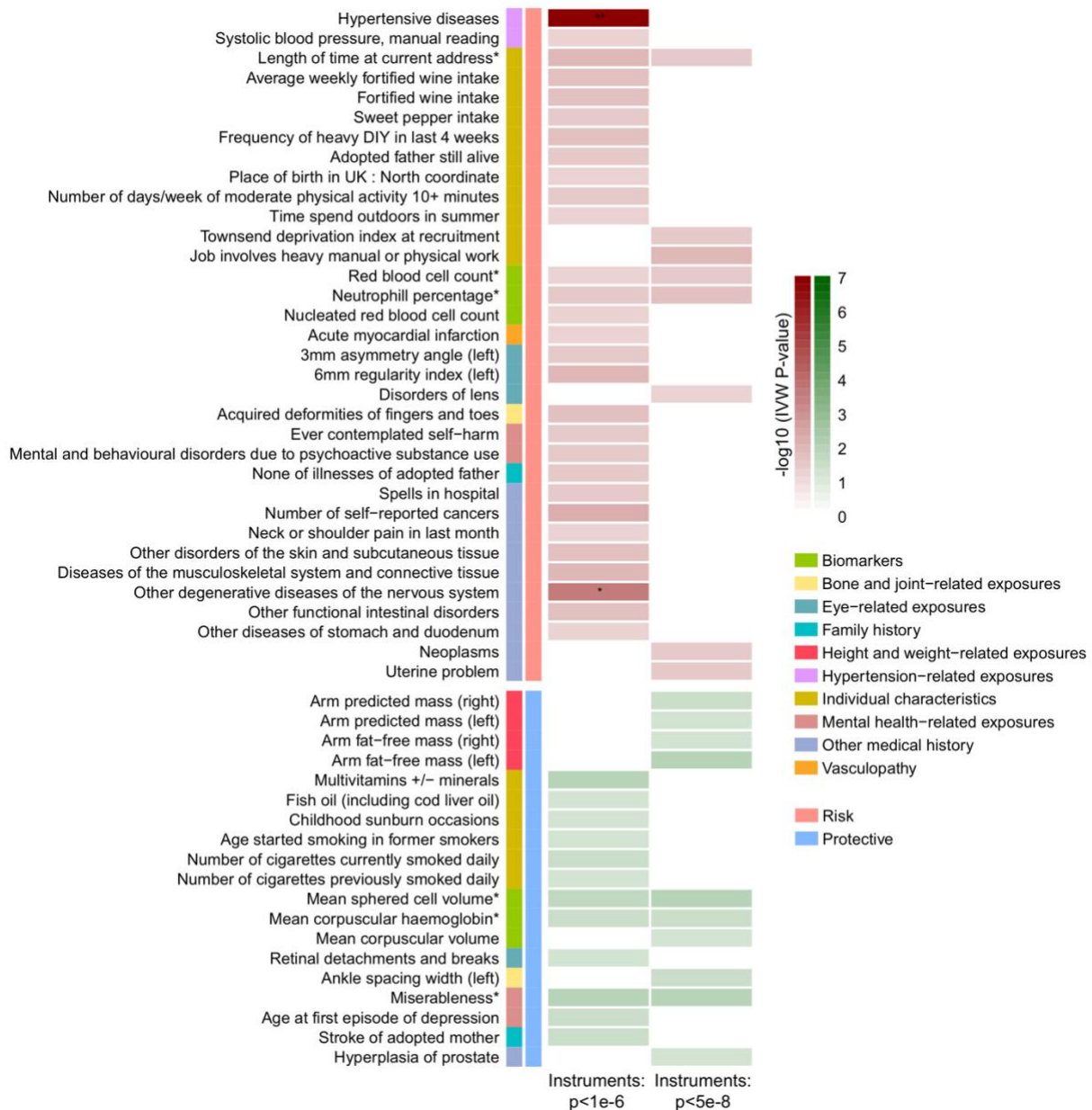
Supplement 2 Figure II Exposures suggestively associated with non-lobar hemorrhage..... 4

**Supplement 3 The single SNP analysis, leave-one-out analysis and comparison of results
using different MR methods for 42 exposures with $P_{FDR} < 0.05$ for clinical outcomes 5**

Figure 1. Self-reported hypertension	5
Figure 2. Hypertension diagnosed by doctor	6
Figure 3. Systolic blood pressure, automated reading	7
Figure 4. Diastolic blood pressure, automated reading.....	8
Figure 5. Essential (primary) hypertension.....	9
Figure 6. Hypertensive diseases.....	10
Figure 7. Anti-hypertensive medication	11
Figure 8. Hypertension of siblings.....	12
Figure 9. High cholesterol.....	13
Figure 10. Cholesterol lowering medication.....	14
Figure 11. Cholesterol lowering medication : simvastatin	15
Figure 12. Body mass index (BMI)	16
Figure 13. Leg fat percentage (right)	17
Figure 14. Leg fat percentage (left)	18
Figure 15. Current tobacco smoking.....	19
Figure 16. None of qualifications	20
Figure 17. Time spent watching television	21
Figure 18. Variation in diet.....	22
Figure 19. Overall health rating	23
Figure 20. Frequency of tiredness / lethargy in last 2 weeks.....	24
Figure 21. Days /week of moderate physical activity >10 minutes.....	25
Figure 22. Number of treatments/medications taken	26
Figure 23. Long-standing illness, disability or infirmity	27
Figure 24. Hypertension of mother	28
Figure 25. Self-reported diabetes	29
Figure 26. Average monthly intake of other alcoholic drinks	30
Figure 27. White blood cell count.....	31

Figure 28. Neutrophil count.....	32
Figure 29. Self-reported non-cancer illnesses.....	33
Figure 30. Never smoked.....	34
Figure 31. Usual walking pace.....	35
Figure 32. Age first had sexual intercourse	36
Figure 33. A /AS levels qualifications	37
Figure 34. College or university degree.....	38
Figure 35. Forced vital capacity (FVC)	39
Figure 36. Forced expiratory volume in 1-second (FEV1).....	40
Figure 37. None of vascular/heart problems	41
Figure 38. No medication for cholesterol, hypertension, diabetes, no exogenous hormones...	42
Figure 39. Standing height.....	43
Figure 40. Cheese intake	44
Figure 41. None of illnesses of siblings.....	45
Figure 42. Peak expiratory flow (PEF)	46
Supplement 4 The single SNP analysis, leave-one-out analyses and comparison of results using different MR methods for 10 exposures with $P_{FDR}<0.05$ for WMH.....	47
Figure 1. Self-reported hypertension	47
Figure 2. Hypertension: diagnosed by doctor	48
Figure 3. Leg fat-free mass (right).....	49
Figure 4. Arm fat-free mass (left)	50
Figure 5. Leg predicted mass (right).....	51
Figure 6. Leg predicted mass (left)	52
Figure 7. Sitting height	53
Figure 8. None of vascular/heart problems	54
Figure 9. Impedance of leg (right)	55
Figure 10. No medication for cholesterol, hypertension or diabetes	56
Supplement 5 Table I. IVW analyses, sensitivity, horizontal pleiotropy and heterogeneity analyses for exposures with $P_{FDR}<0.05$ for MD.....	57
Supplement 6 Reverse causation analysis for significant modifiable exposures	58

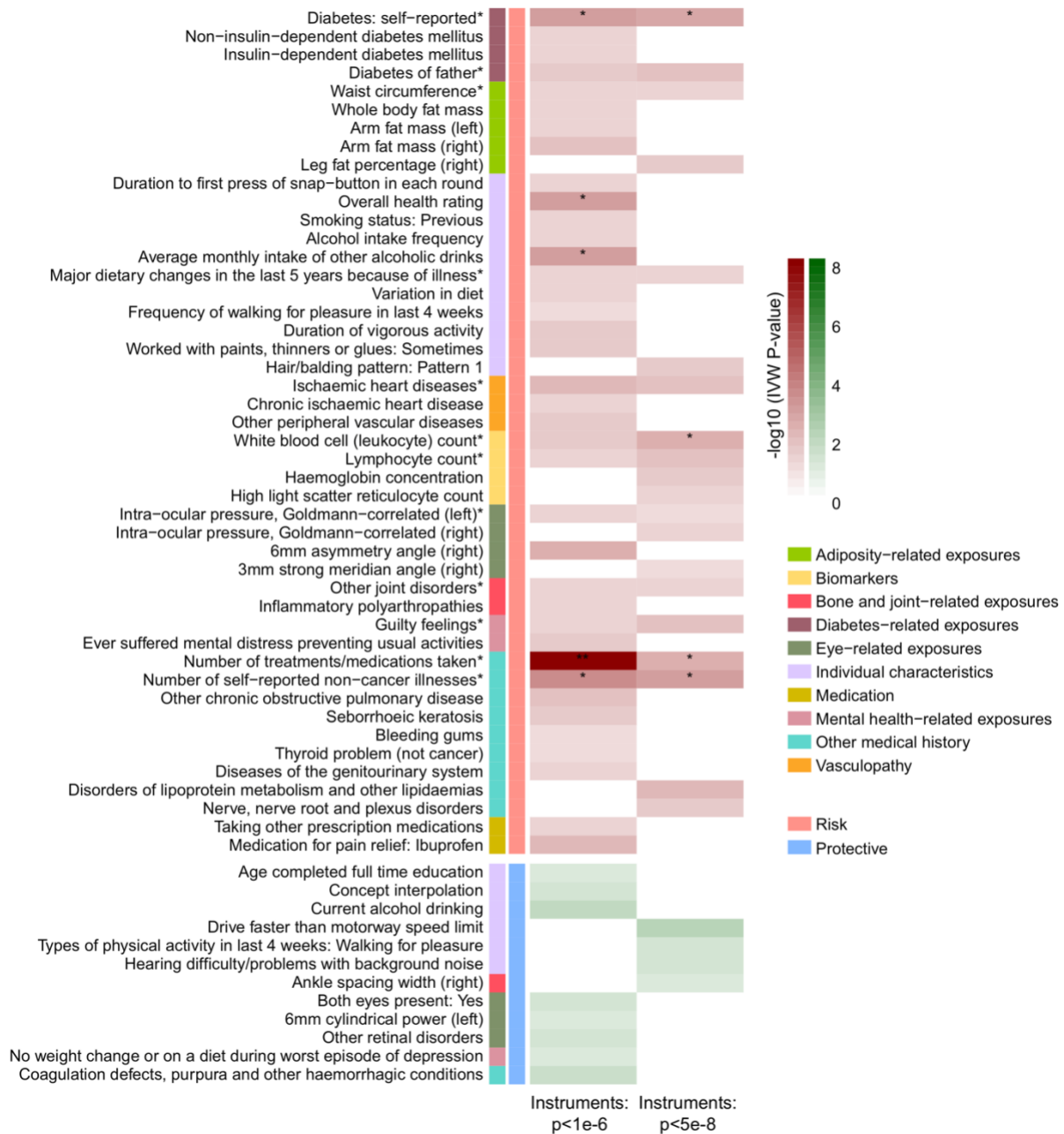
Supplement 1 Figure I. Exposures suggestively associated with lobar hemorrhage



This figure includes exposures with IVW $P < 0.05$ for “lobar hemorrhage or SVS”, but not for “non-lobar hemorrhage or SVS”. Exposures qualified for this criterion in analysis with instruments of $p < 1e-6$ (left, 41 exposures) and $p < 5e-8$ (right, 18 exposures) were all presented. The robustness of suggestive associations between individual exposures and the outcome “lobar hemorrhage or SVS” was roughly reflected by the uncorrected IVW P values. Red indicates risk exposures and green indicates protective exposures, with darker color suggesting stronger association. Significant results after FDR correction were marked. $*P_{FDR} < 0.05$, $**P_{FDR} < 0.01$.

Abbreviations: SVS, small vessel stroke; IVW, Inverse Variance Weighted.

Supplement 2 Figure II. Exposures suggestively associated with non-lobar hemorrhage



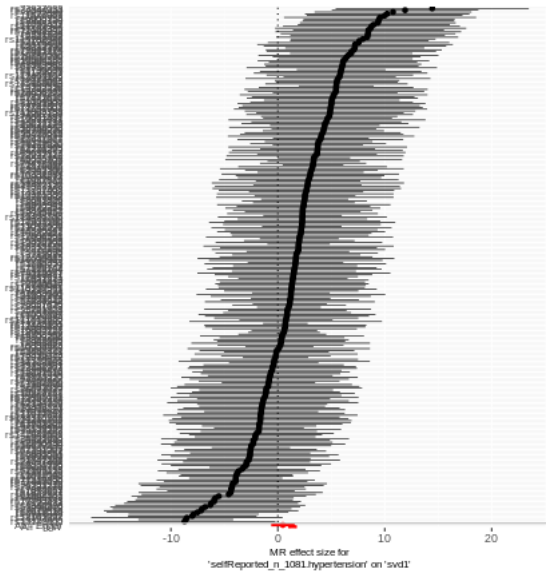
This figure includes exposures with IVW $P < 0.05$ for “non-lobar hemorrhage or SVS”, but not for “lobar hemorrhage or SVS”. Exposures qualified for this criterion in analysis with instruments of $p < 1e-6$ (left, 46 exposures) and $p < 5e-8$ (right, 24 exposures) were all presented. The robustness of suggestive associations between individual exposures and the outcome “non-lobar hemorrhage or SVS” was roughly reflected by the uncorrected IVW P values. Red indicates risk exposures and green indicates protective exposures, with darker color suggesting stronger association. Significant results after FDR correction were marked. * $P_{FDR} < 0.05$, ** $P_{FDR} < 0.01$.

Abbreviations: SVS, small vessel stroke; IVW, Inverse Variance Weighted.

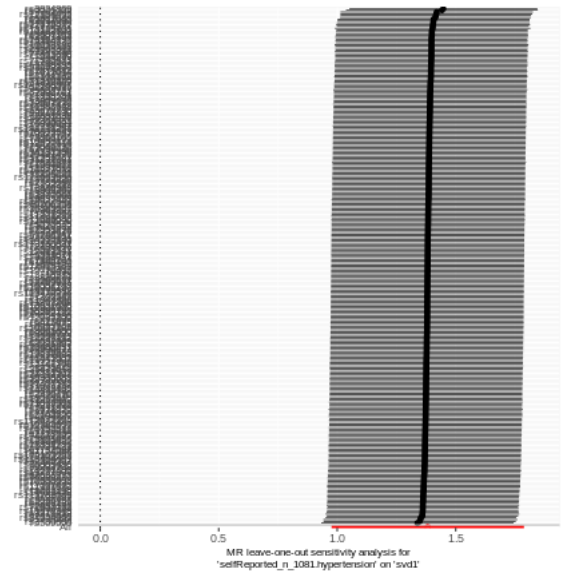
Supplement 3 The single SNP analysis, leave-one-out analysis and comparison of results using different MR methods for 42 exposures with $P_{FDR} < 0.05$ for clinical outcomes

Supplement 3 Figure 1. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for self-reported hypertension on ICH or SVS.

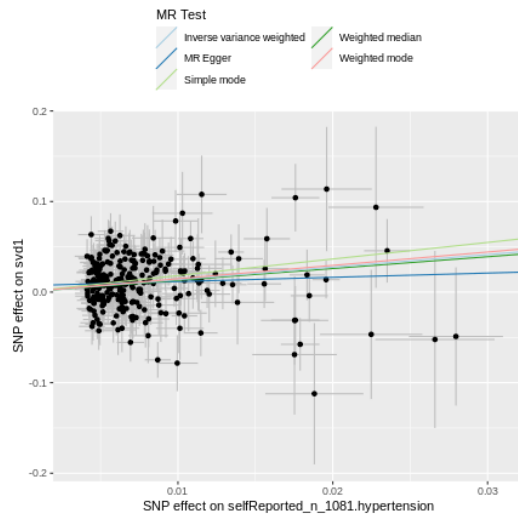
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

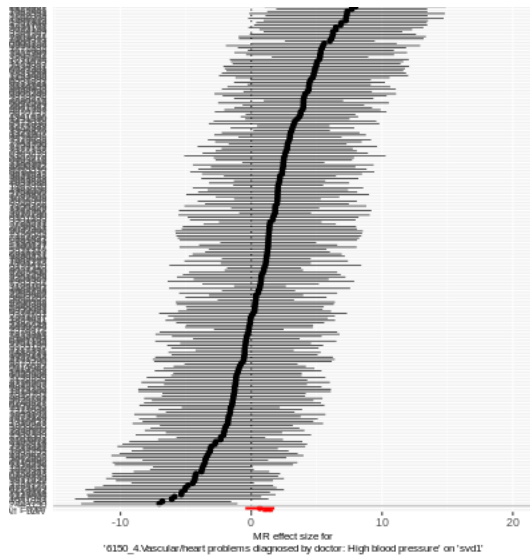


(c) Comparison of results using different MR methods

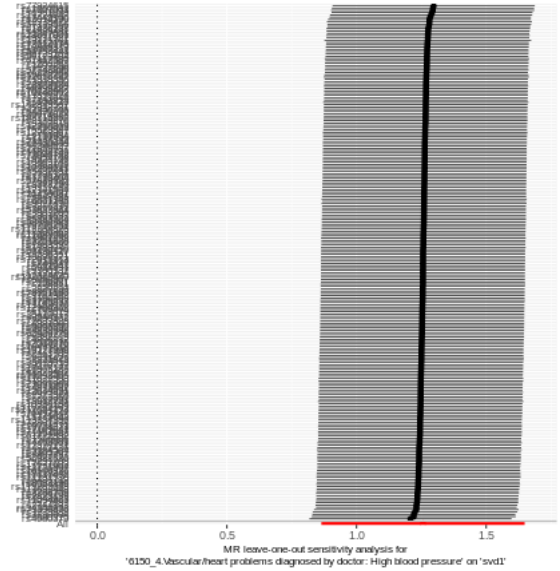


Supplement 3 Figure 2. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for hypertension diagnosed by doctor on ICH or SVS.

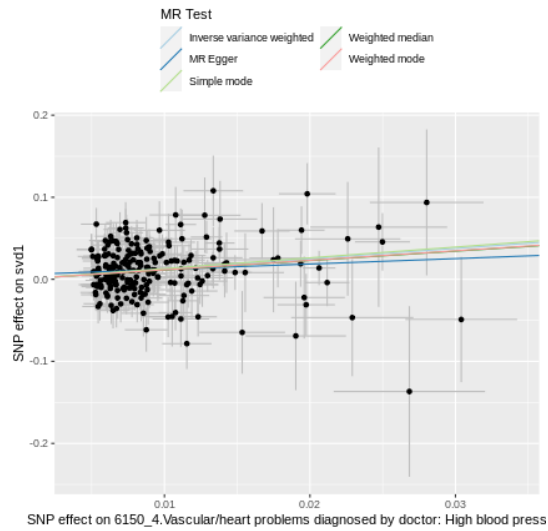
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

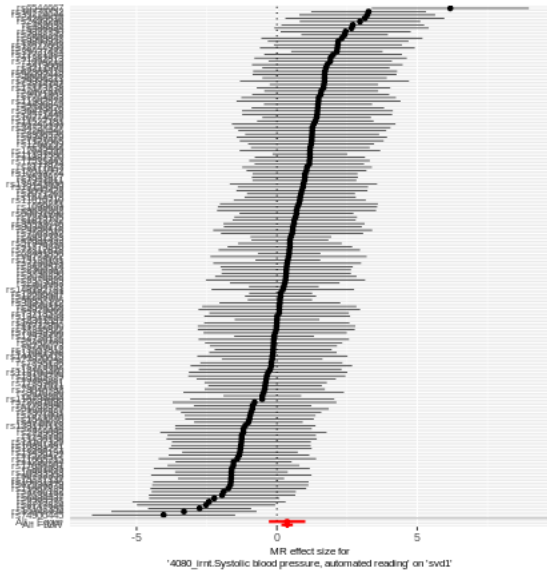


(c) Comparison of results using different MR methods

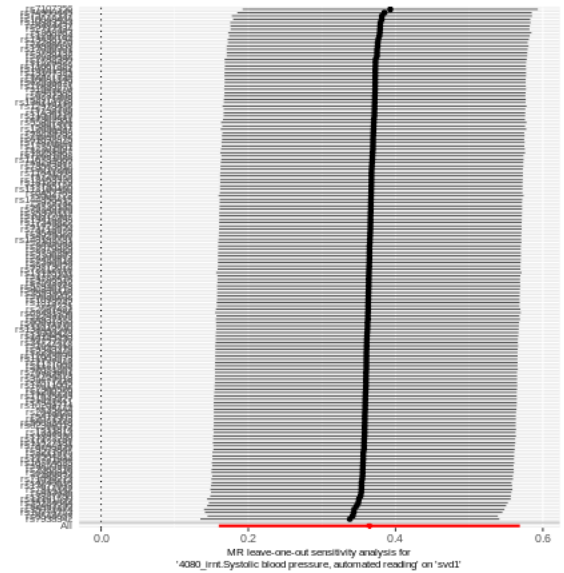


Supplement 3 Figure 3. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for systolic blood pressure (automated reading) on ICH or SVS.

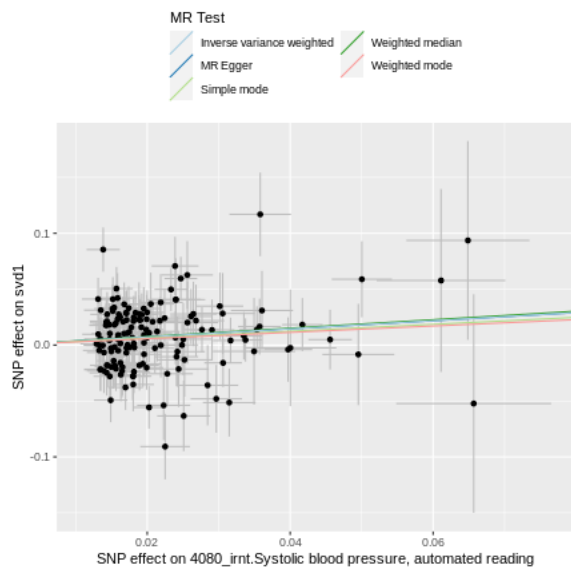
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

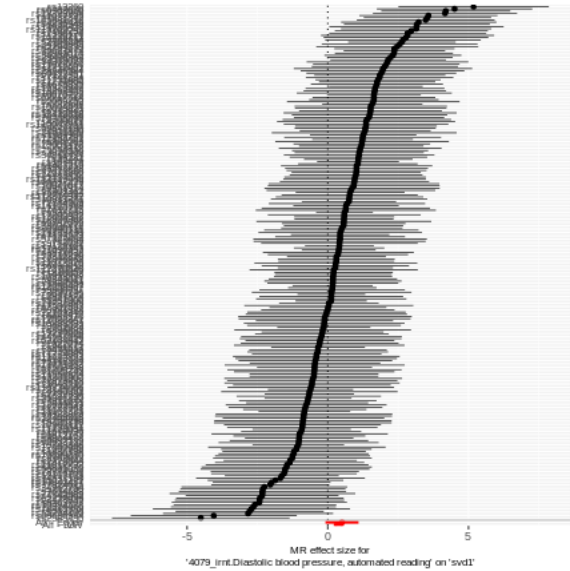


(c) Comparison of results using different MR methods

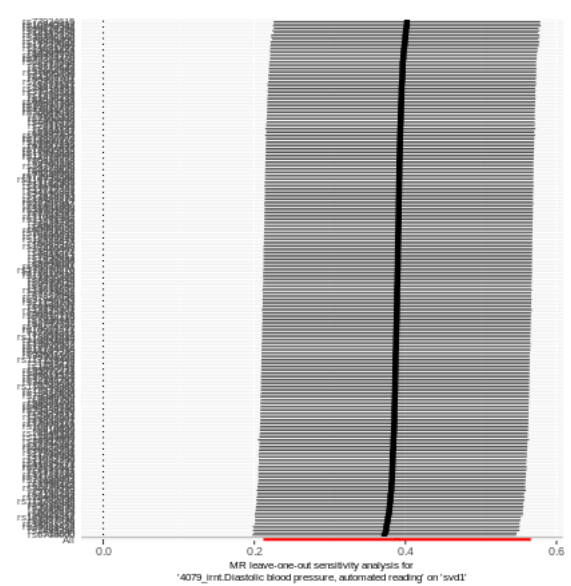


Supplement 3 Figure 4. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for diastolic blood pressure (automated reading) on ICH or SVS.

