

## SUPPLEMENTAL MATERIAL

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## **Supplement 1. GWAS data sets used in the present MR analysis**

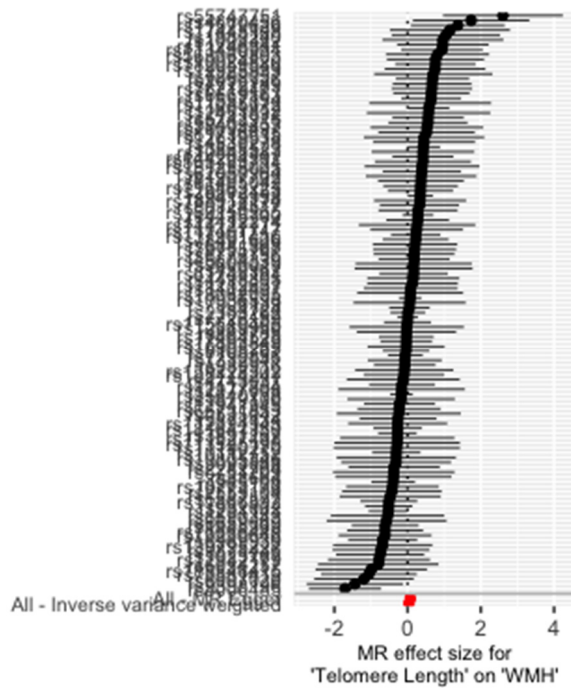
<b>Traits</b>	<b>PubMed ID</b>	<b>Population (Proportion)</b>	<b>Sample size or Cases/Controls</b>
LTL	34611362	European (94%)	472174
GrimAge	34187551	European	34710
PhenoAge	34187551	European	34710
HannumAge	34187551	European	34710
Intrinsic HorvathAge acceleration	34187551	European	34710
WMH volume	32358547	European	18381
FA	32358547	European	17663
MD	32358547	European	17467
lacunar stroke	33773637	European	6030/248929
all location BMB	32913026	European (94%)	3556/25806
lobar BMB	32913026	European (94%)	2179/25806
mixed or deep BMB	32913026	European (94%)	1293/25806
all location ICH or SVS	31430377	European	6255/233058
lobar ICH or SVS	31430377	European	5240/233058
non-lobar ICH or SVS	31430377	European	5500/233058

**Supplement 2.** The single SNP analysis and leave-one-out analysis for exposures on outcomes

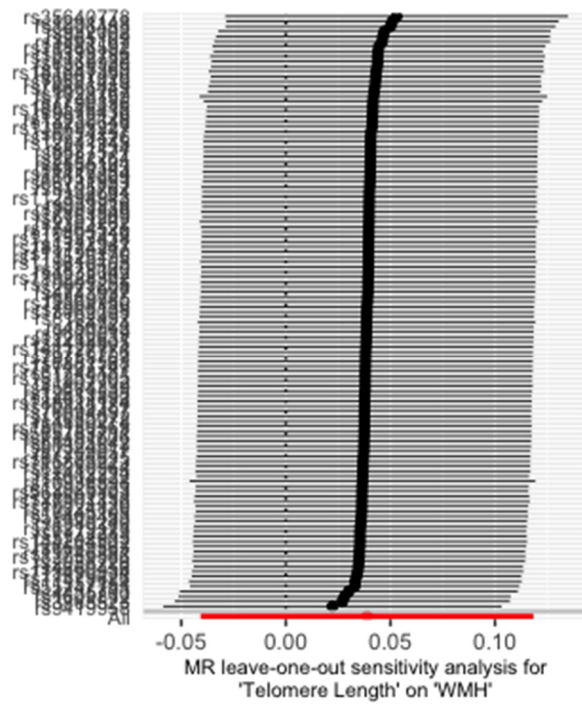
Supplement 2 Figure 1. The single SNP analysis and leave-one-out analysis for LTL on WMH volume

(a) Forest plot of single SNP MR

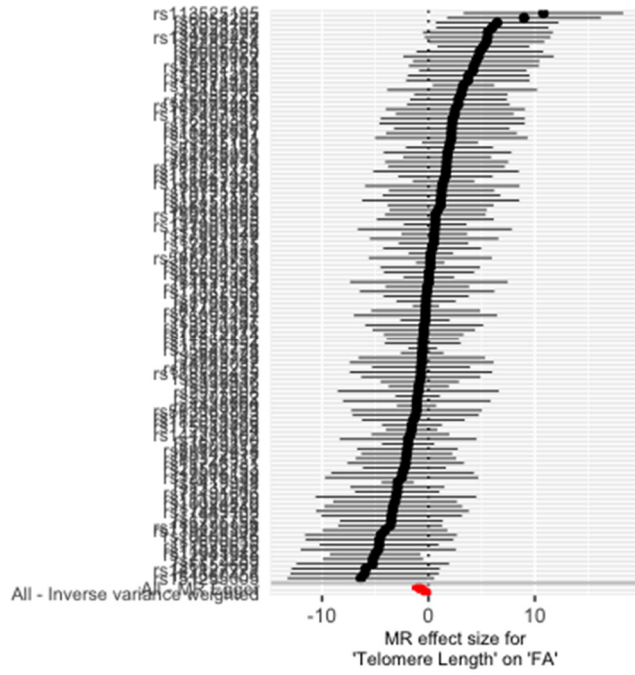




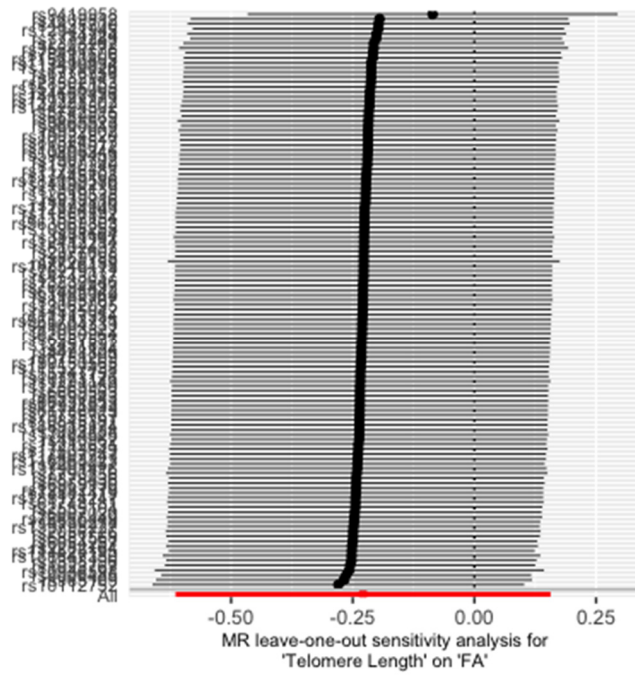
(b) Leave-one-out analysis



Supplement 2 Figure 2. The single SNP analysis and leave-one-out analysis for LTL on FA  
(a) Forest plot of single SNP MR