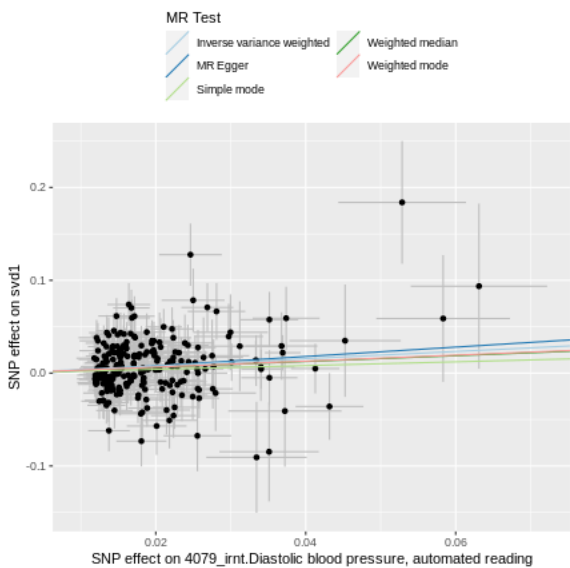
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

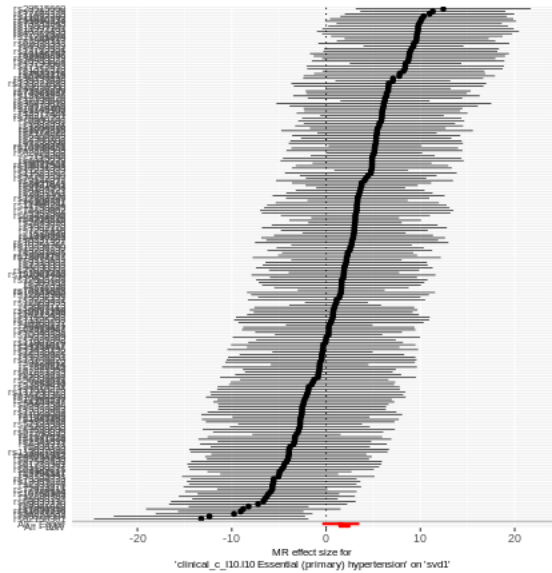


(c) Comparison of results using different MR methods

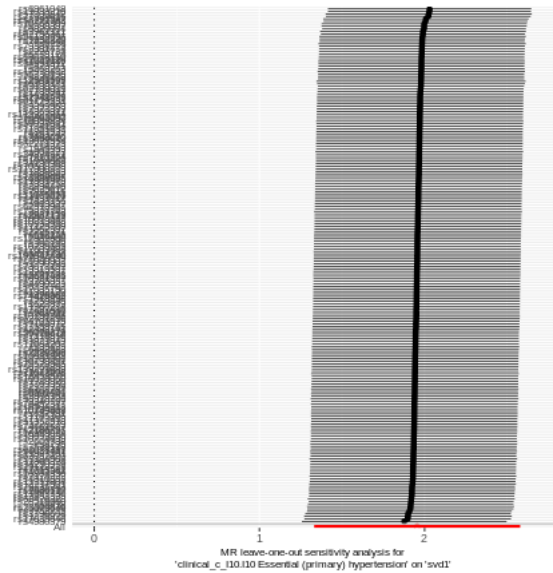


Supplement 3 Figure 5. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for essential (primary) hypertension on ICH or SVS

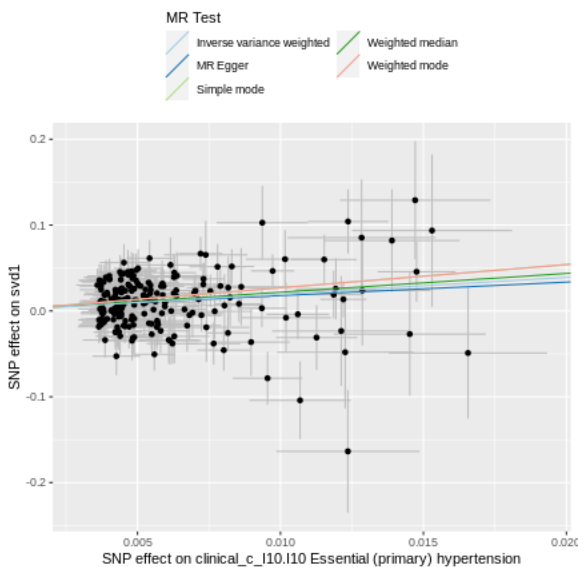
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

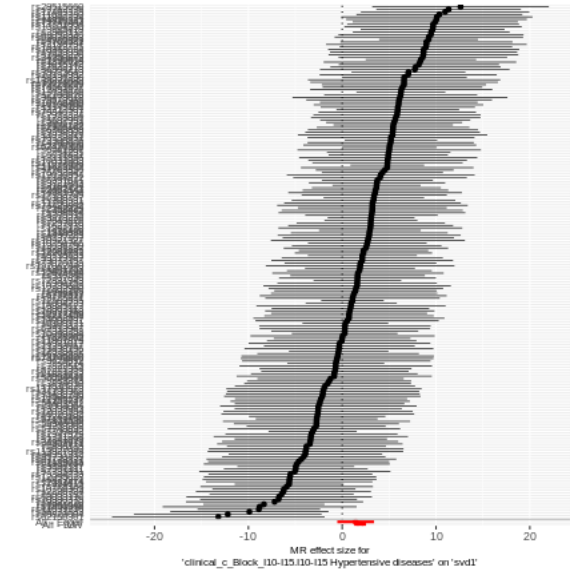


(c) Comparison of results using different MR methods

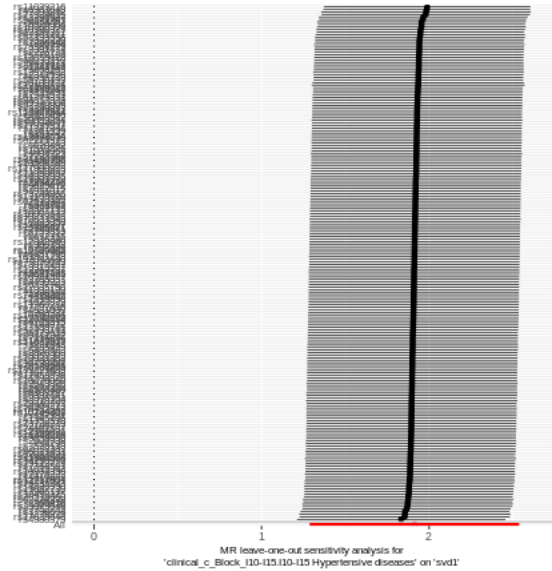


Supplement 3 Figure 6. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for hypertensive diseases on ICH or SVS.

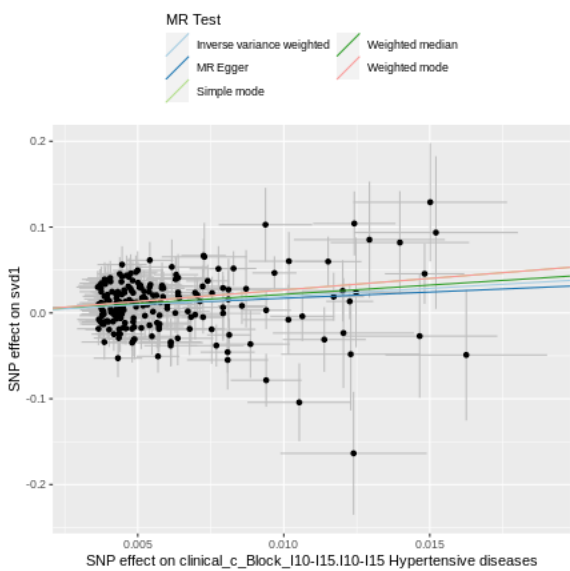
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

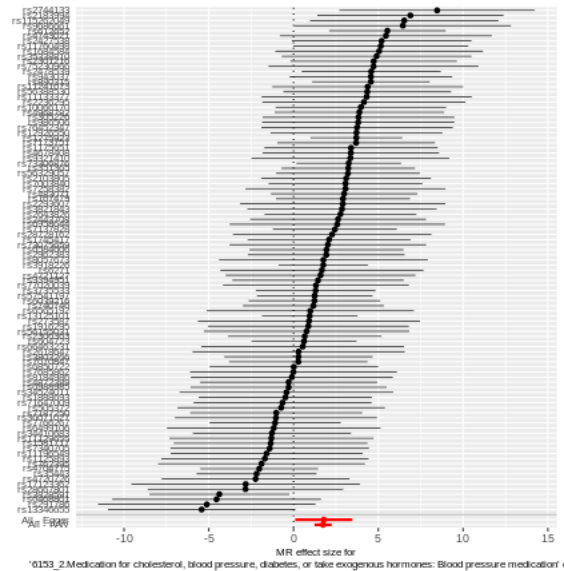


(c) Comparison of results using different MR methods

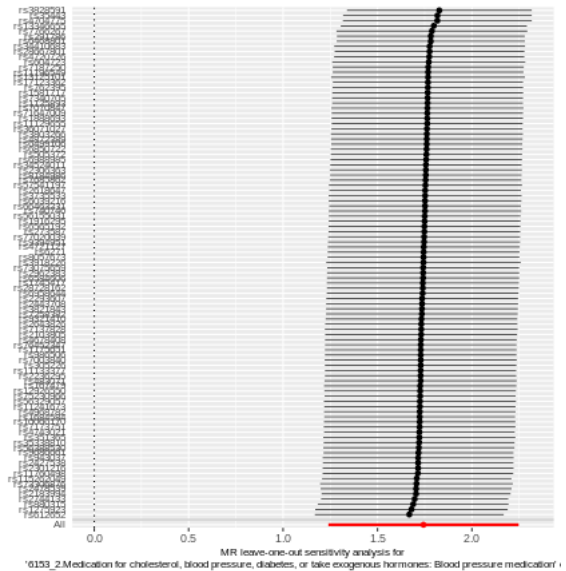


Supplement 3 Figure 7. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for anti-hypertensive medication on ICH or SVS.

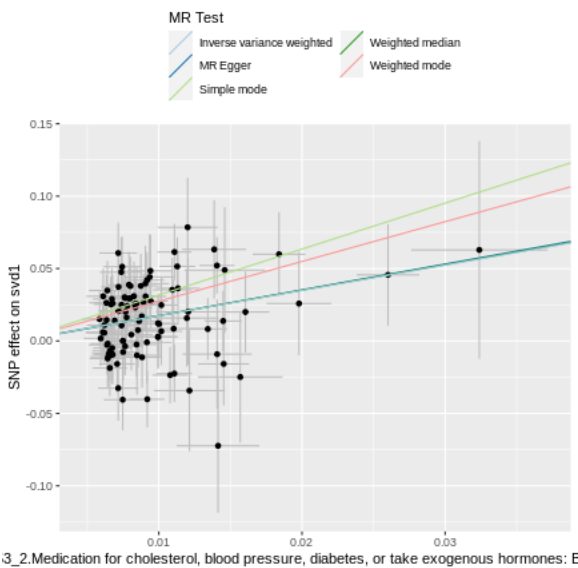
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

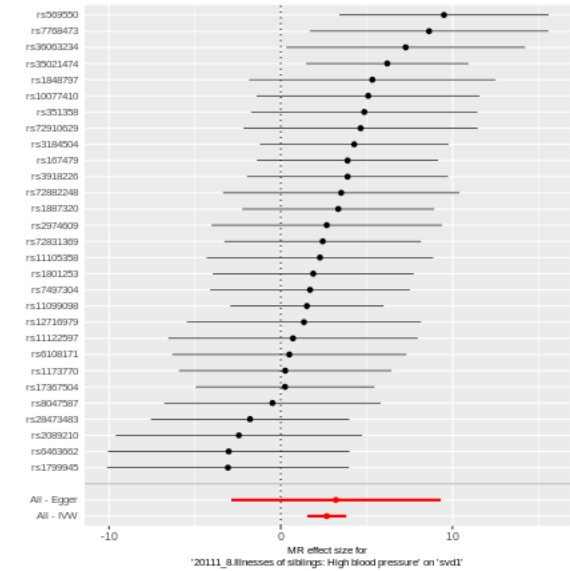


(c) Comparison of results using different MR methods

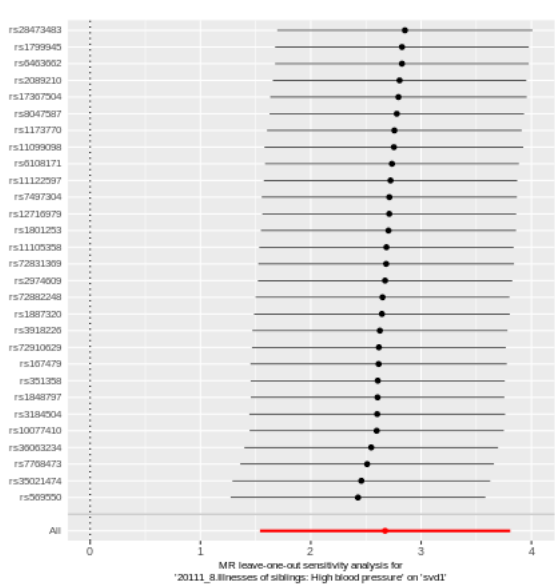


Supplement 3 Figure 8. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for hypertension of siblings on ICH or SVS.

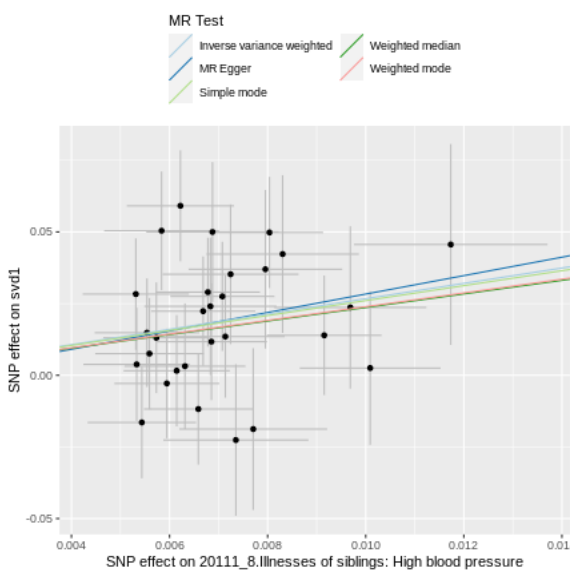
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

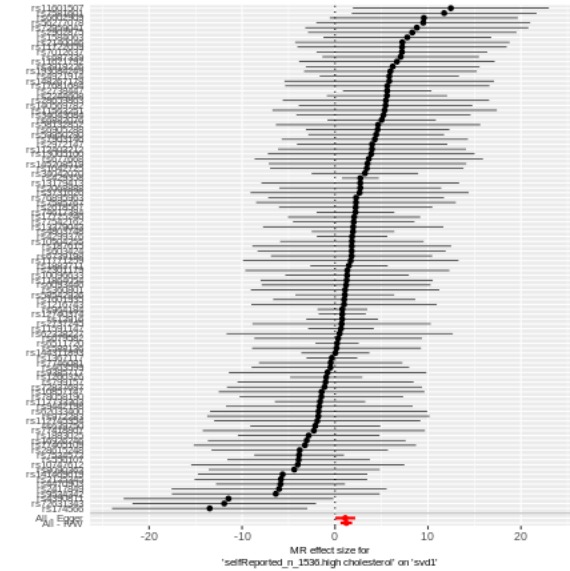


(c) Comparison of results using different MR methods

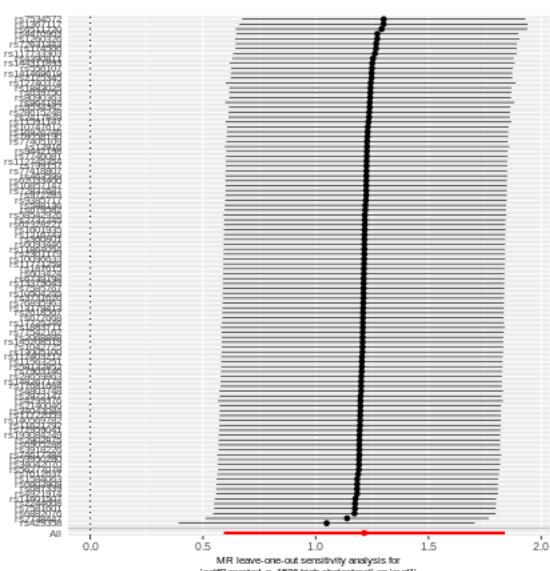


Supplement 3 Figure 9. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for high cholesterol on ICH or SVS.

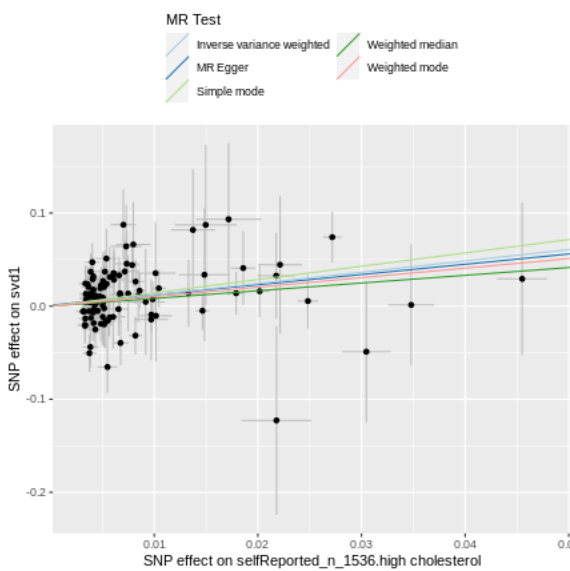
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

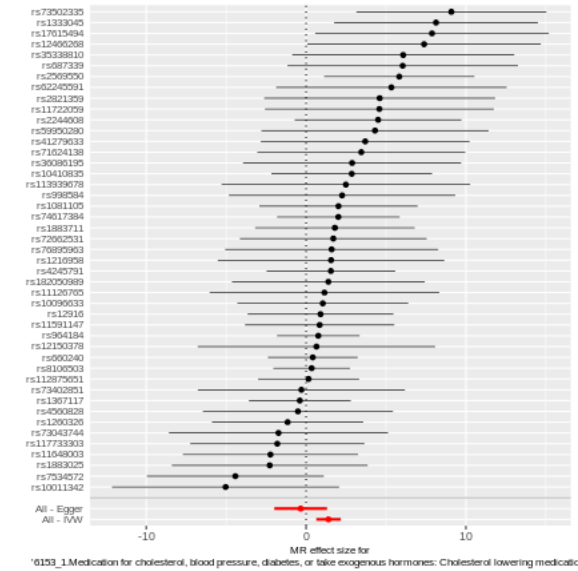


(c) Comparison of results using different MR methods

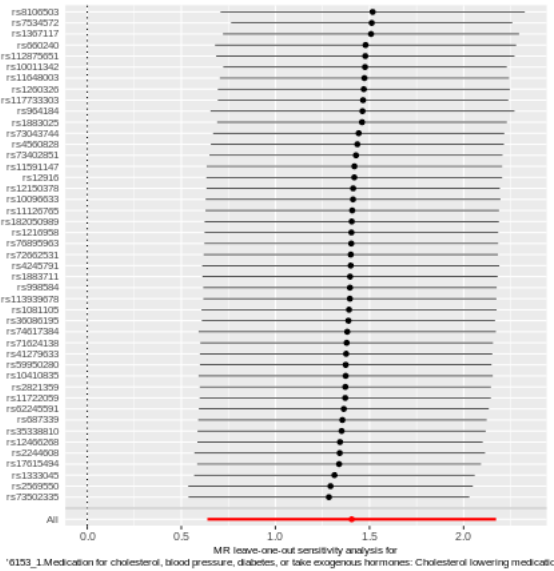


Supplement 3 Figure 10. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for cholesterol lowering medication on ICH or SVS.

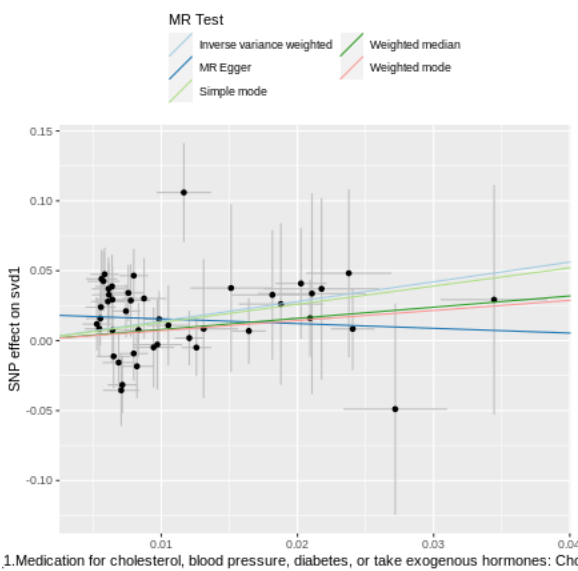
(a) Forest plot of single SNP MR



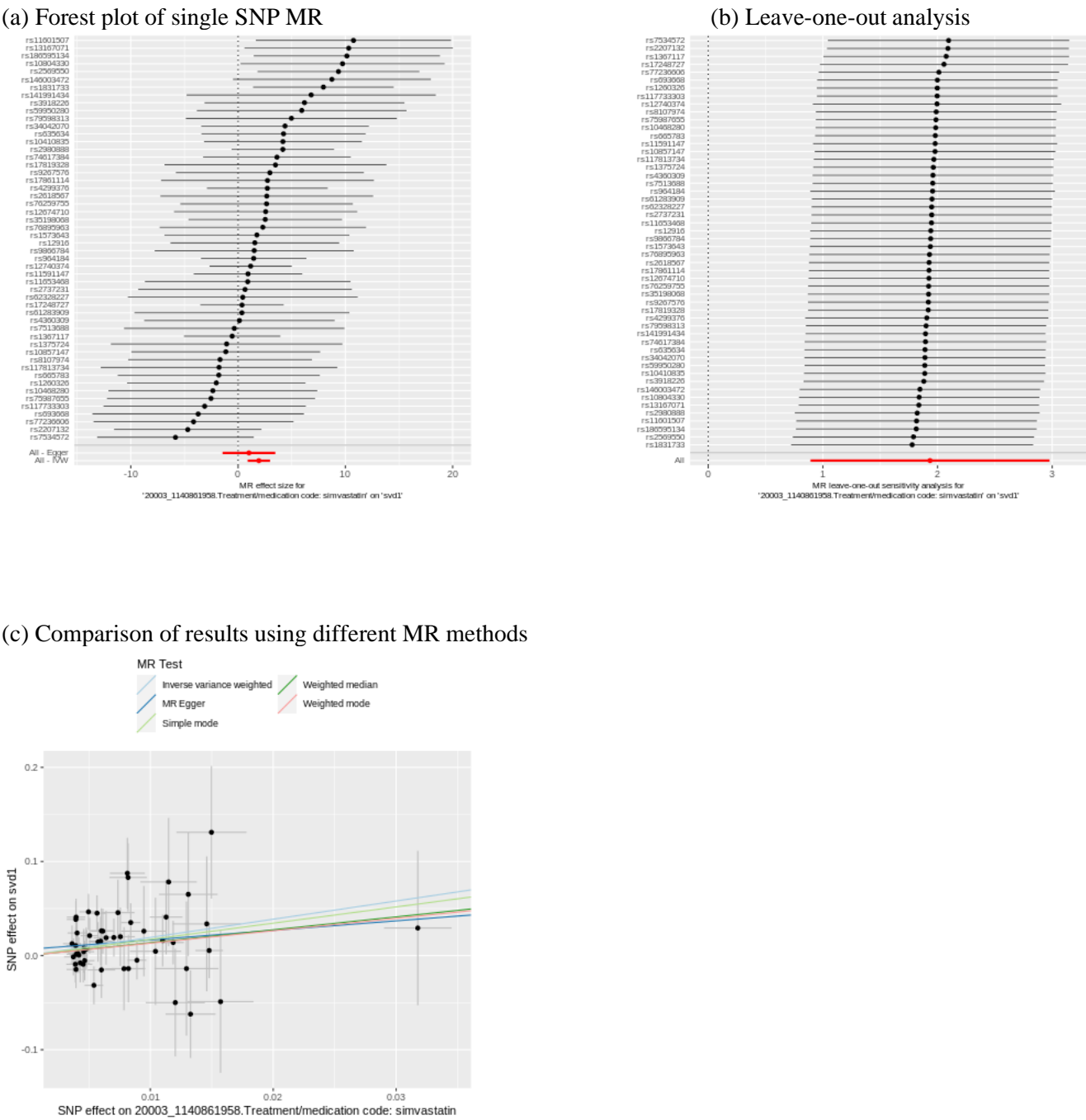
(b) Leave-one-out analysis



(c) Comparison of results using different MR methods

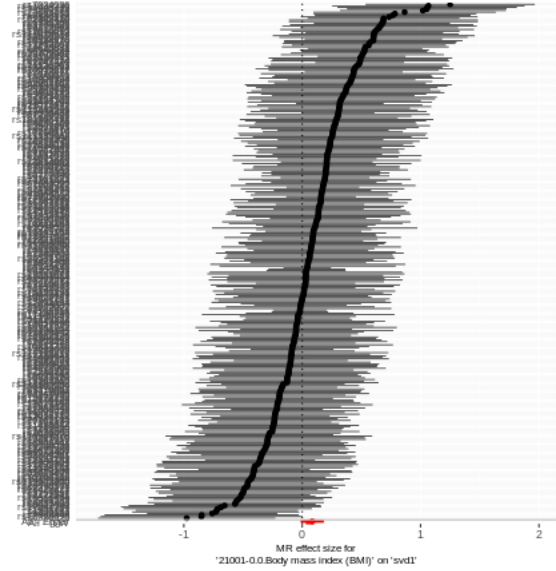


Supplement 3 Figure 11. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for cholesterol lowering medication (simvastatin) on ICH or SVS.

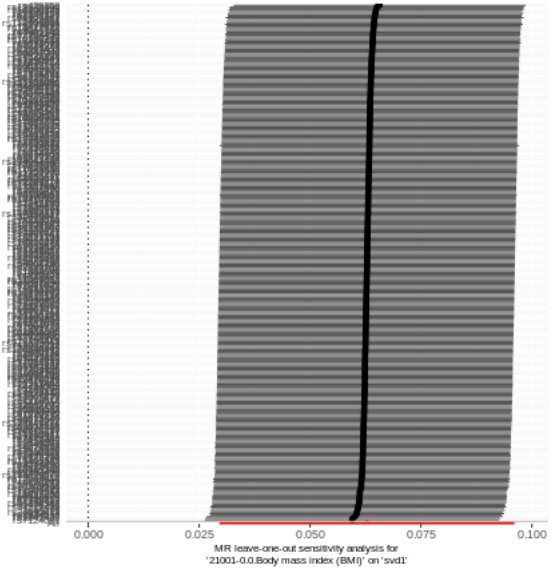


Supplement 3 Figure 12. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for body mass index (BMI) on ICH or SVS.

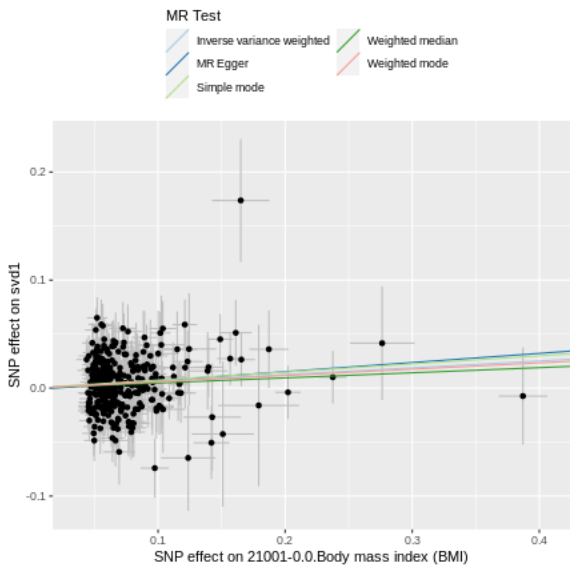
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

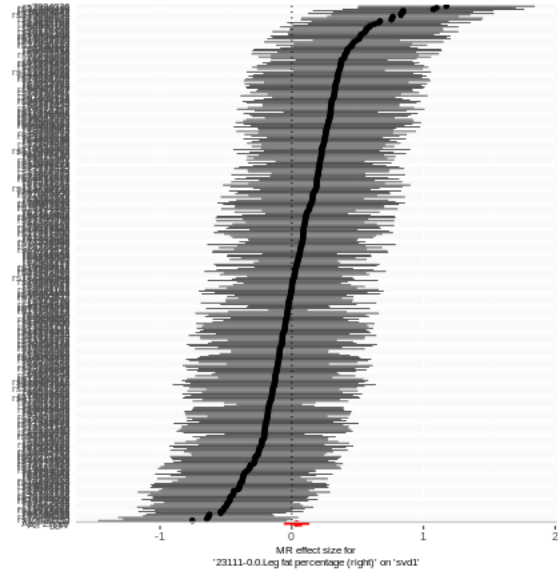


(c) Comparison of results using different MR methods

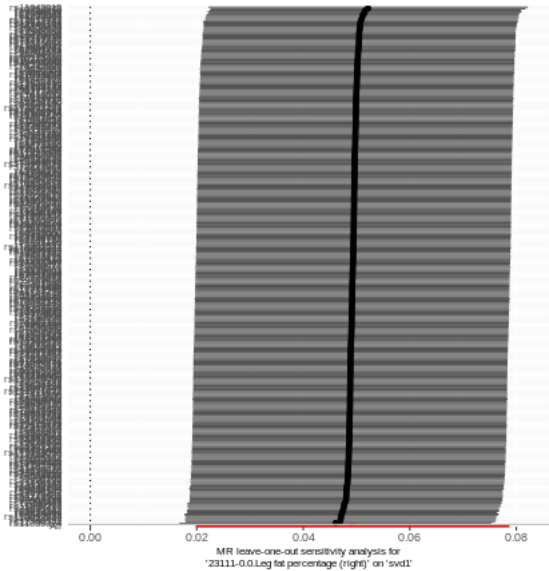


Supplement 3 Figure 13. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for leg fat percentage (right) on ICH or SVS.

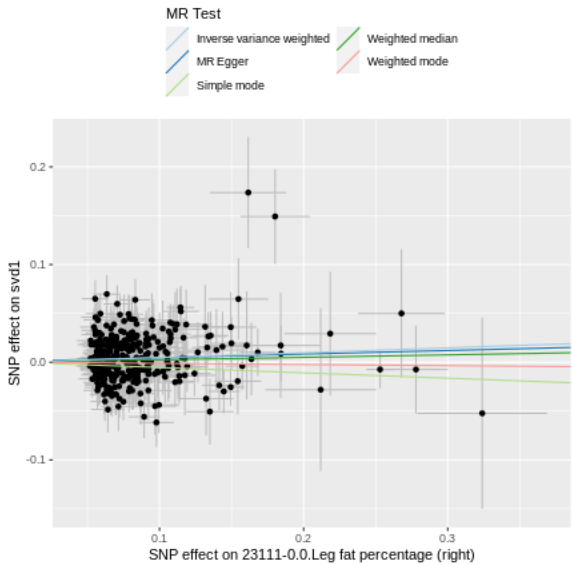
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

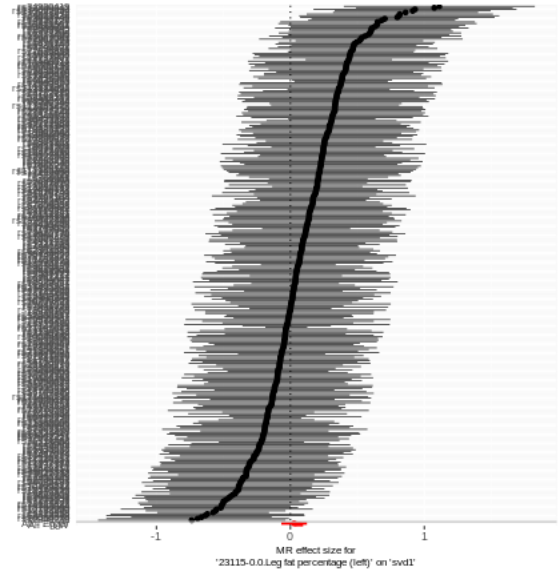


(c) Comparison of results using different MR methods

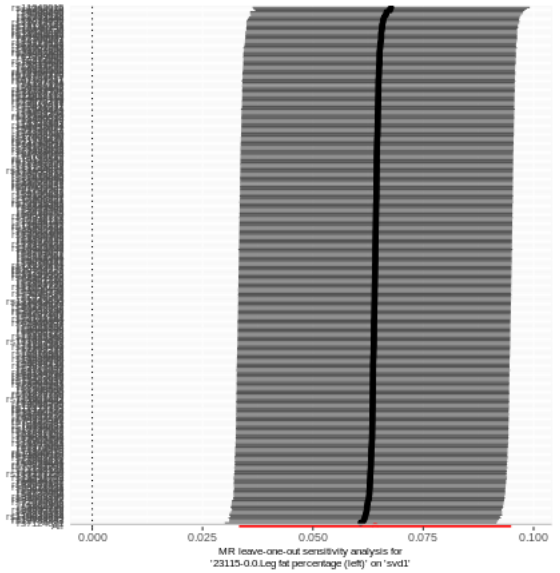


Supplement 3 Figure 14. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for leg fat percentage (left) on ICH or SVS.

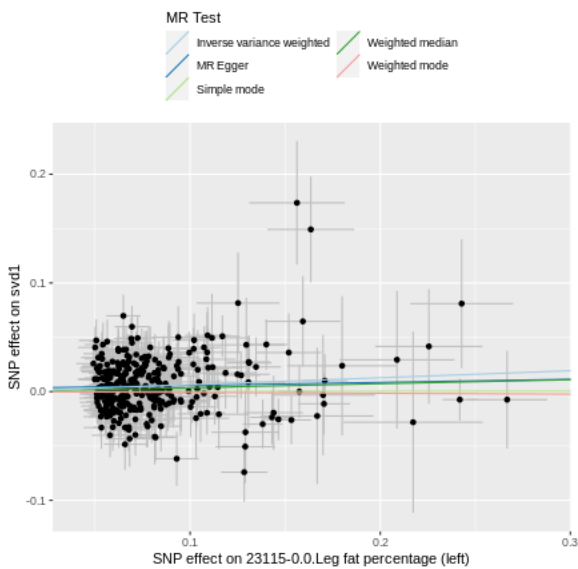
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

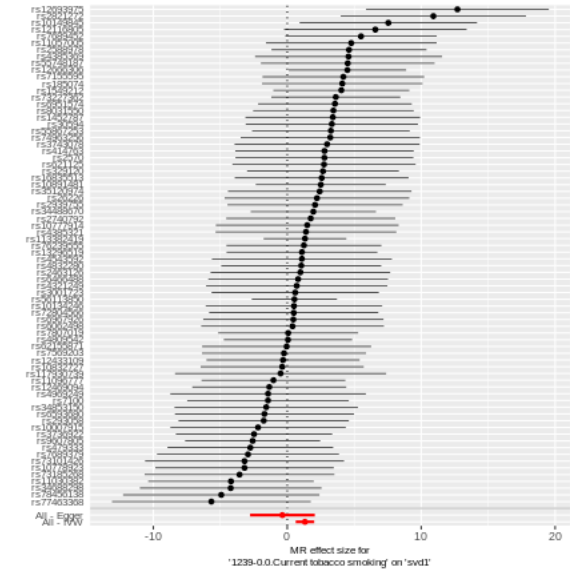


(c) Comparison of results using different MR methods

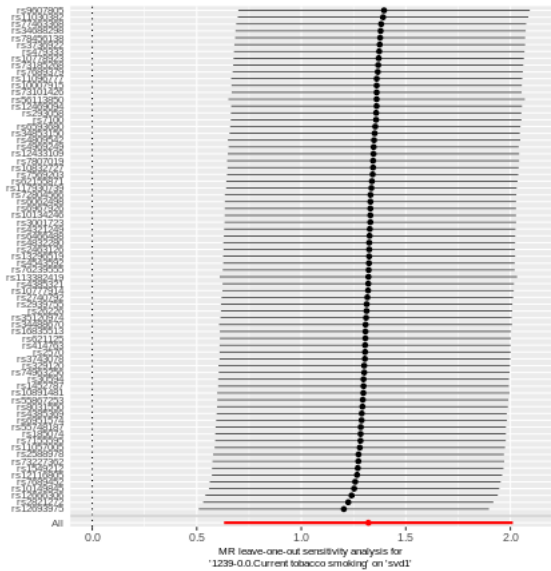


Supplement 3 Figure 15. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for current tobacco smoking on ICH or SVS.

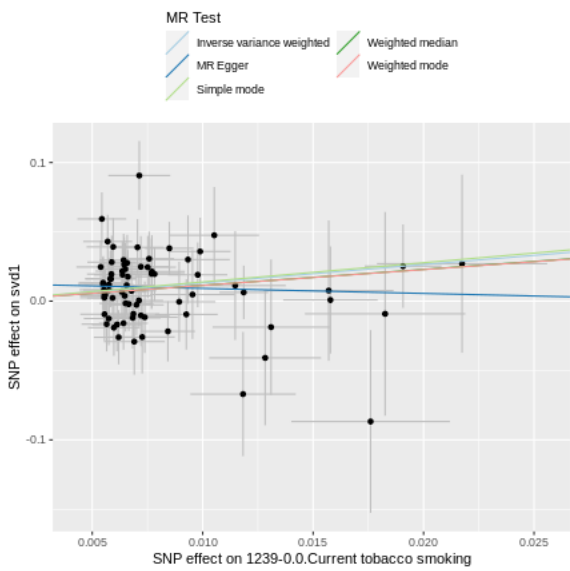
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

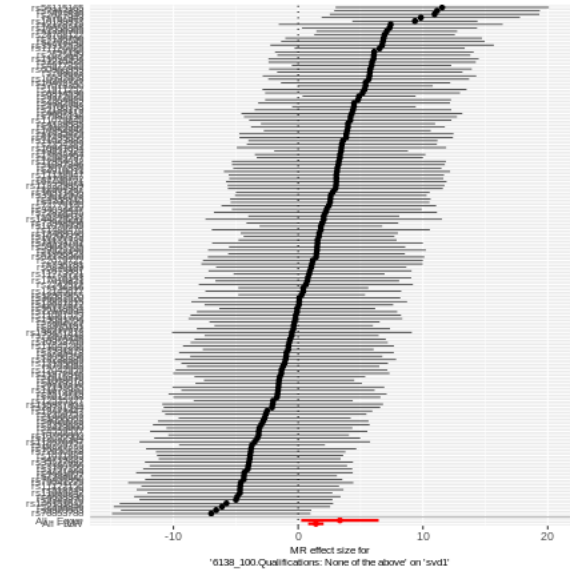


(c) Comparison of results using different MR methods

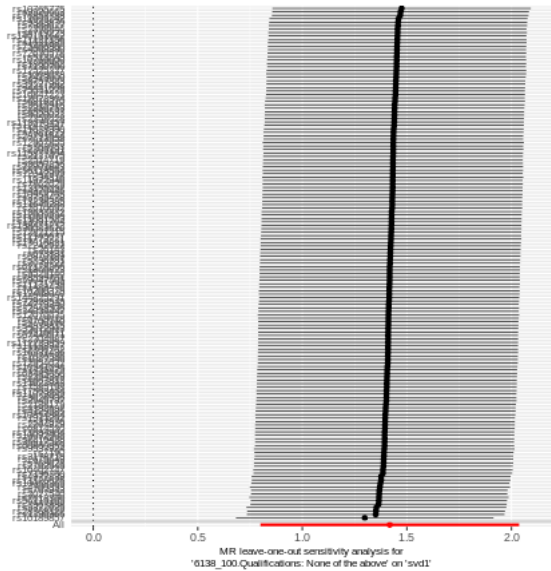


Supplement 3 Figure 16. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for none of qualifications on ICH or SVS.

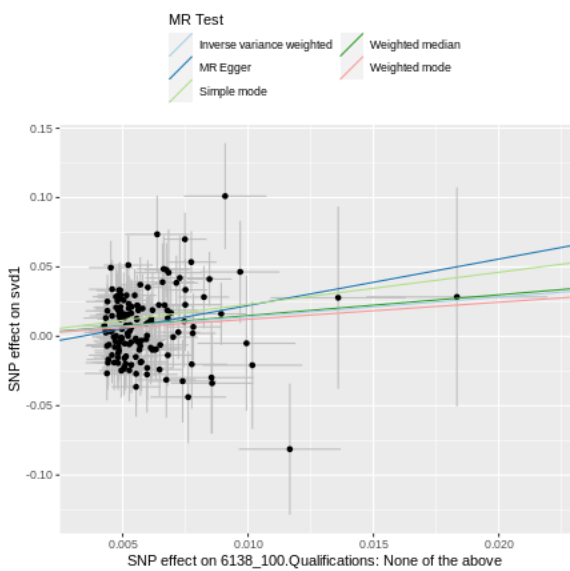
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

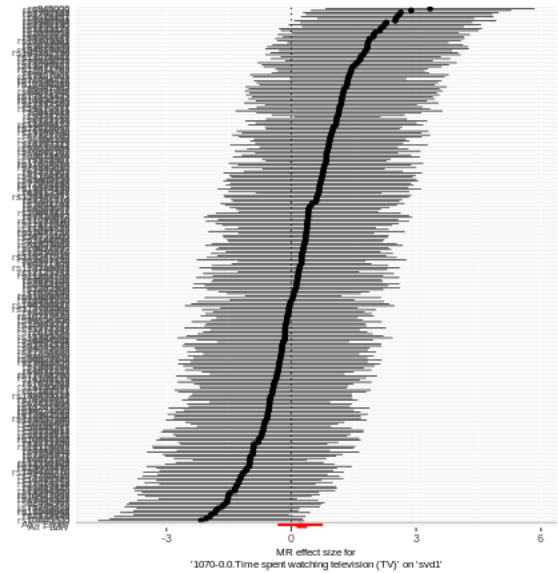


(c) Comparison of results using different MR methods

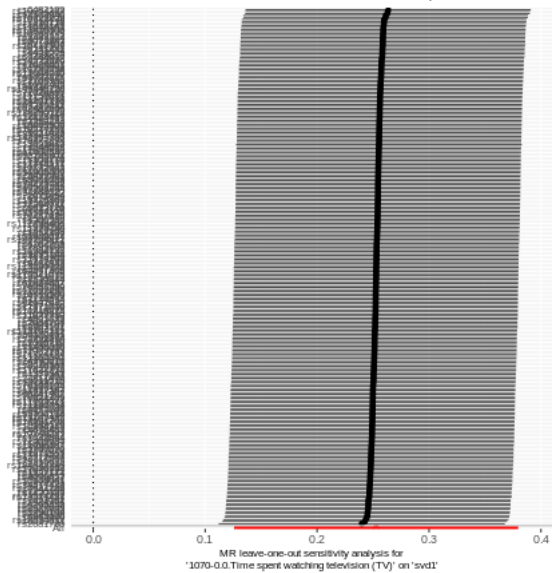


Supplement 3 Figure 17. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for time spent watching television on ICH or SVS.

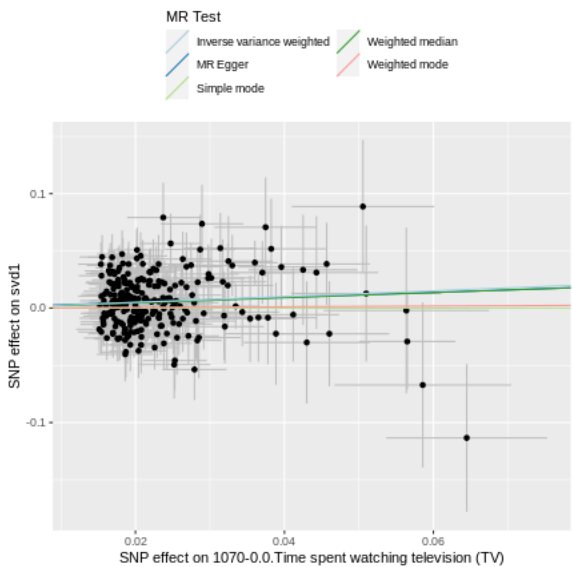
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

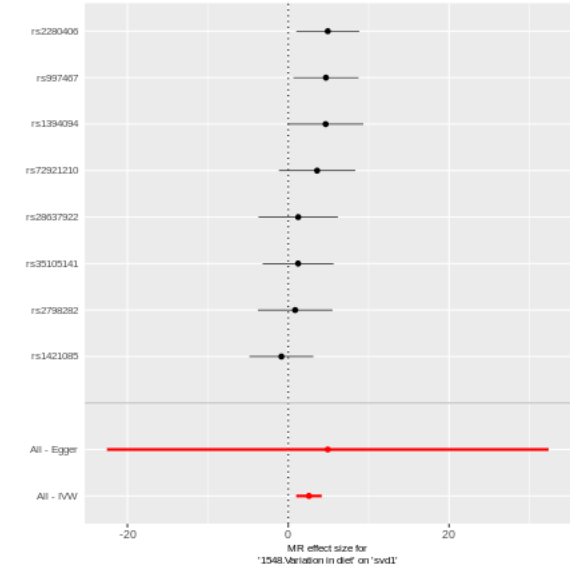


(c) Comparison of results using different MR methods

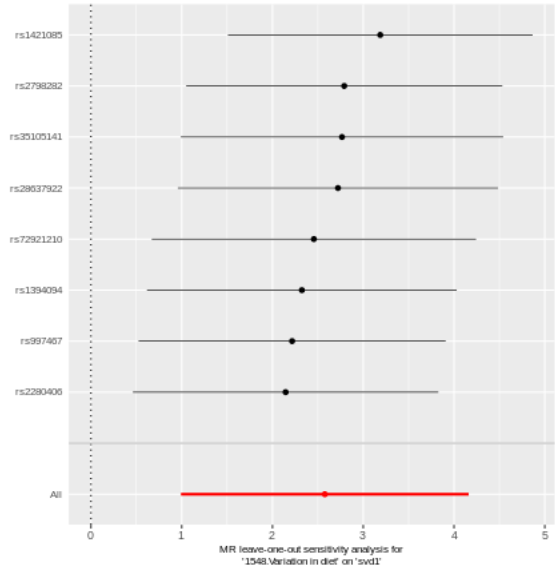


Supplement 3 Figure 18. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for variation in diet on ICH or SVS.