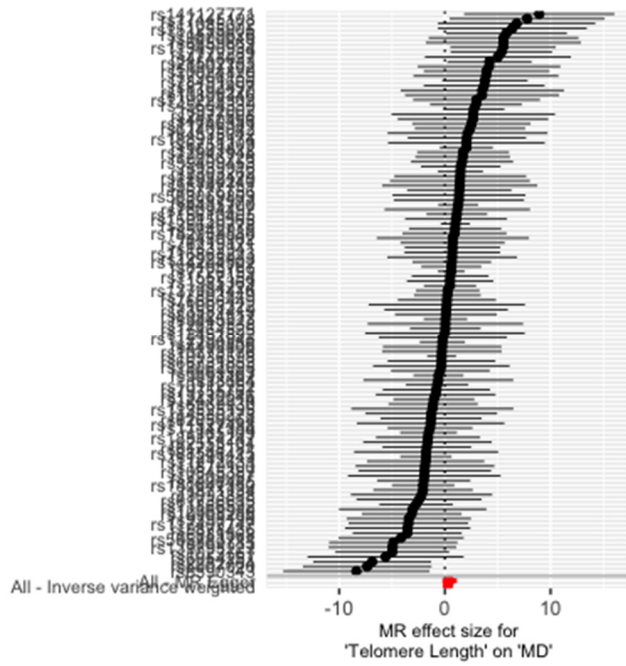


(b) Leave-one-out analysis

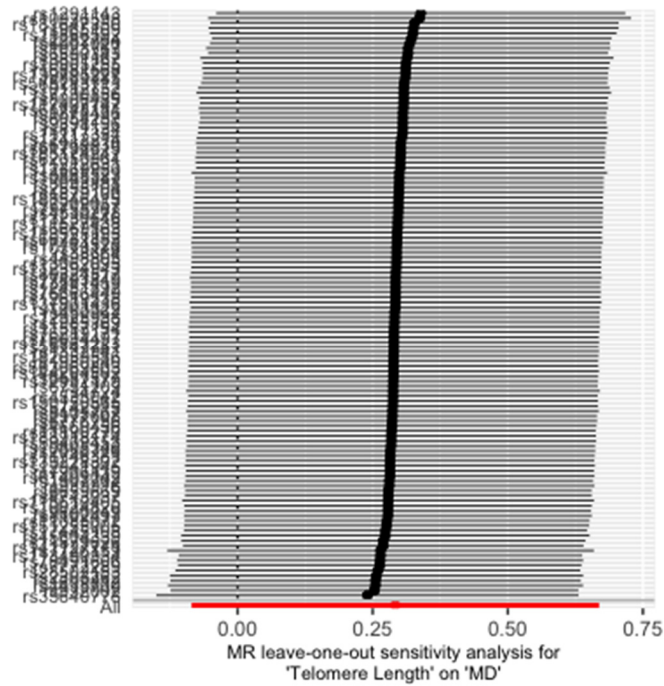


Supplement 2 Figure 3. The single SNP analysis and leave-one-out analysis for LTL on MD