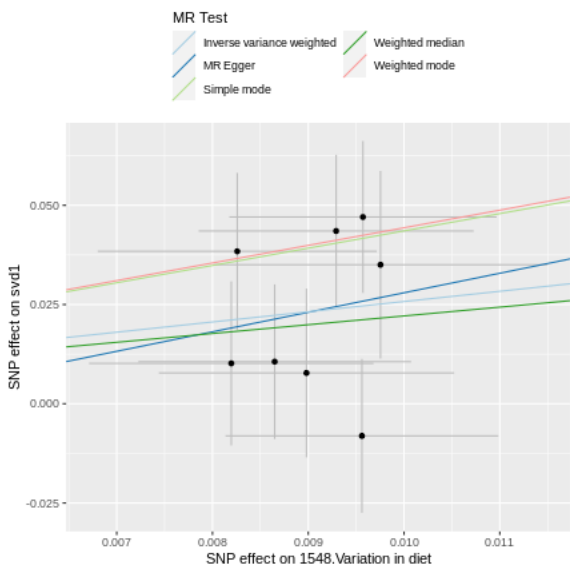
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

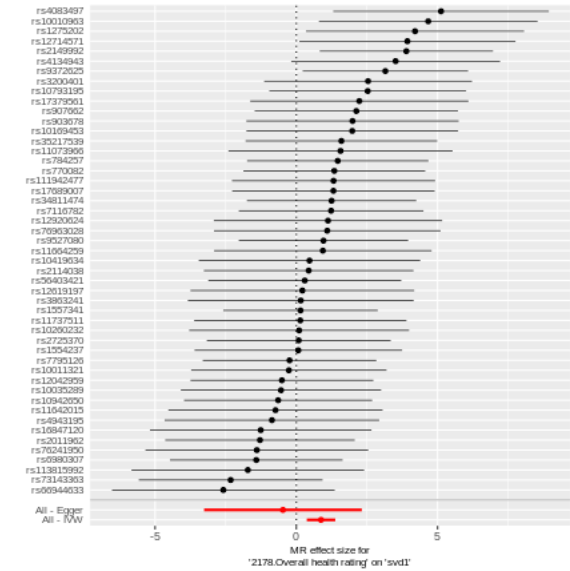


(c) Comparison of results using different MR methods

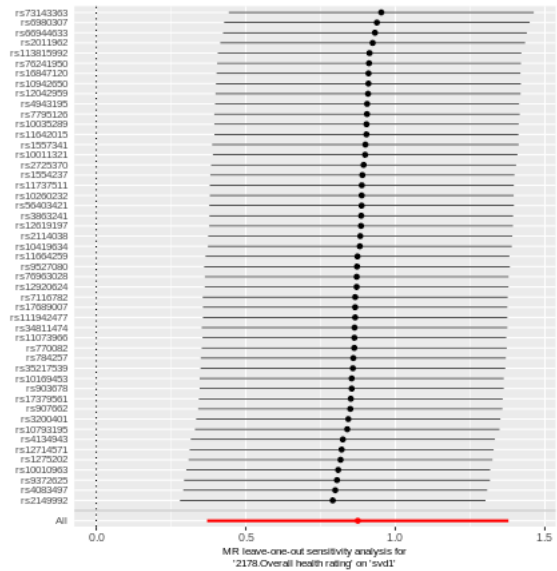


Supplement 3 Figure 19. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for overall health rating on ICH or SVS.

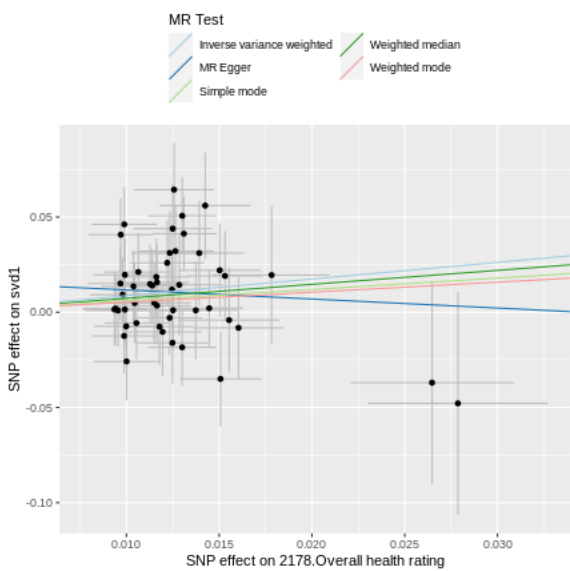
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

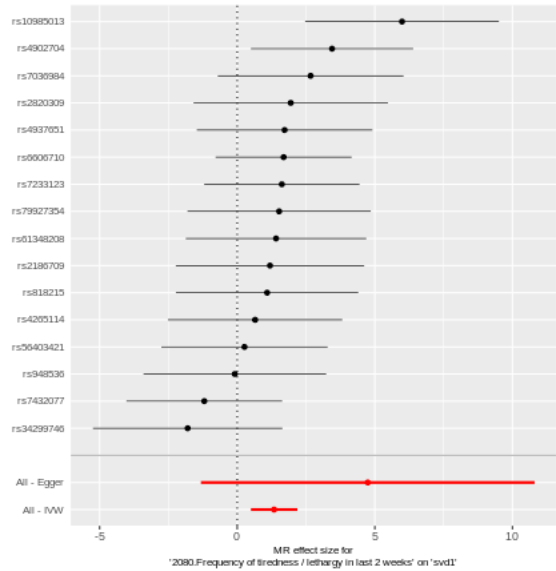


(c) Comparison of results using different MR methods

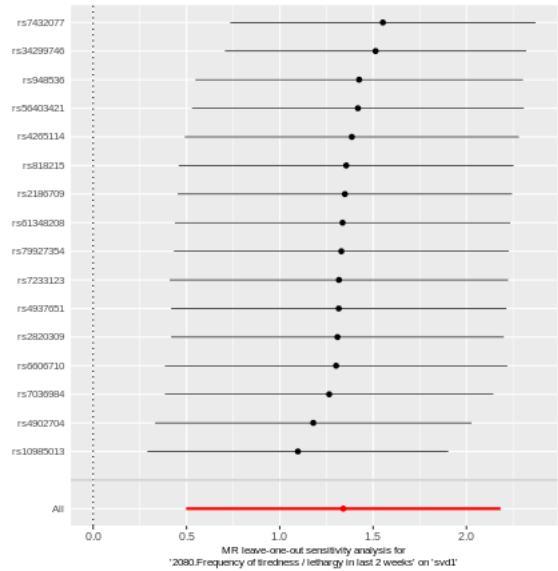


Supplement 3 Figure 20. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for frequency of tiredness / lethargy in last 2 weeks on ICH or SVS.

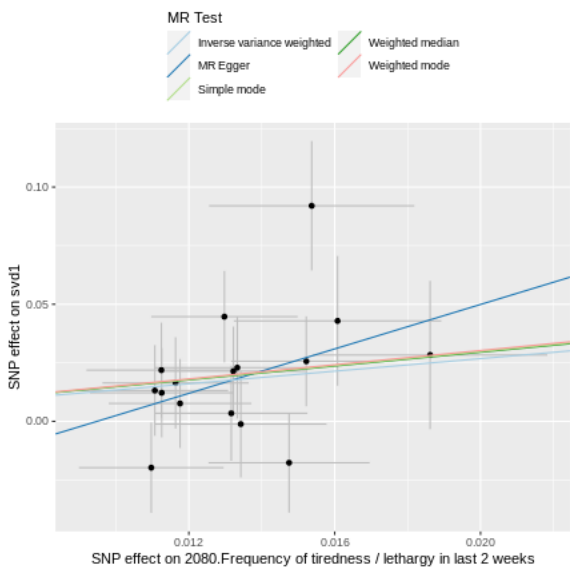
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

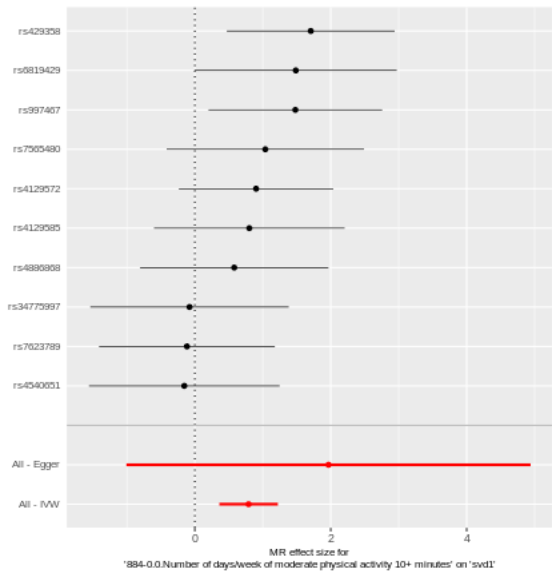


(c) Comparison of results using different MR methods

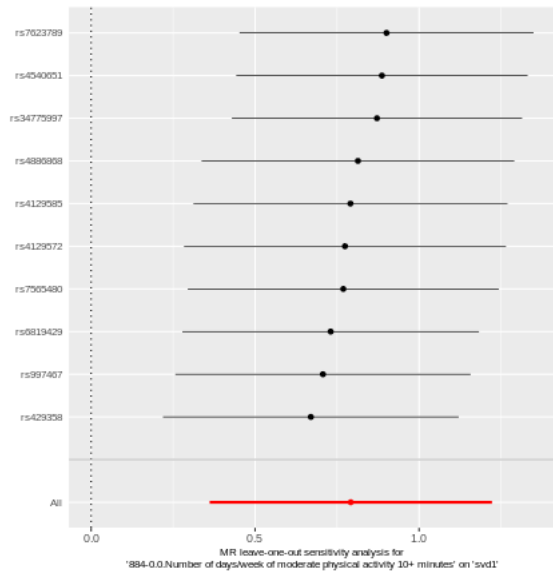


Supplement 3 Figure 21. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for days /week of moderate physical activity >10 minutes on ICH or SVS.

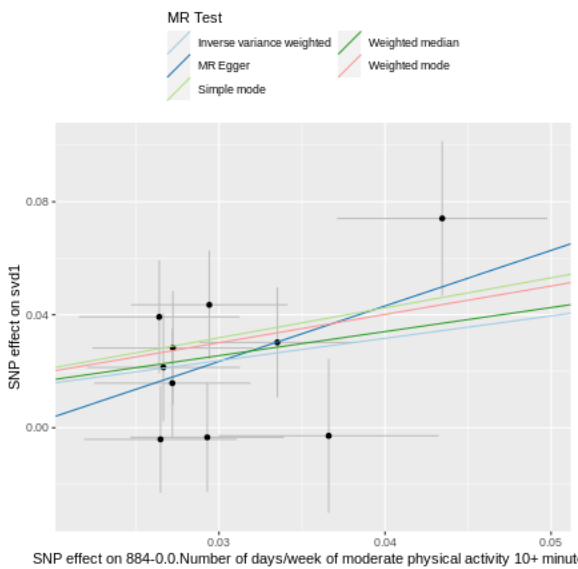
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

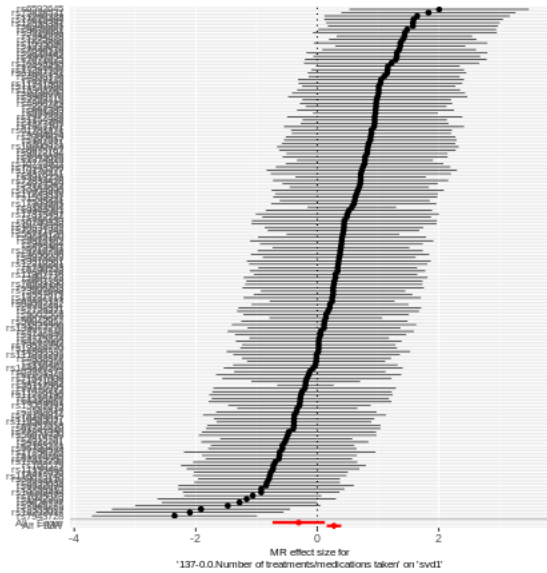


(c) Comparison of results using different MR methods

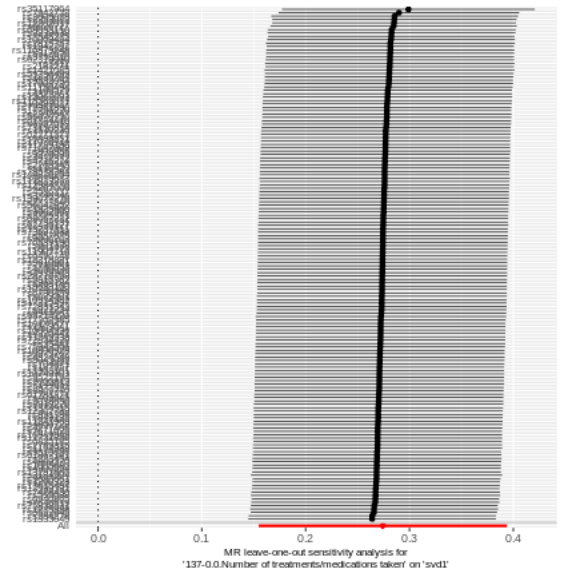


Supplement 3 Figure 22. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for number of treatments/medications taken on ICH or SVS.

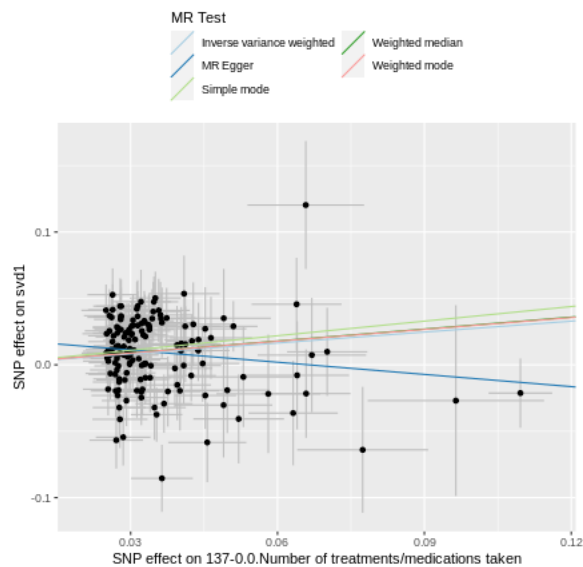
(a) Forest plot of single SNP MR



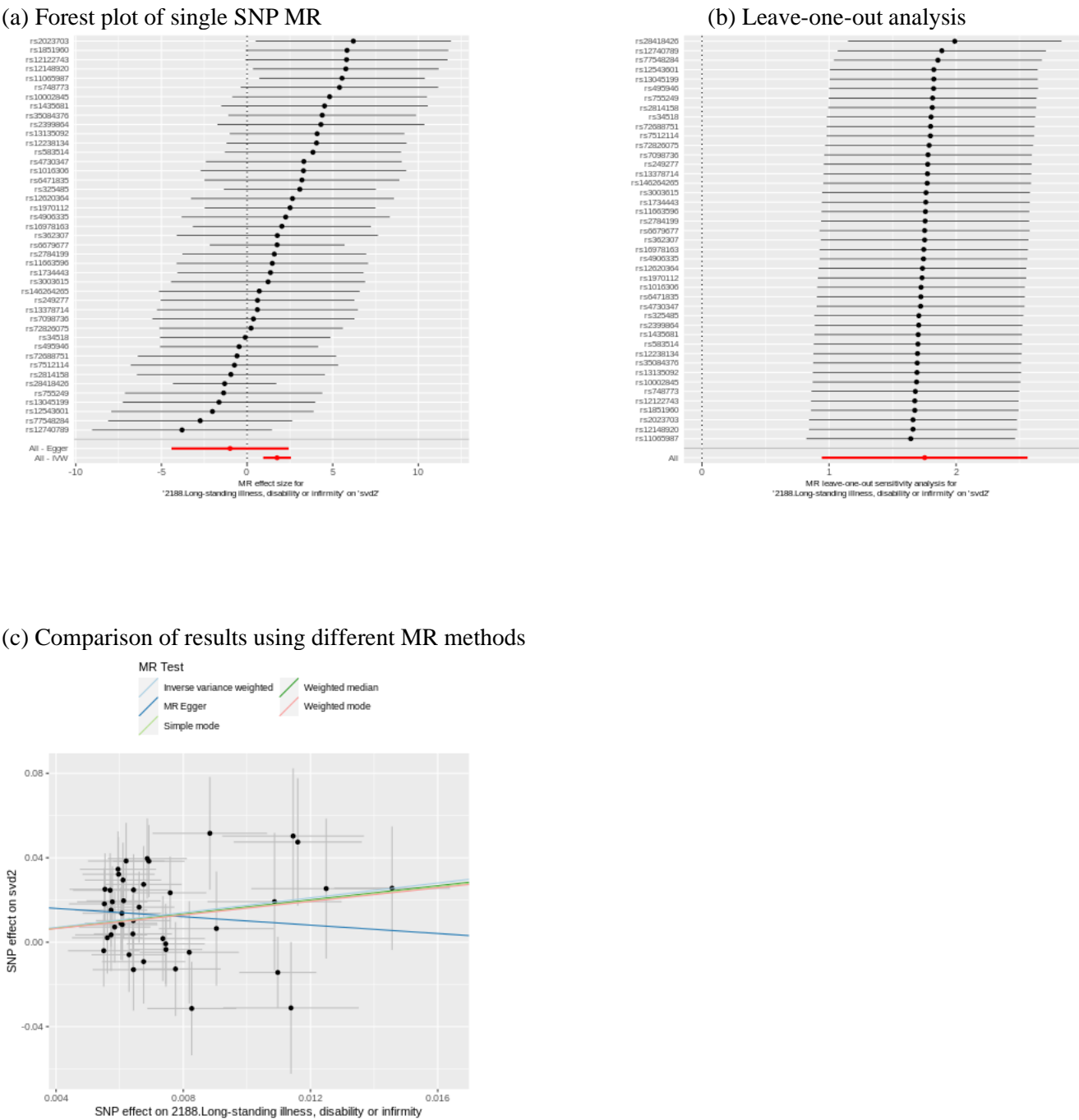
(b) Leave-one-out analysis



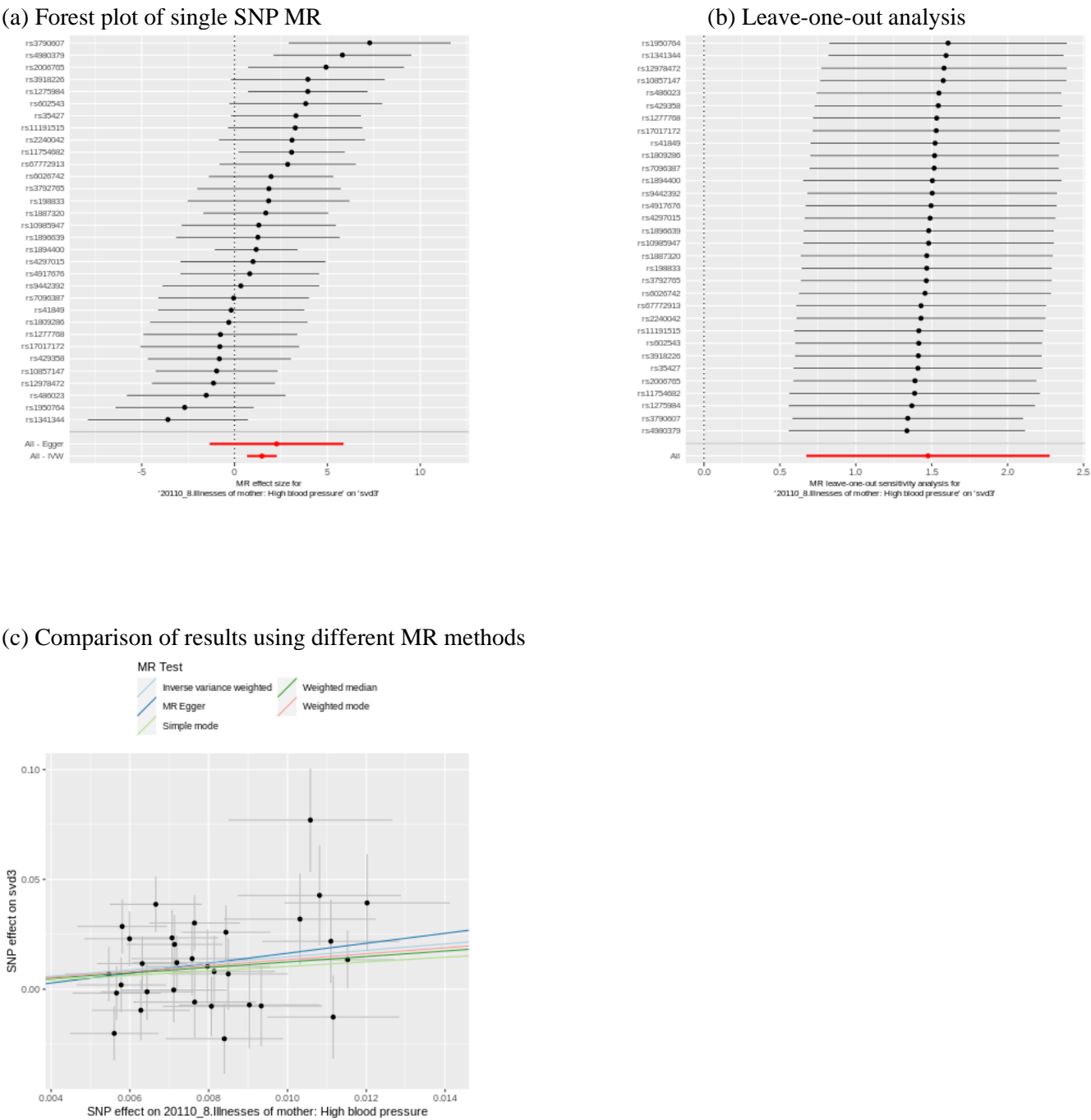
(c) Comparison of results using different MR methods



Supplement 3 Figure 23. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for long-standing illness, disability or infirmity on lobar hemorrhage or SVS.

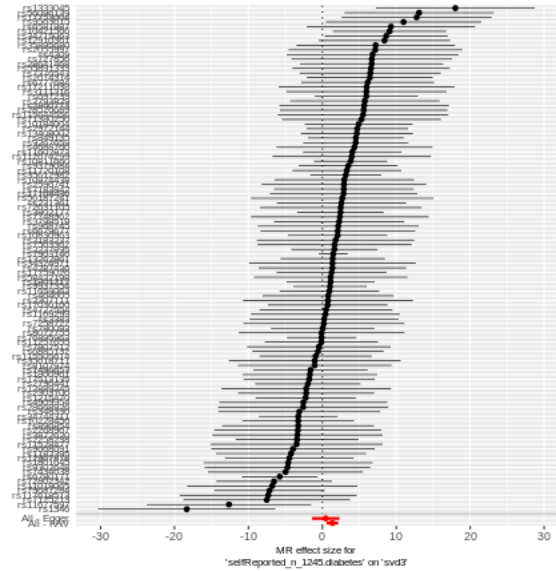


Supplement 3 Figure 24. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for hypertension of mother on non-lobar hemorrhage or SVS.

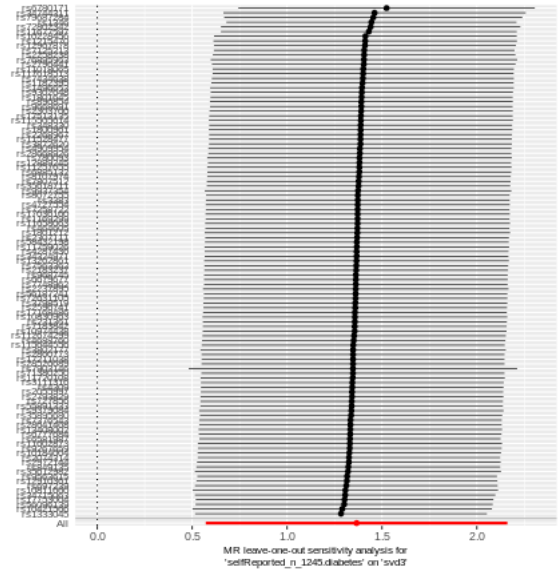


Supplement 3 Figure 25. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for self-reported diabetes on non-lobar hemorrhage or SVS.