(a) Forest plot of single SNP MR

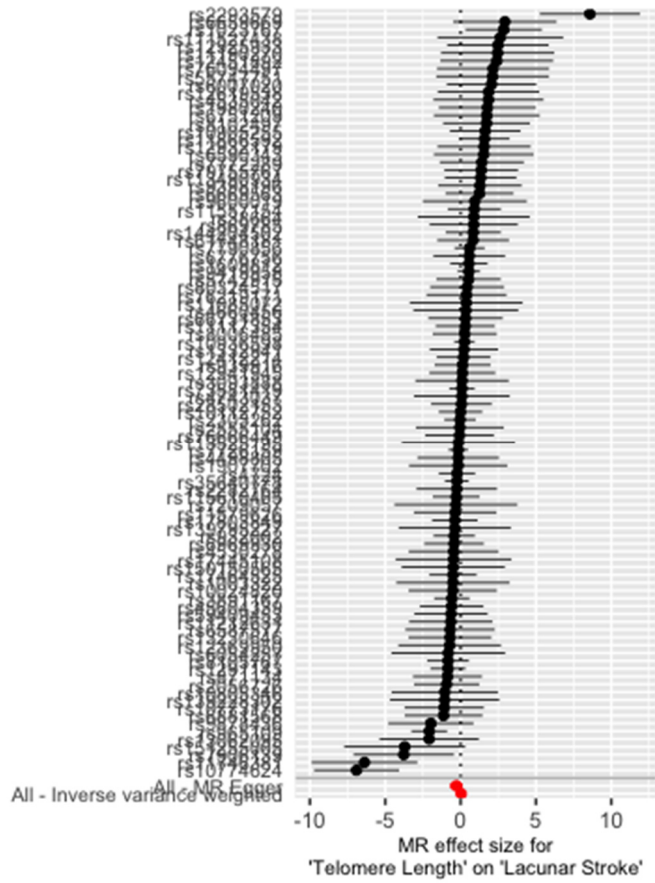


(b) Leave-one-out analysis

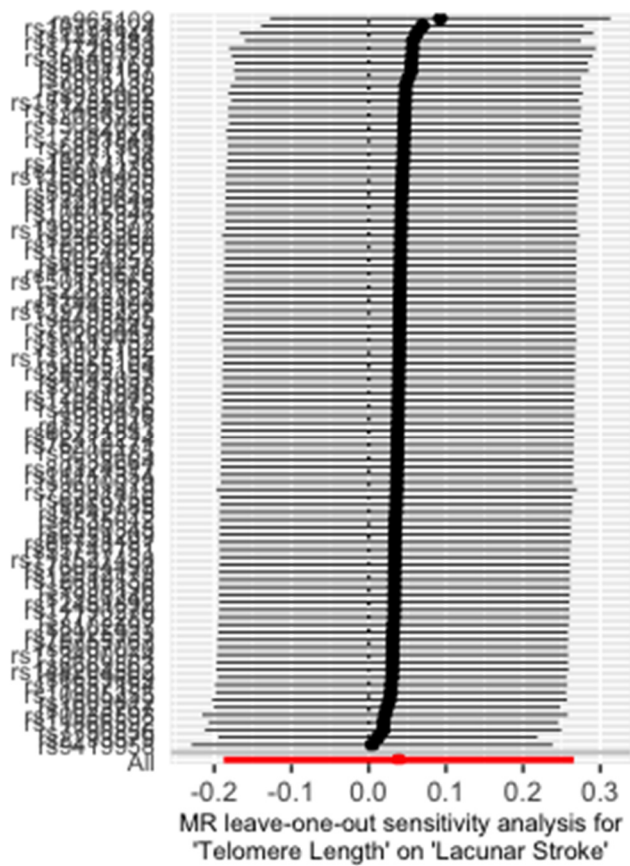


Supplement 2 Figure 4. The single SNP analysis and leave-one-out analysis for LTL on lacunar stroke