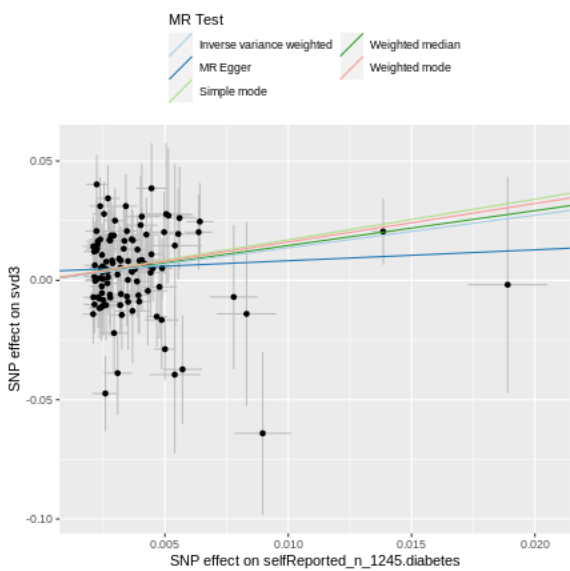
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

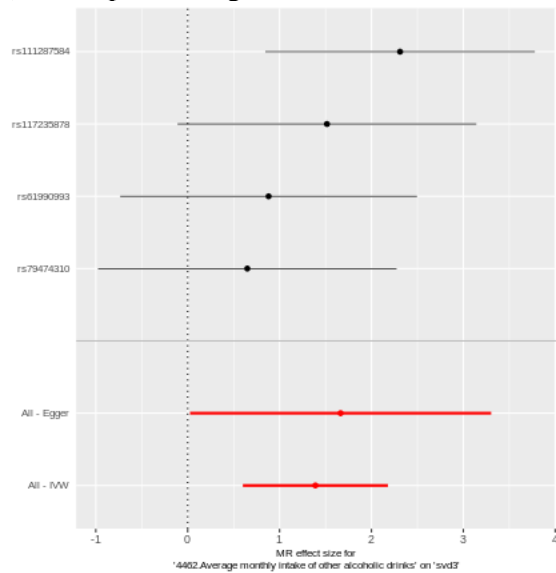


(c) Comparison of results using different MR methods

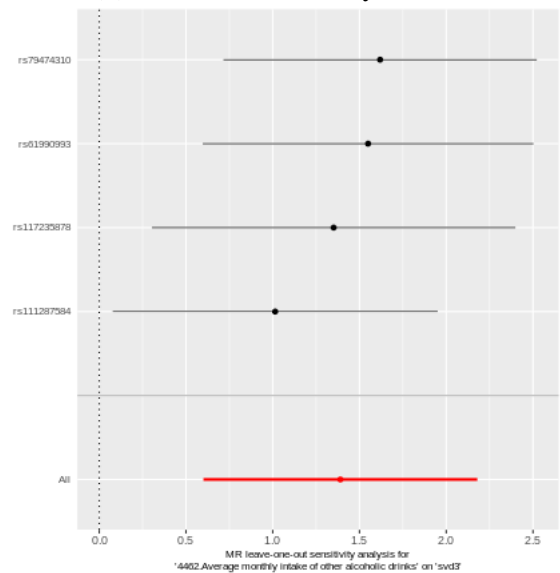


Supplement 3 Figure 26. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for average monthly intake of other alcoholic drinks on non-lobar hemorrhage or SVS.

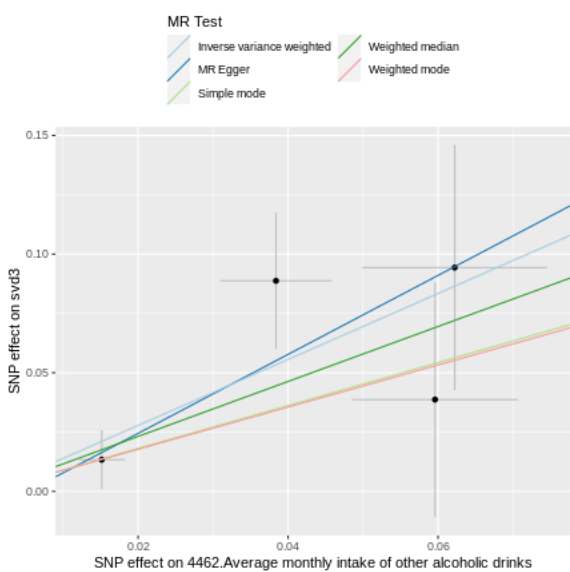
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

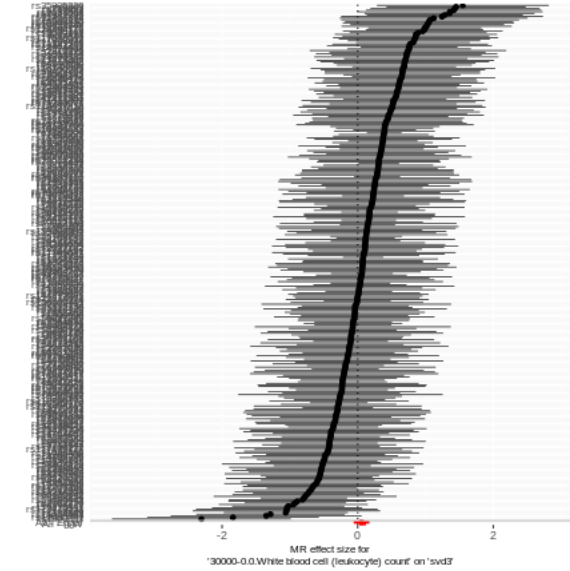


(c) Comparison of results using different MR methods

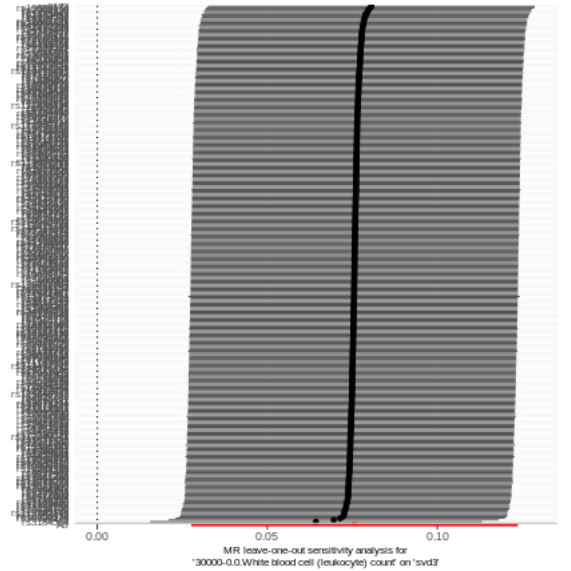


Supplement 3 Figure 27. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for white blood cell count on non-lobar hemorrhage or SVS.

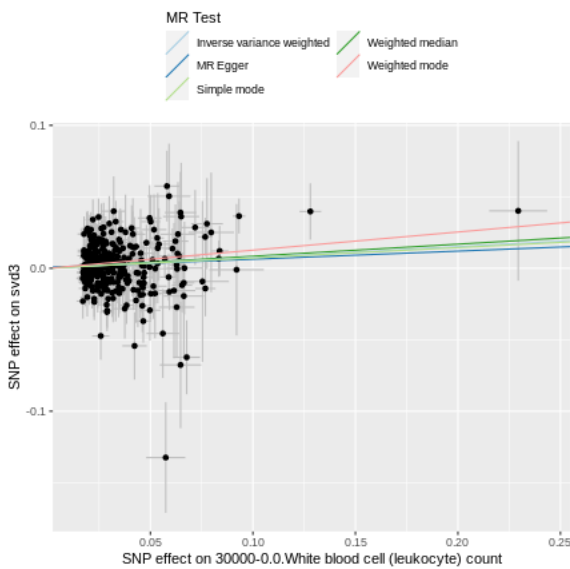
(a) Forest plot of single SNP MR



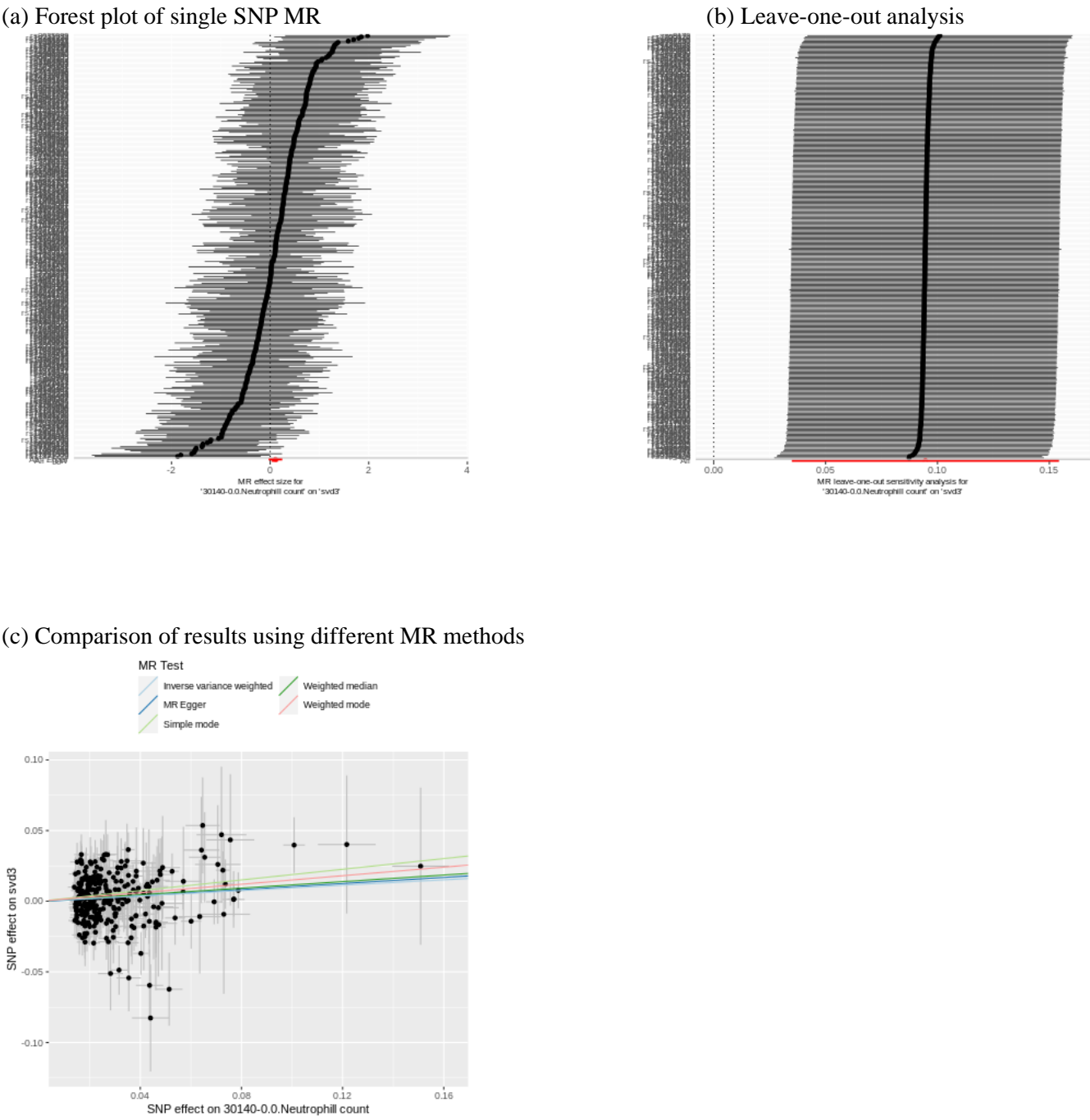
(b) Leave-one-out analysis



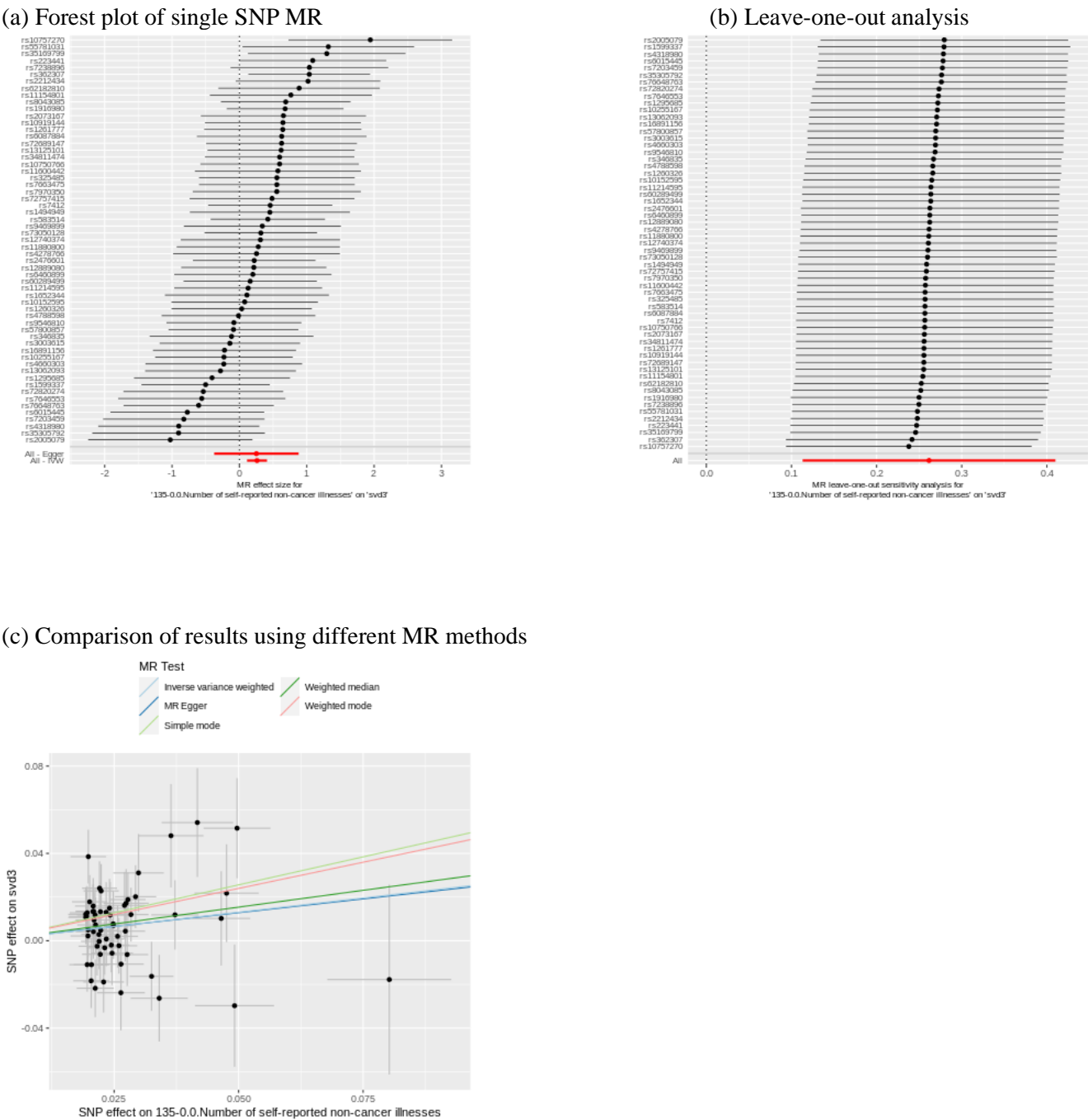
(c) Comparison of results using different MR methods



Supplement 3 Figure 28. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for neutrophil count on non-lobar hemorrhage or SVS.

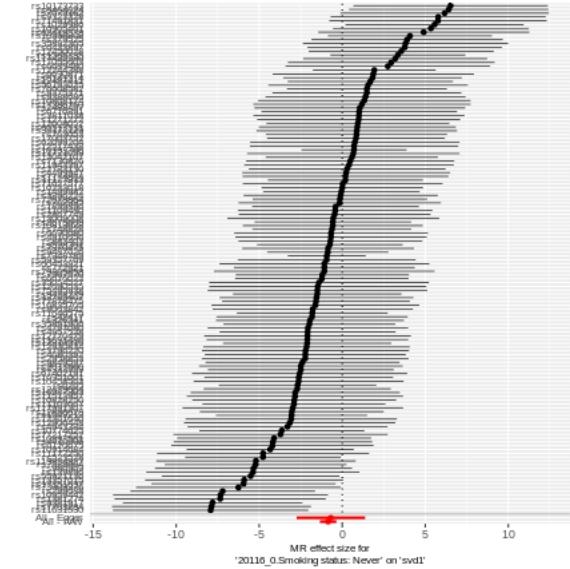


Supplement 3 Figure 29. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for number of self-reported non-cancer illnesses on non-lobar hemorrhage or SVS.

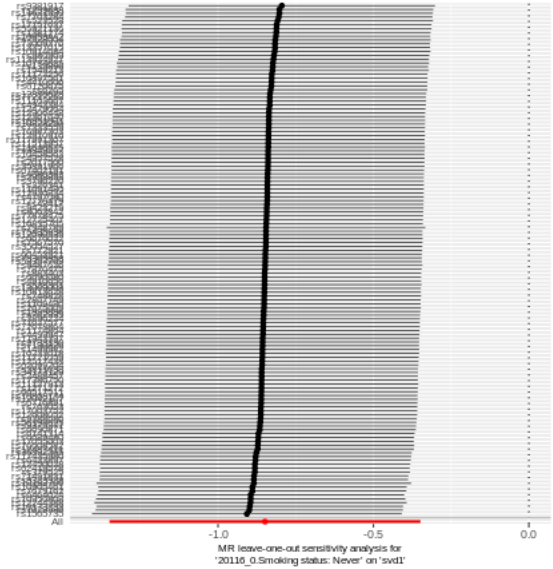


Supplement 3 Figure 30. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for never smoked on ICH or SVS.

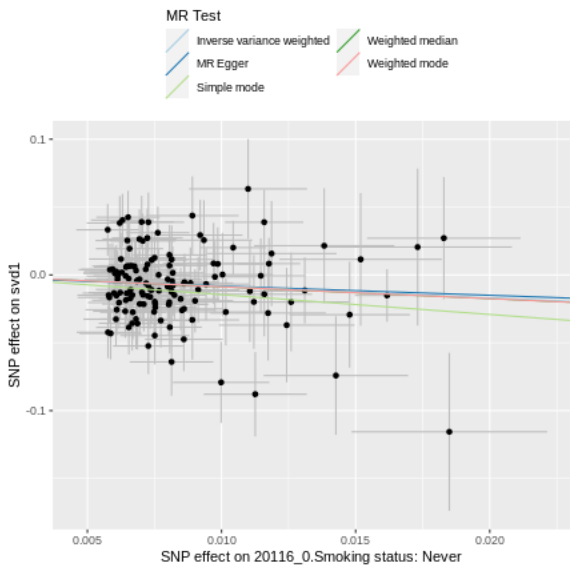
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

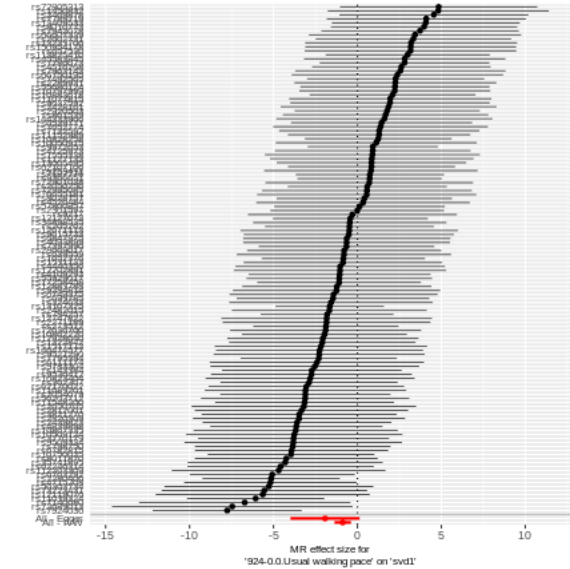


(c) Comparison of results using different MR methods

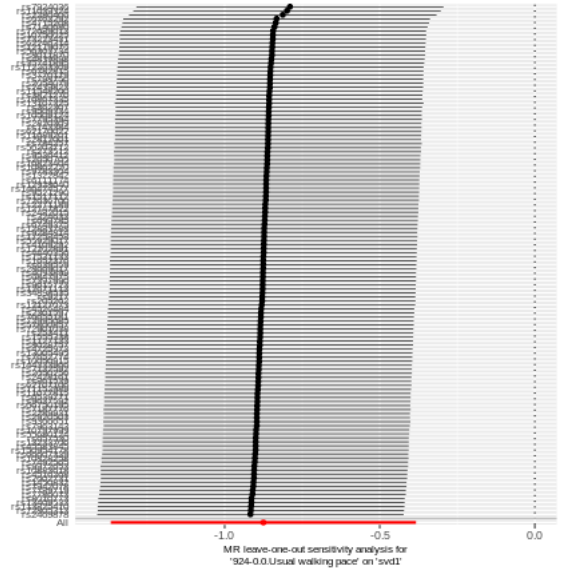


Supplement 3 Figure 31. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for usual walking pace on ICH or SVS.

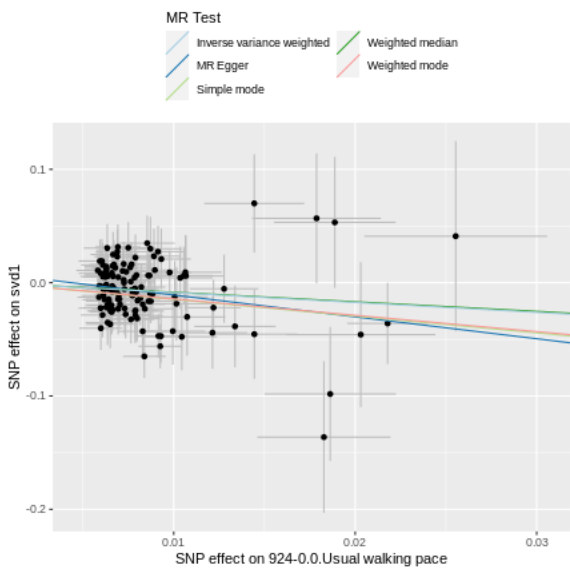
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

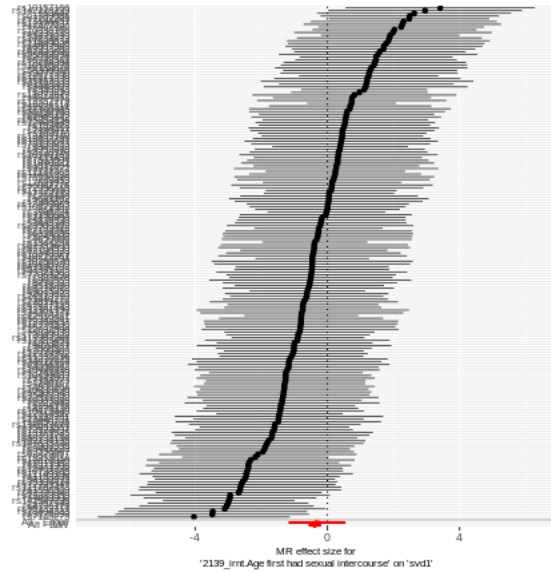


(c) Comparison of results using different MR methods

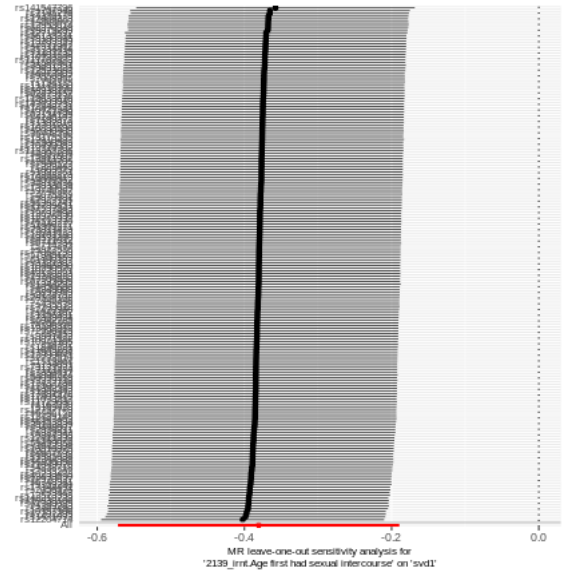


Supplement 3 Figure 32. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for age first had sexual intercourse on ICH or SVS.

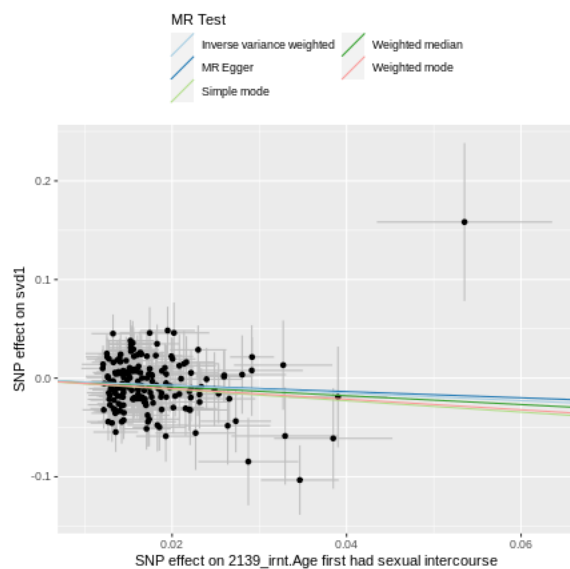
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

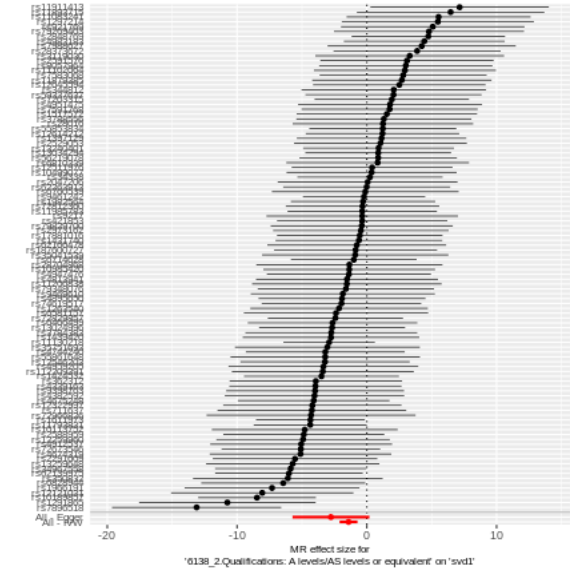


(c) Comparison of results using different MR methods

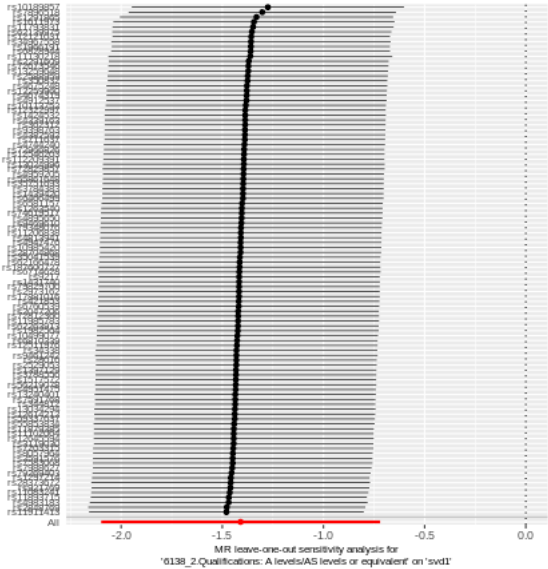


Supplement 3 Figure 33. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for A /AS levels qualifications on ICH or SVS.

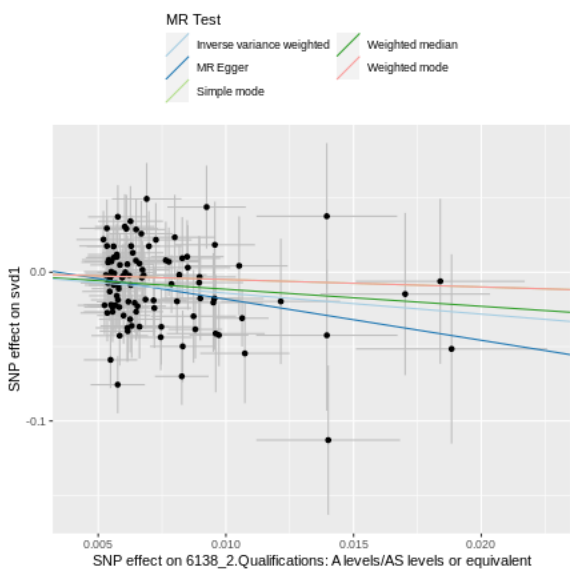
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

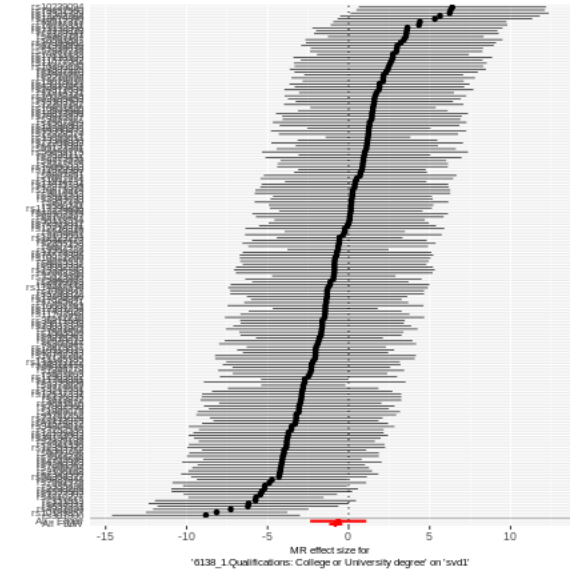


(c) Comparison of results using different MR methods

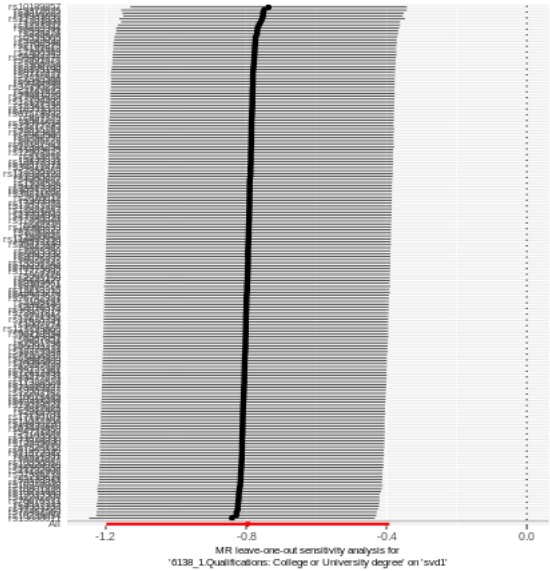


Supplement 3 Figure 34. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for college or university degree on ICH or SVS.

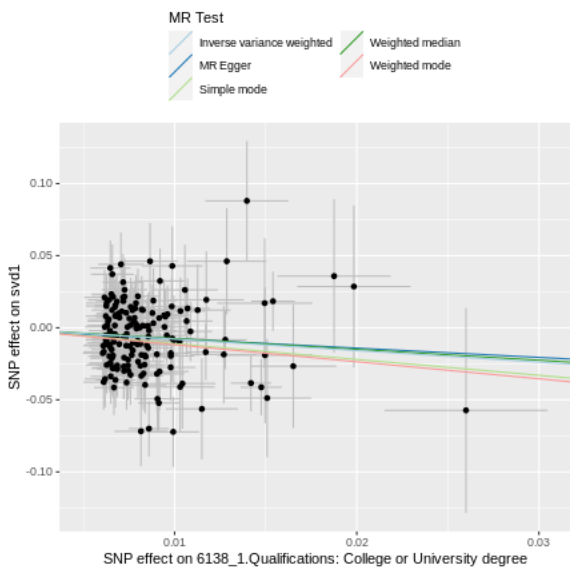
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

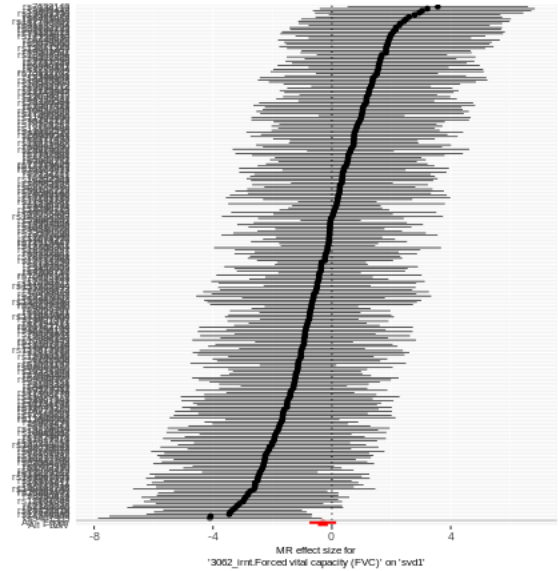


(c) Comparison of results using different MR methods

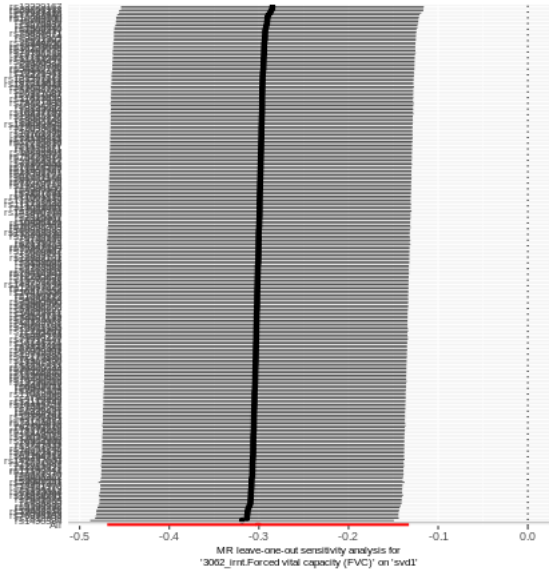


Supplement 3 Figure 35. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for forced vital capacity (FVC) on ICH or SVS.

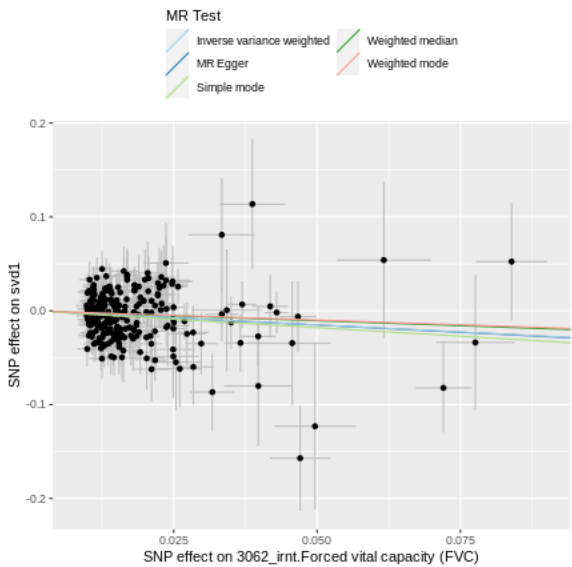
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

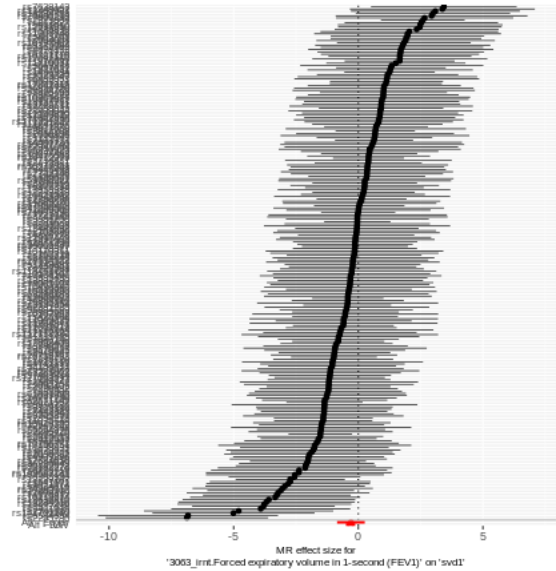


(c) Comparison of results using different MR methods

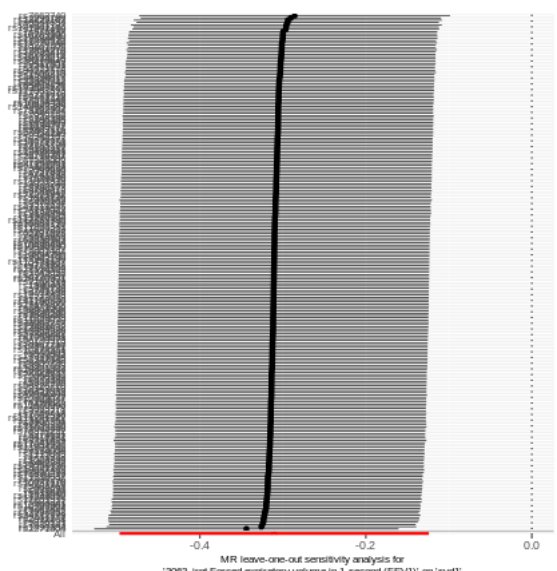


Supplement 3 Figure 36. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for forced expiratory volume in 1-second (FEV1) on ICH or SVS.

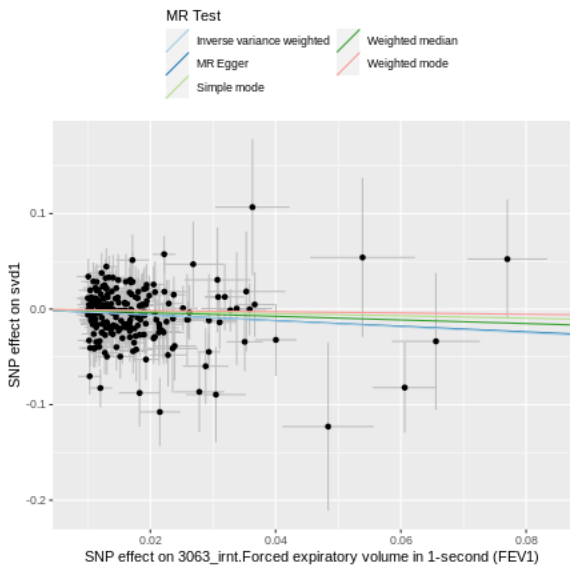
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

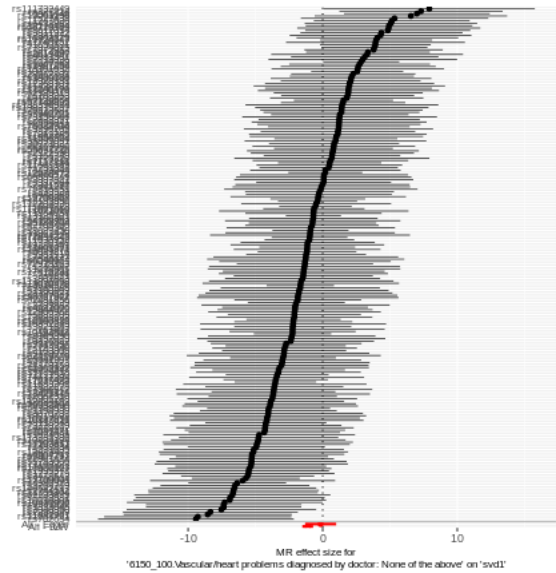


(c) Comparison of results using different MR methods

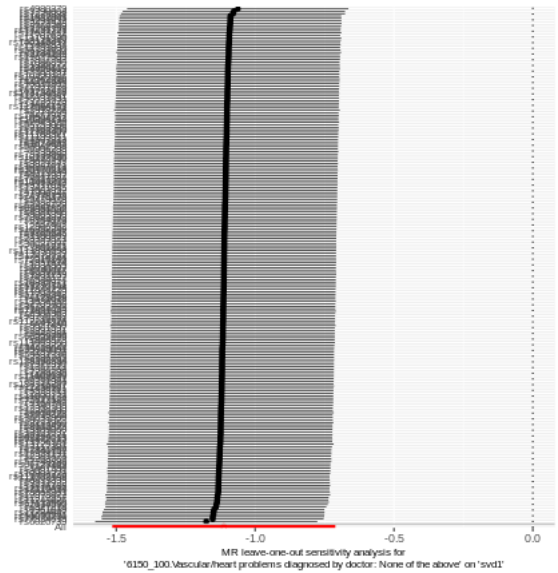


Supplement 3 Figure 37. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for none of vascular/heart problems on ICH or SVS.

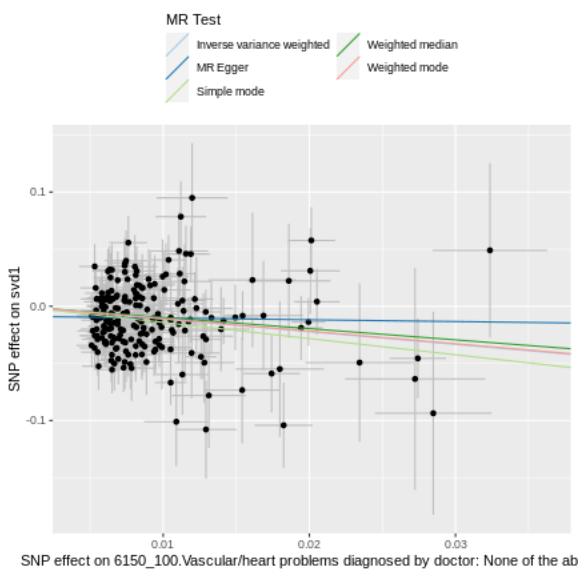
(a) Forest plot of single SNP MR



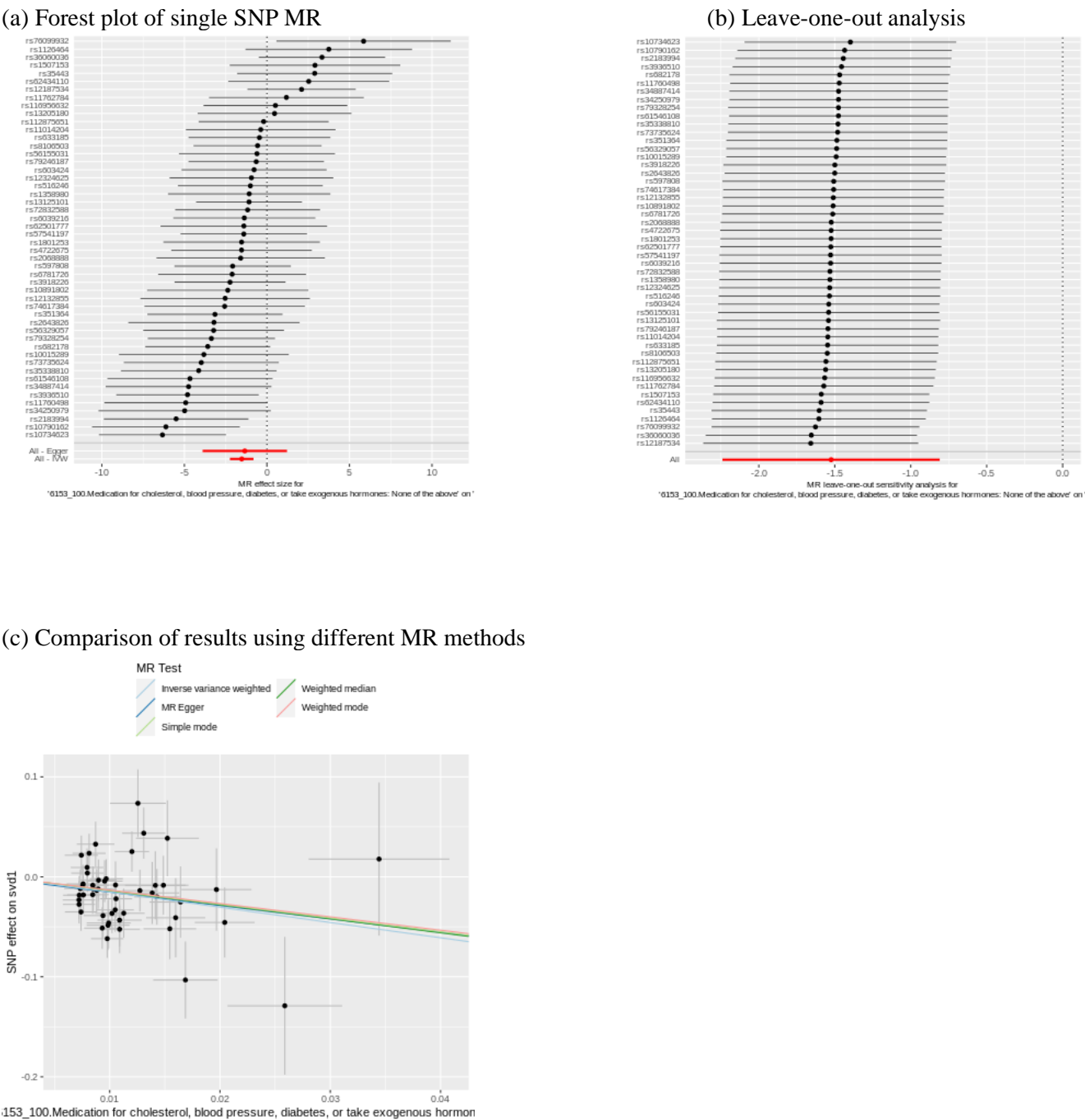
(b) Leave-one-out analysis



(c) Comparison of results using different MR methods

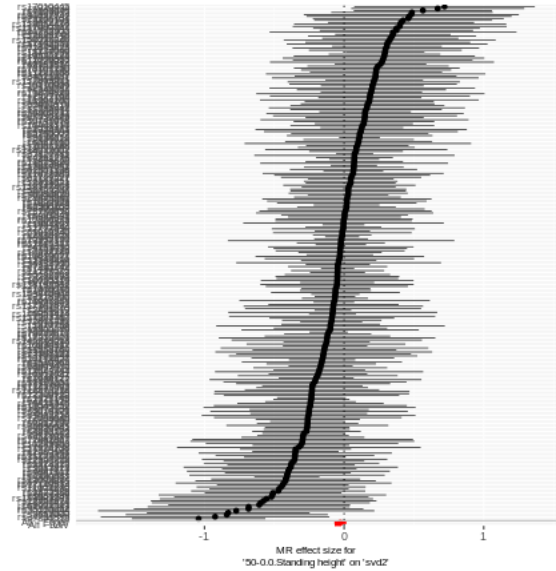


Supplement 3 Figure 38. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for no medication for cholesterol, hypertension, diabetes, no exogenous hormones on ICH or SVS.

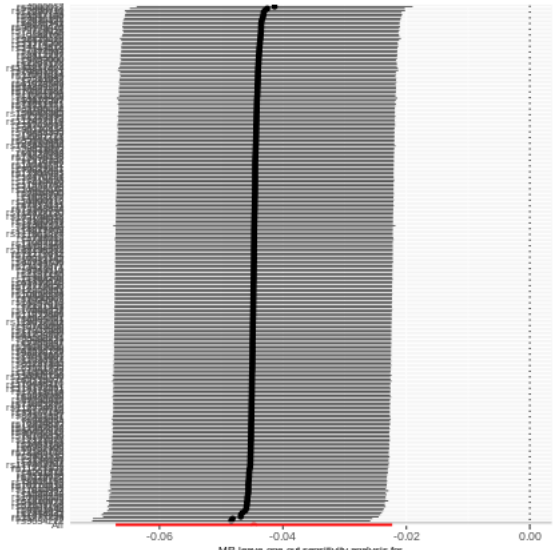


Supplement 3 Figure 39. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for standing height on lobar hemorrhage or SVS.