(a) Forest plot of single SNP MR

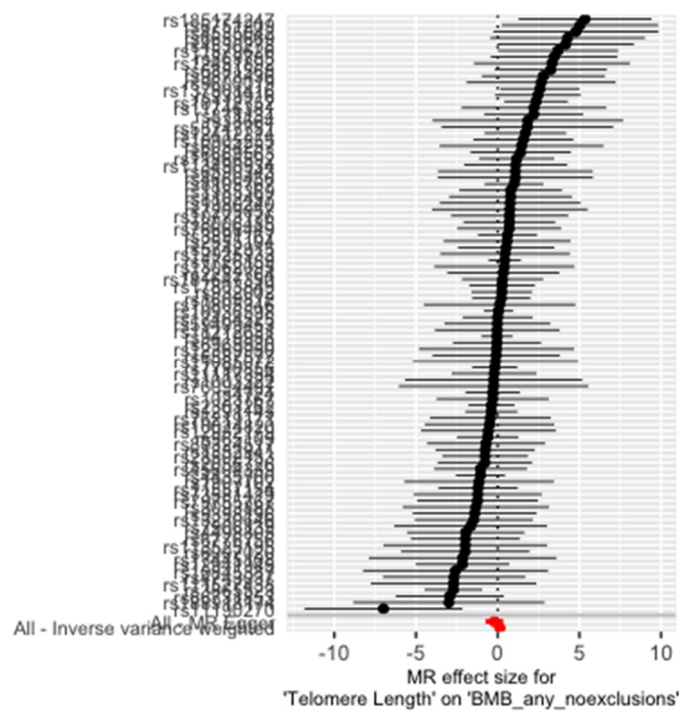


(b) Leave-one-out analysis

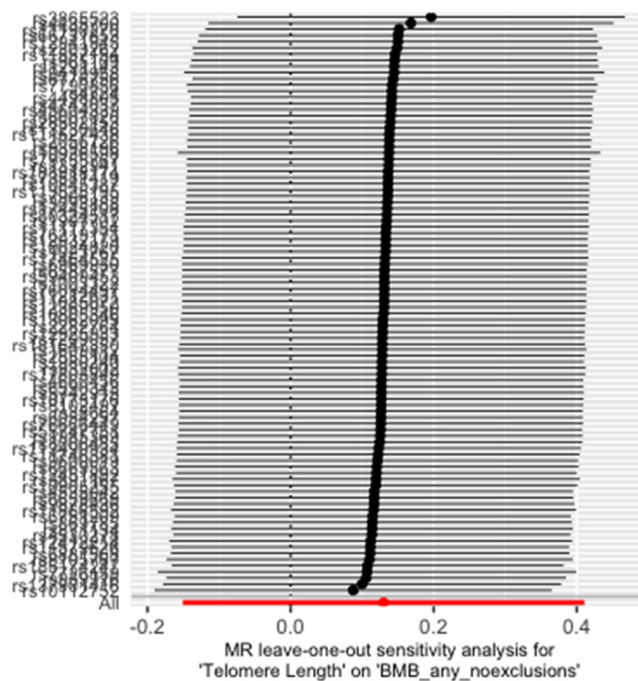


Supplement 2 Figure 5. The single SNP analysis and leave-one-out analysis for LTL on all location BMB

(a) Forest plot of single SNP MR

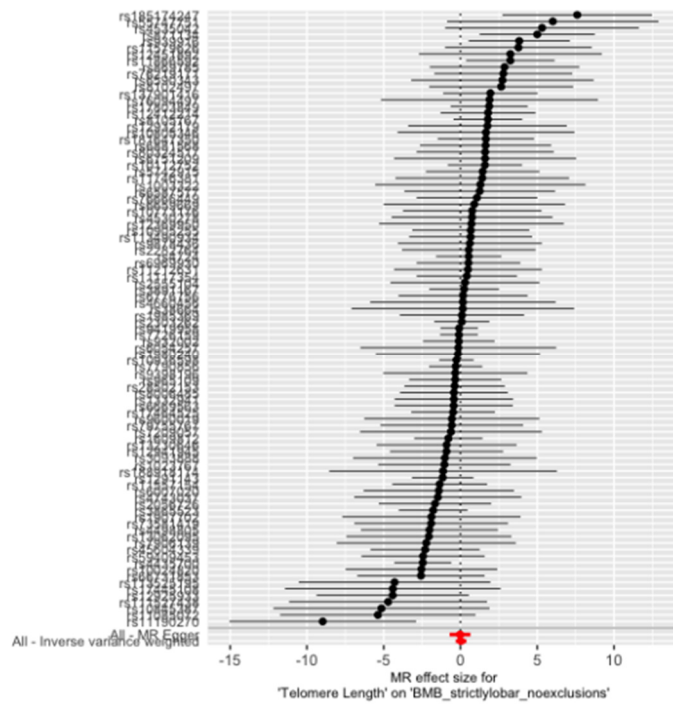


(b) Leave-one-out analysis

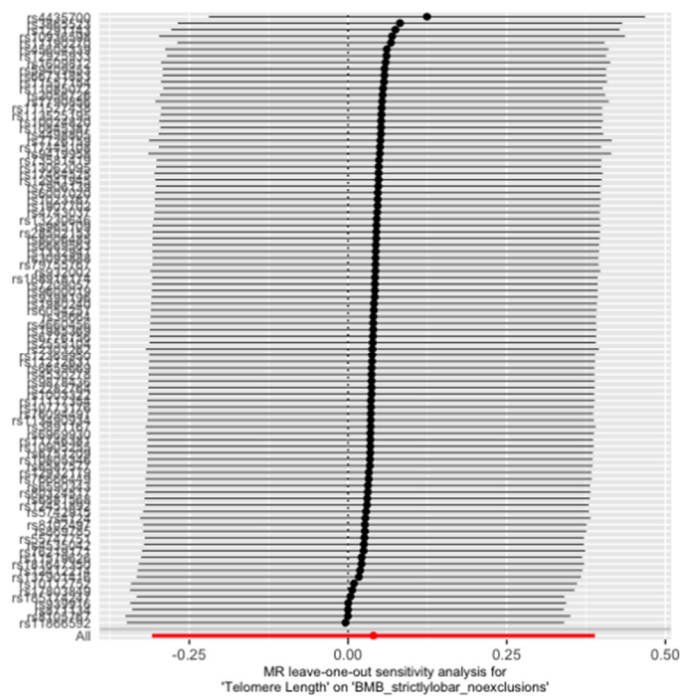


Supplement 2 Figure 6. The single SNP analysis and leave-one-out analysis for LTL on lobar BMB