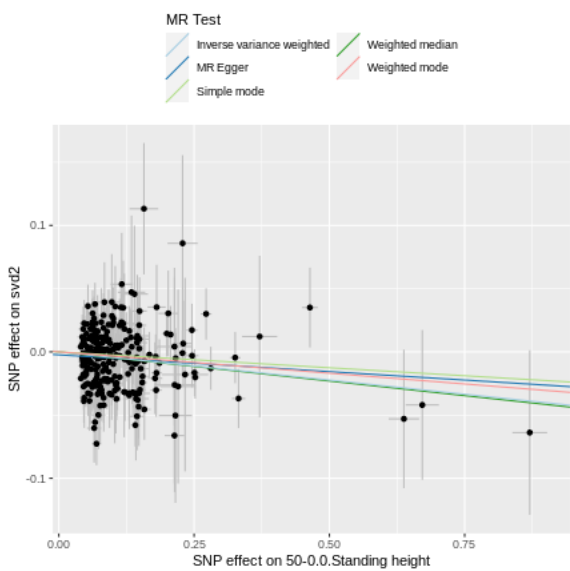
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

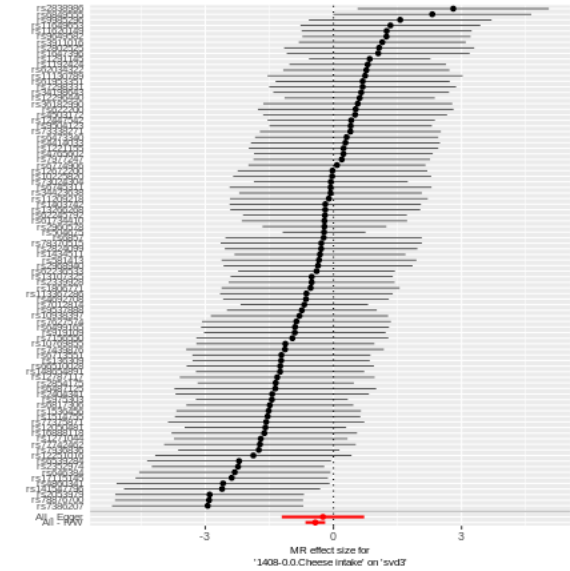


(c) Comparison of results using different MR methods

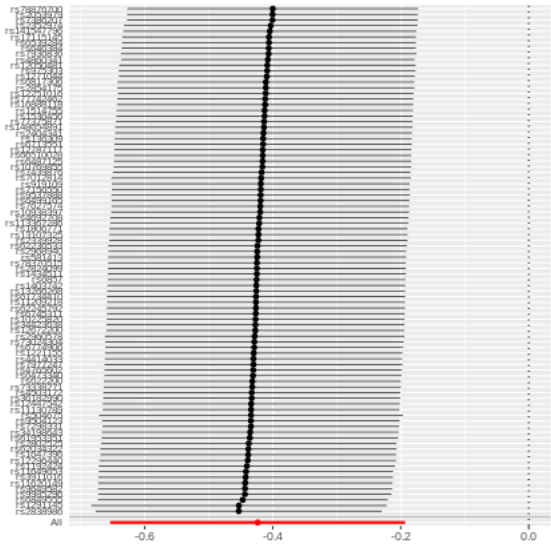


Supplement 3 Figure 40. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for cheese intake on non-lobar hemorrhage or SVS.

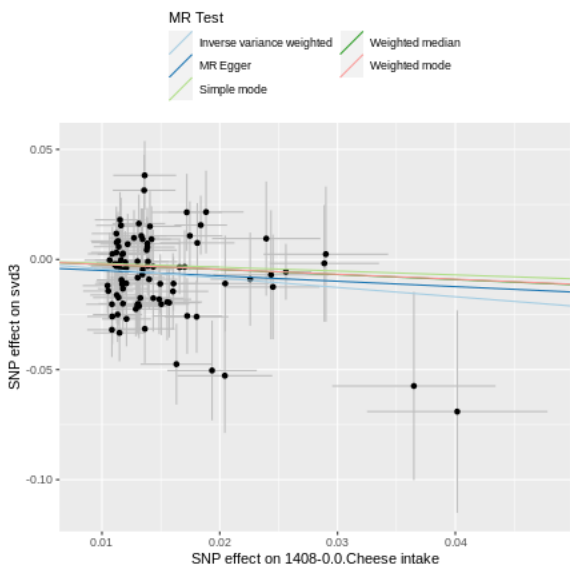
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

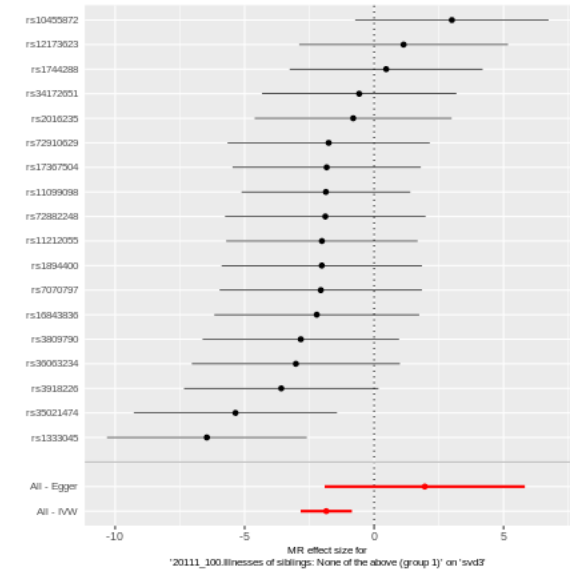


(c) Comparison of results using different MR methods

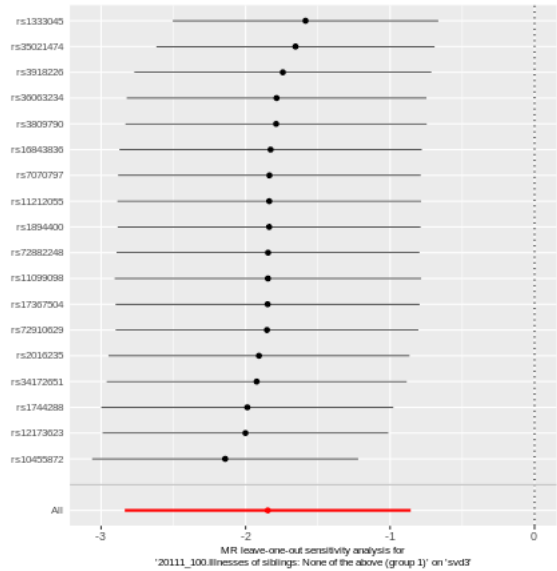


Supplement 3 Figure 41. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for none of illnesses of siblings on non-lobar hemorrhage or SVS.

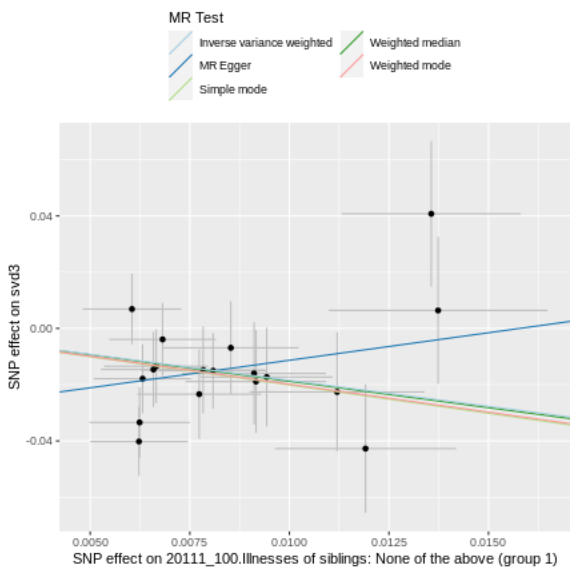
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

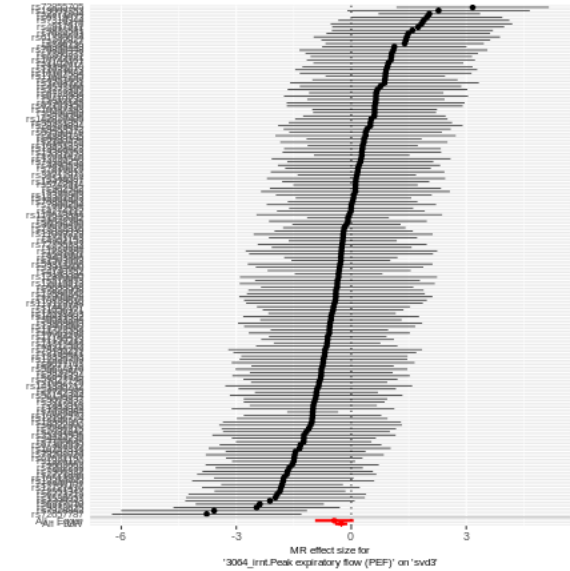


(c) Comparison of results using different MR methods

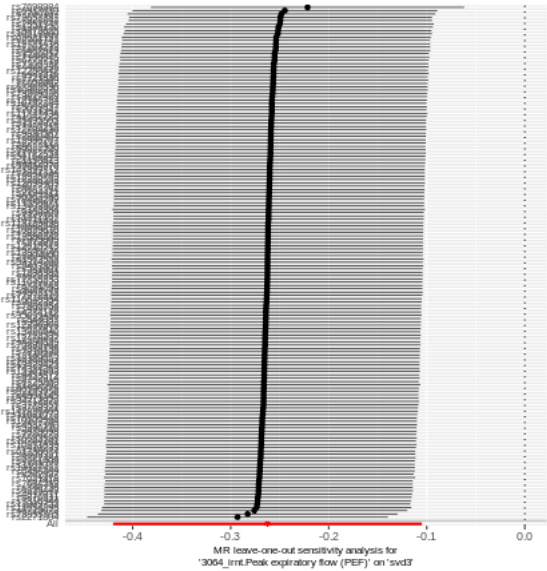


Supplement 3 Figure 42. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for peak expiratory flow (PEF) on non-lobar hemorrhage or SVS.

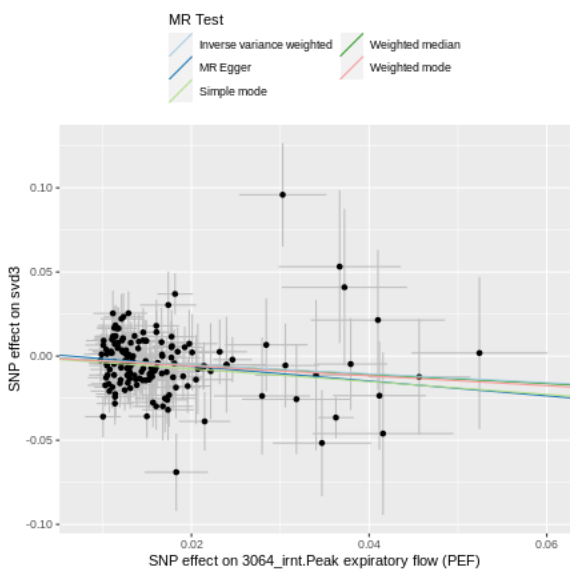
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis



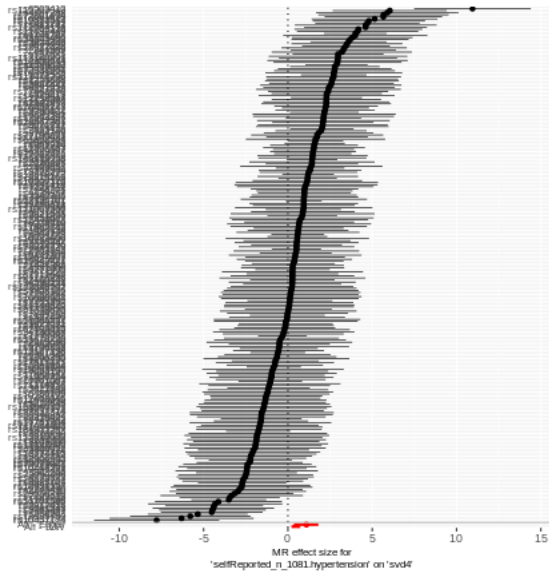
(c) Comparison of results using different MR methods



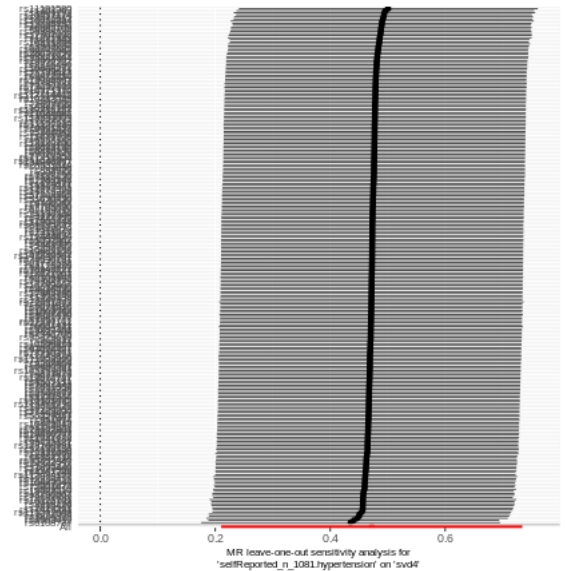
Supplement 4 The single SNP analysis, leave-one-out analyses and comparison of results using different MR methods for 10 exposures with $P_{FDR} < 0.05$ for WMH

Supplement 4 Figure 1. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for self-reported hypertension on WMH.

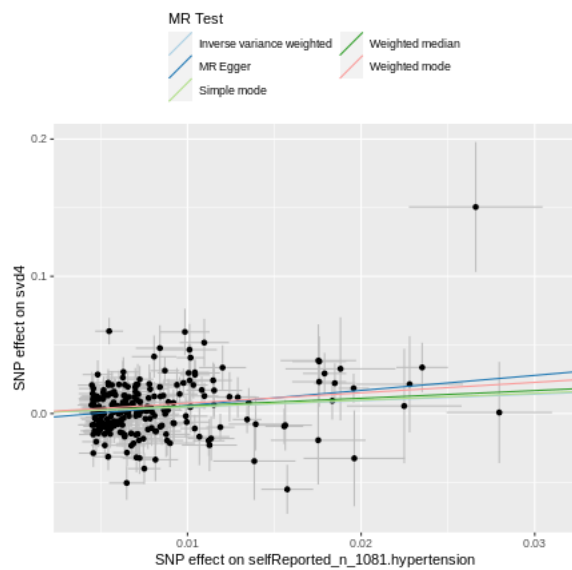
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

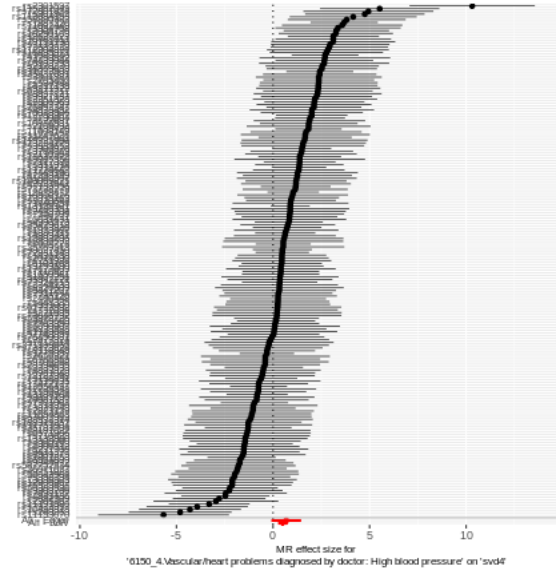


(c) Comparison of results using different MR methods

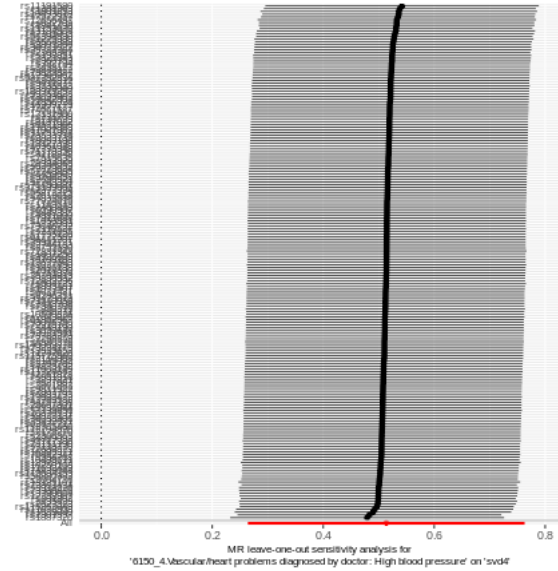


Supplement 4 Figure 2. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for hypertension diagnosed by doctor on WMH

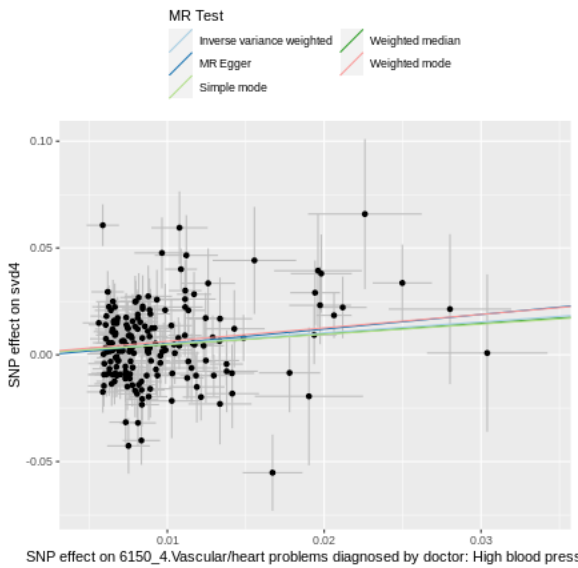
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

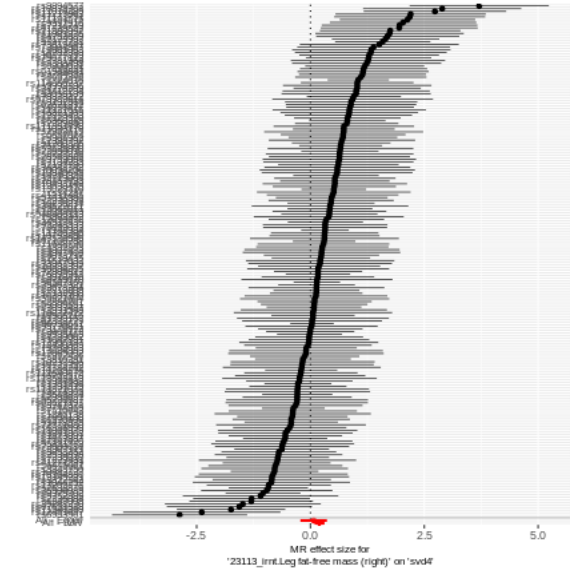


(c) Comparison of results using different MR methods

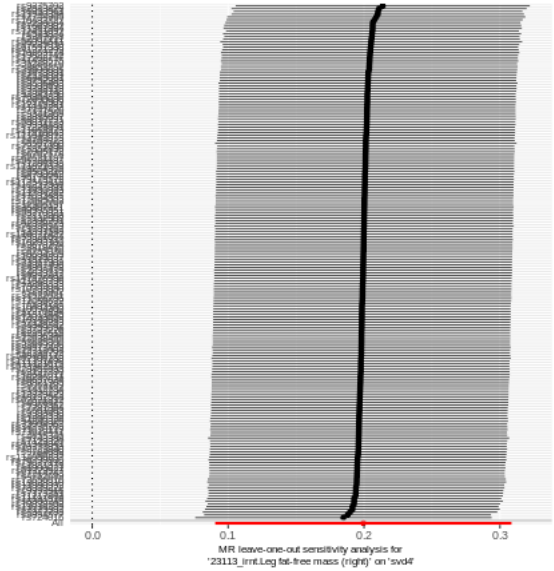


Supplement 4 Figure 3. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for leg fat-free mass (right) on WMH

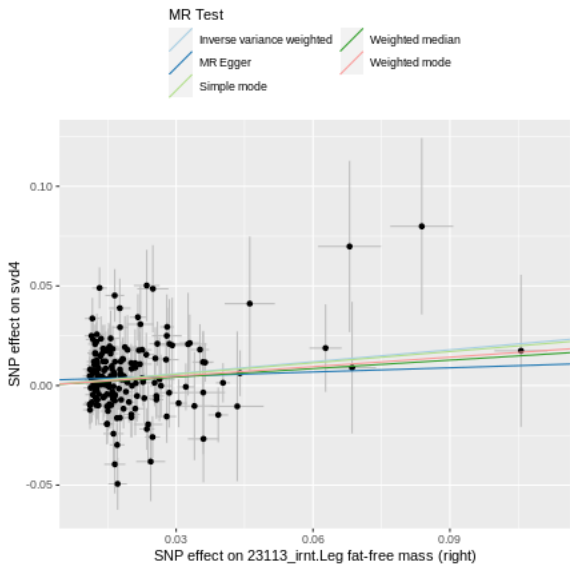
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

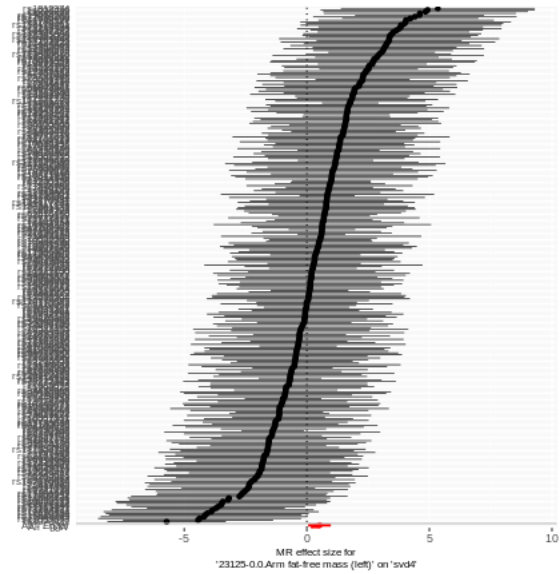


(c) Comparison of results using different MR methods

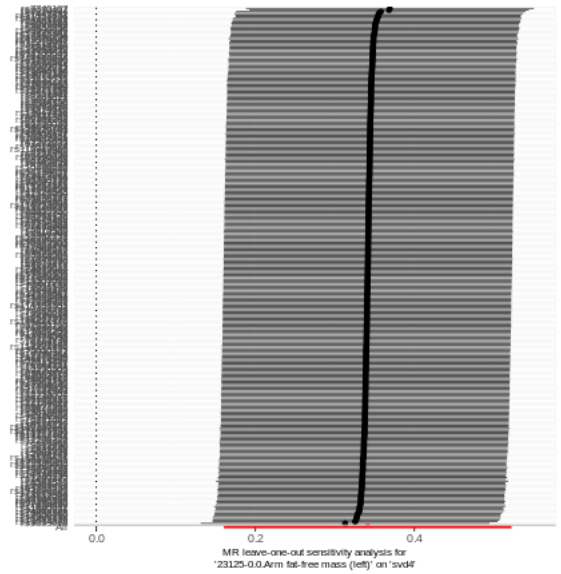


Supplement 4 Figure 4. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for arm fat-free mass (left) on WMH

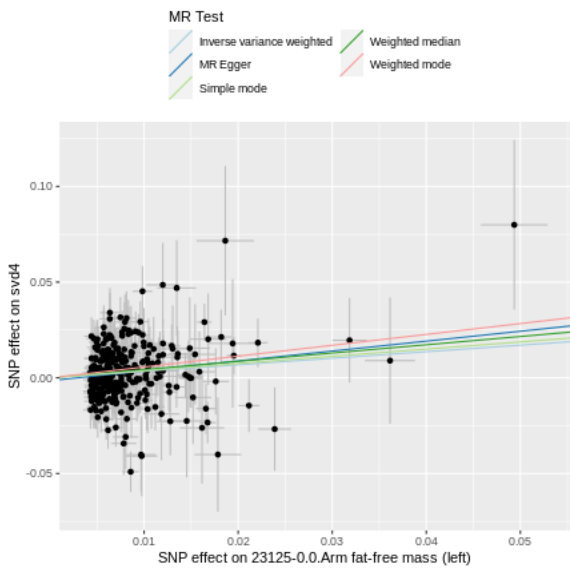
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

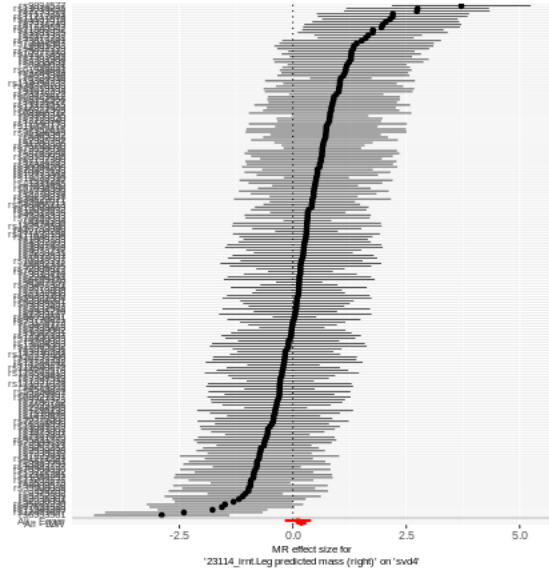


(c) Comparison of results using different MR methods

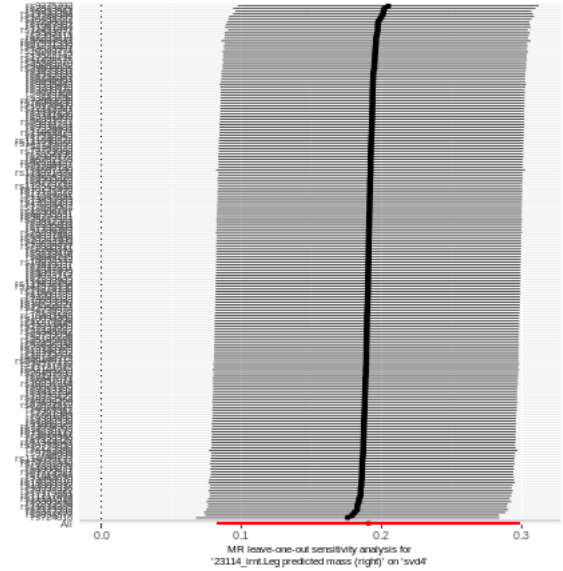


Supplement 4 Figure 5. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for leg predicted mass (right) on WMH

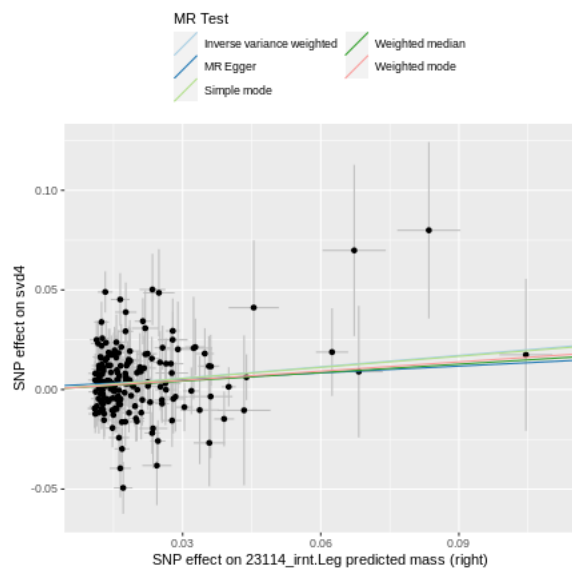
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

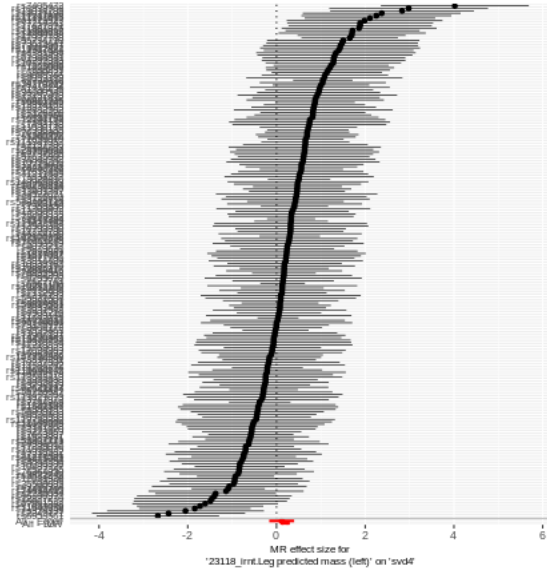


(c) Comparison of results using different MR methods

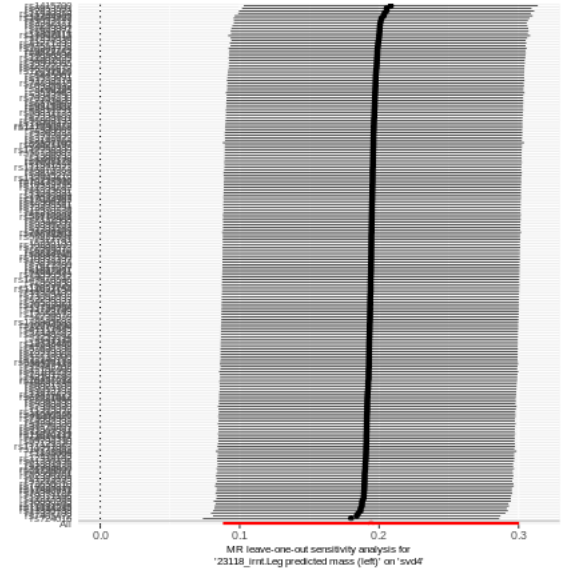


Supplement 4 Figure 6. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for leg predicted mass (left) on WMH

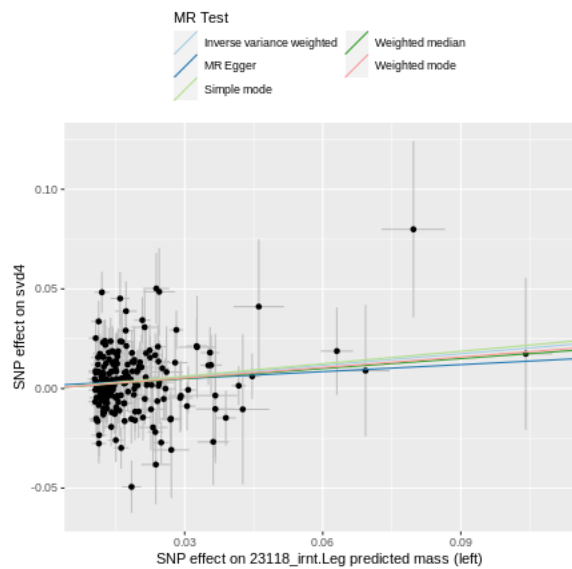
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

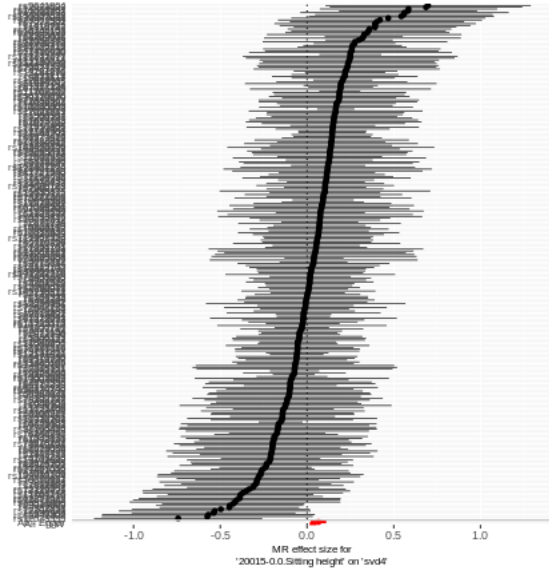


(c) Comparison of results using different MR methods

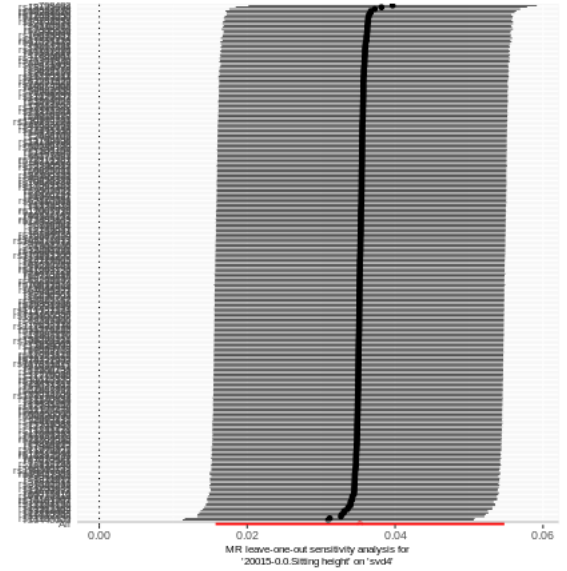


Supplement 4 Figure 7. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for sitting height on WMH

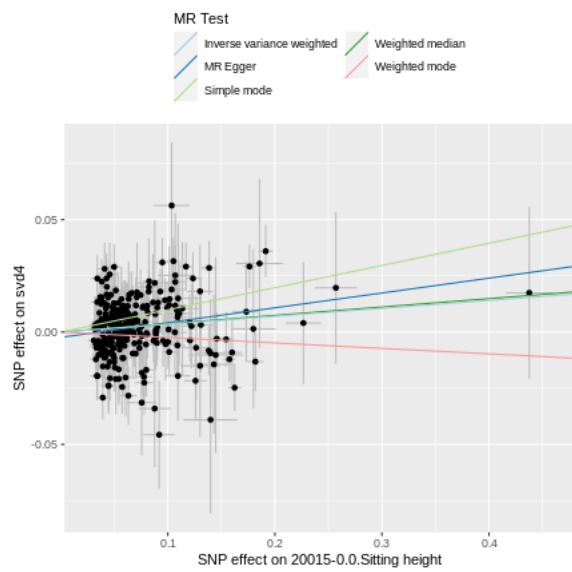
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

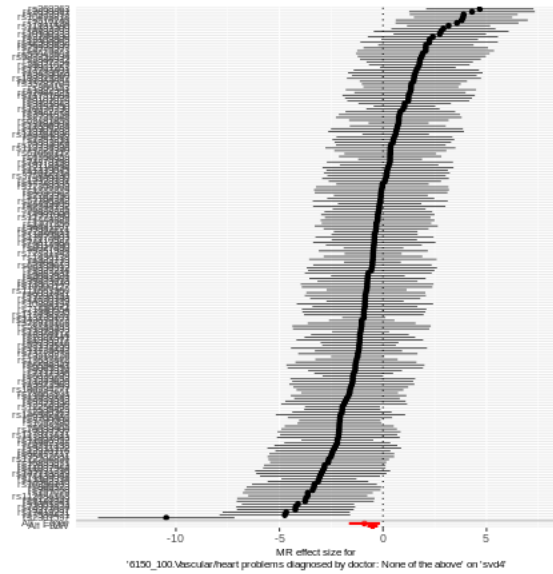


(c) Comparison of results using different MR methods

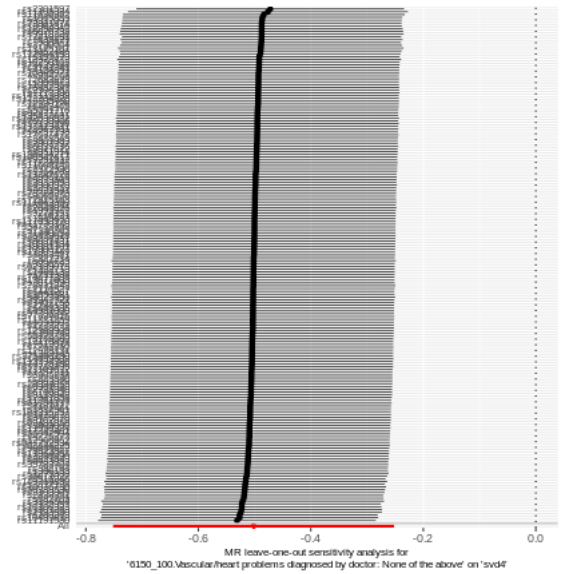


Supplement 4 Figure 8. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for none of vascular/heart problems on WMH

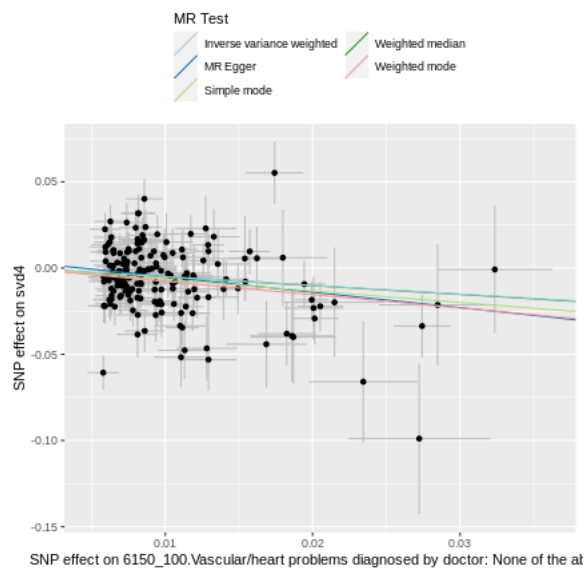
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

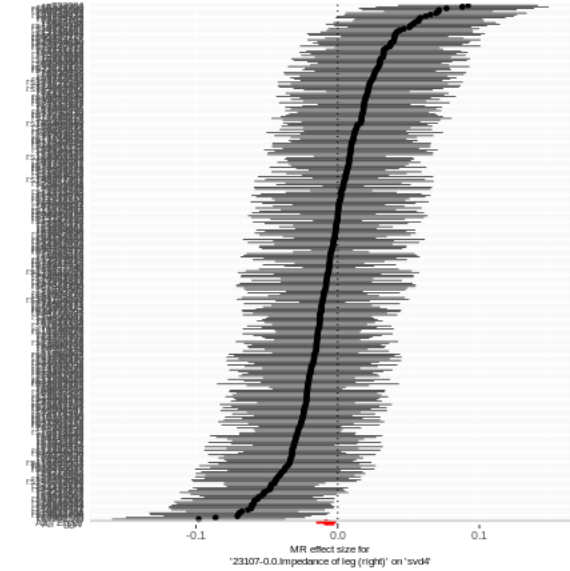


(c) Comparison of results using different MR methods

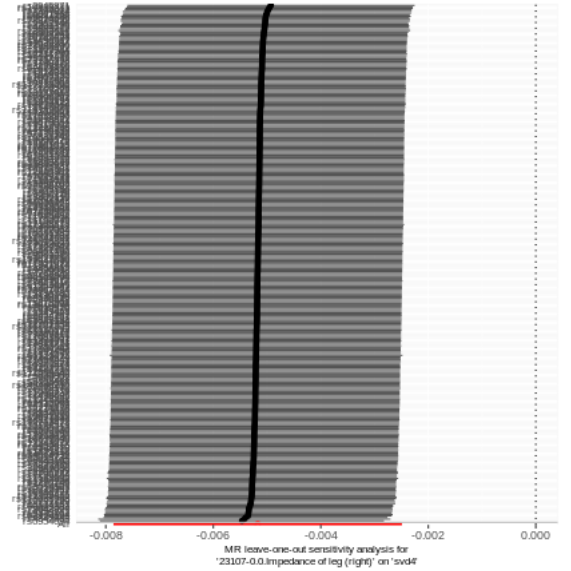


Supplement 4 Figure 9. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for impedance of leg (right) on WMH

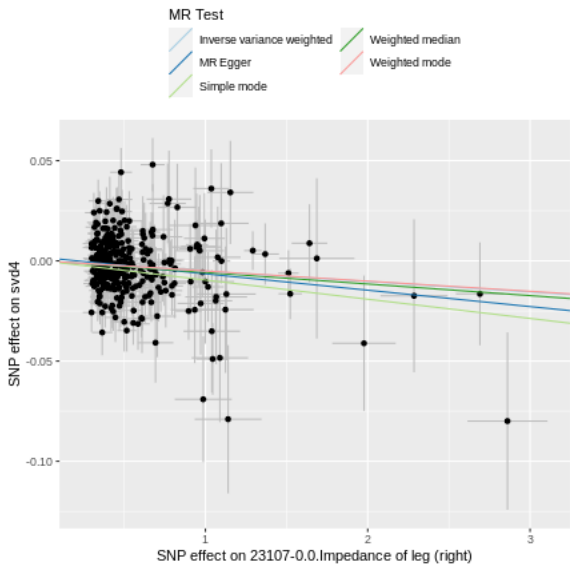
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis

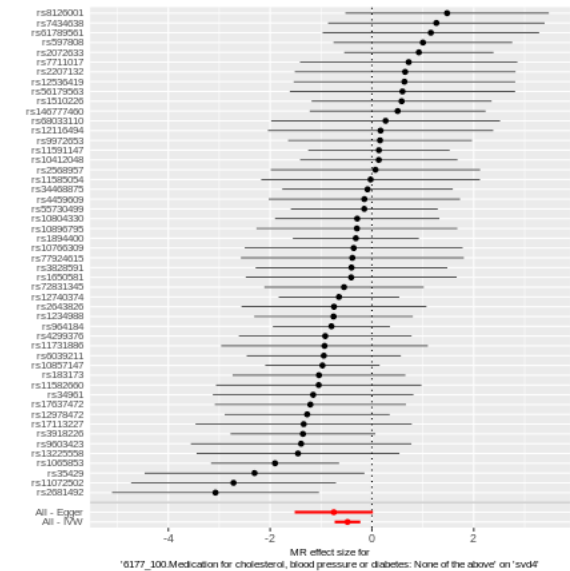


(c) Comparison of results using different MR methods

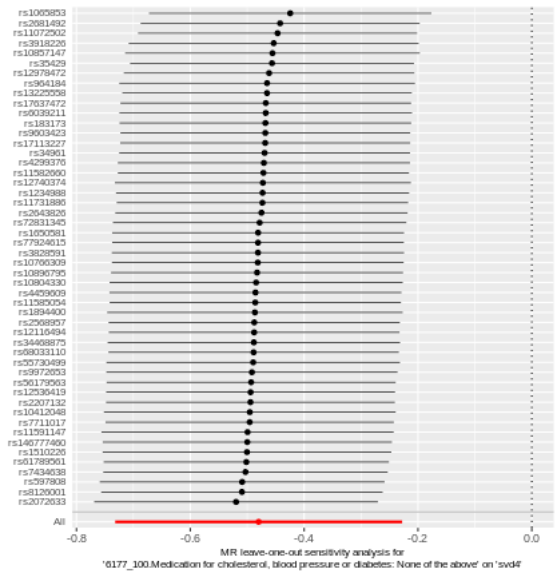


Supplement 4 Figure 10. The single SNP analysis, leave-one-out analysis, comparison of results using different MR methods for no medication for cholesterol, hypertension or diabetes on WMH

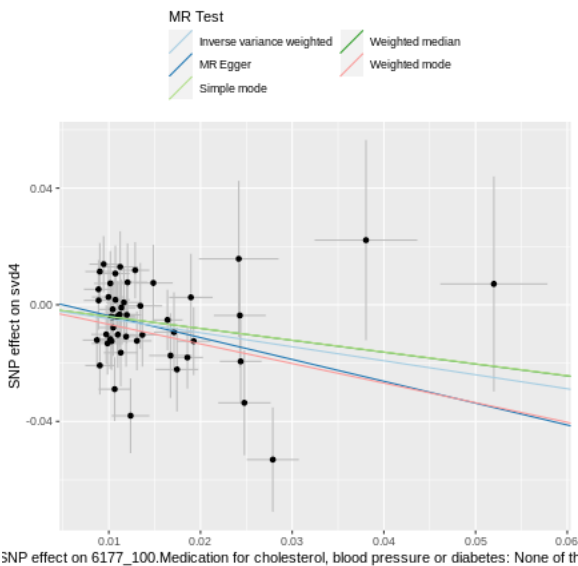
(a) Forest plot of single SNP MR



(b) Leave-one-out analysis



(c) Comparison of results using different MR methods



Supplement 5 Table I. IVW analyses, sensitivity, horizontal pleiotropy and heterogeneity analyses for exposures with $P_{FDR}<0.05$ for MD.

Risk exposures	IVW			Sensitivity analysis		Horizontal pleiotropy	Heterogeneity
	SNPs	IVW P	FDR P	MR Egger P	Weighted Median P	Egger intercept P	IVW Q test P
Hypertension: self-reported ^{a,b}	266	3.64E-06	0.002	0.022	7.18E-04	0.449	1.85E-05
Hypertension: diagnosed by doctor ^{a,b}	263	4.02E-06	0.002	0.009	5.81E-04	0.272	2.85E-07
Antihypertensive medication ^b	56	4.37E-04	0.026	0.007	2.65E-04	0.070	0.002
Family relationship satisfaction ^a	6	2.22E-04	0.036	0.342	5.29E-03	0.948	0.249
Protective exposures							
Leg fat percentage (left) ^b	337	8.90E-04	0.040	0.264	9.38E-02	0.956	0.003
Trunk fat percentage ^b	346	2.40E-04	0.016	0.138	2.59E-02	0.768	1.61E-05
Number of cigarettes previously smoked daily ^{a,b}	13	3.40E-04	0.049	0.143	2.57E-03	0.884	0.497
Lamb/mutton intake ^b	16	4.20E-05	0.004	0.160	3.15E-03	0.466	0.294
Father still alive ^a	5	1.11E-05	0.003	0.170	1.24E-04	0.323	0.415
Inflammatory polyarthropathies ^b	8	1.73E-04	0.014	0.319	2.36E-02	0.827	0.487
Connective tissue disorder ^{a,b}	6	2.72E-05	0.005	0.118	5.19E-04	0.435	0.383
Intestinal malabsorption ^b	13	3.30E-05	0.004	0.018	2.49E-02	0.738	0.279
Malabsorption/coeliac disease ^b	17	2.13E-05	0.004	0.001	2.61E-05	0.185	0.049

Thirteen exposures presented IVW $P_{FDR}<0.05$ for mean diffusivity (MD). Exposures with odds ratios greater than 1 were considered as risk exposures, while exposures with odds ratios less than 1 were considered as protective exposures. ^aData derived from analyses with instruments of $p<1e-6$; ^bData derived from analyses with instruments of $p<5e-8$; ^{a,b}Data derived from analyses with instruments of $p<1e-6$, but this exposure showed $P_{FDR}<0.05$ with both sets of instruments.

Abbreviations: MD, mean diffusivity; SNP, single nucleotide polymorphism; IVW, Inverse Variance Weighted; FDR, false discovery rate; Q test, Cochran's Q test.

Supplement 6 Reverse causation analysis for significant modifiable exposures.

Exposure: ICH or SVS	SNPs	IVW OR (95% CI)	IVW P
Time spent watching television	3	0.99(0.96-1.03)	0.645
None of qualifications	3	1.00(0.99-1.01)	0.840
Frequency of tiredness / lethargy in last 2 weeks	8	1.00(0.99-1.02)	0.904
Days /week of moderate physical activity >10 minutes	3	1.10(1.04 -1.16)	0.001
Variation in diet	8	0.98(0.96-1.00)	0.016
Usual walking pace	3	1.04(1.01-1.07)	0.009
A /AS levels qualifications	3	1.01(0.99-1.02)	0.487
College or University degree	3	1.00(0.99-1.01)	0.763
Forced vital capacity (FVC)	3	1.03(0.99-1.06)	0.108
Forced expiratory volume in 1-second (FEV1)	3	1.03(0.99-1.06)	0.138
Peak expiratory flow (PEF)	3	1.01(0.97-1.05)	0.777
Exposure: Non-lobar hemorrhage or SVS			
Time spent watching television	11	1.00(0.97-1.02)	0.825
None of qualifications	11	1.00(0.99-1.01)	0.925
Days /week of moderate physical activity >10 minutes	11	1.03(0.97-1.10)	0.340
Usual walking pace	11	1.01(0.99-1.03)	0.159
A /AS levels qualifications	11	1.00(0.98-1.01)	0.470
College or University degree	11	1.00(1.00-1.01)	0.325
Forced vital capacity (FVC)	11	1.03(1.00-1.05)	0.065
Forced expiratory volume in 1-second (FEV1)	11	1.03(1.00-1.05)	0.045
Peak expiratory flow (PEF)	11	1.01(0.98-1.03)	0.703

In reverse causation analysis, each of the listed modifiable factors was individually used as an outcome trait, with the trait “all location ICH or SVS” or “non-lobar hemorrhage or SVS” being the exposure trait. The analysis was performed with instruments of $p < 1e-6$. The trait “lobar hemorrhage or SVS” was not analyzable as no instrumental SNPs of $p < 1e-6$ were present for any of those outcome traits. Abbreviations: ICH, intracerebral hemorrhage; SVS, small vessel stroke; SNP, single nucleotide polymorphism.