(a) Forest plot of single SNP MR

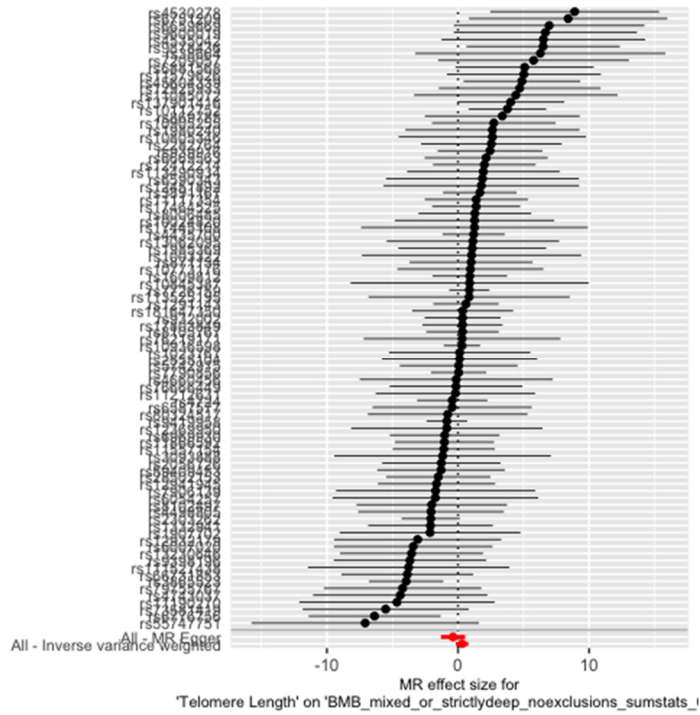


(b) Leave-one-out analysis

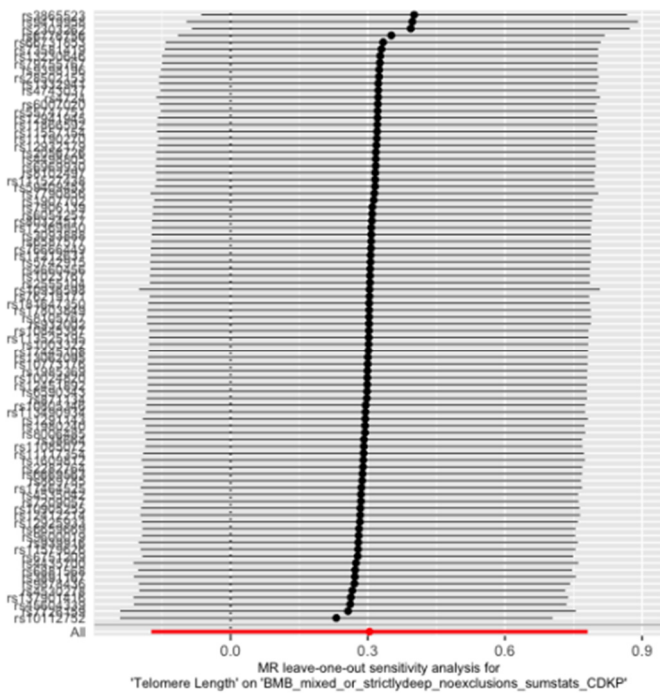


Supplement 2 Figure 7. The single SNP analysis and leave-one-out analysis for LTL on mixed or deep BMB

(a) Forest plot of single SNP MR



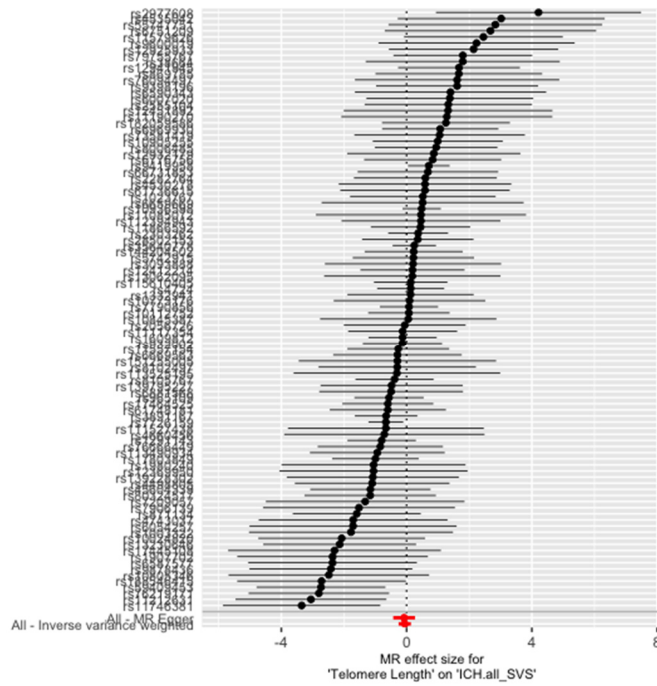
(b) Leave-one-out analysis



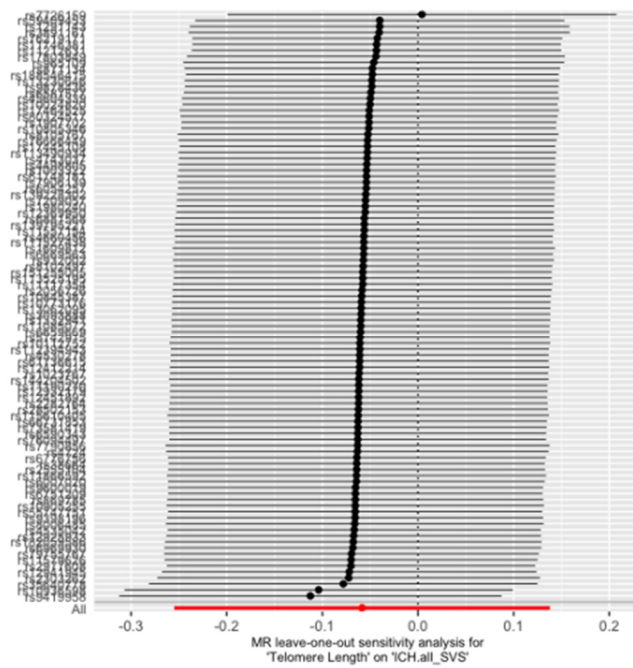
Supplement 2 Figure 8. The single SNP analysis and leave-one-out analysis for LTL on all location ICH or SVS

(a) Forest plot of single SNP MR





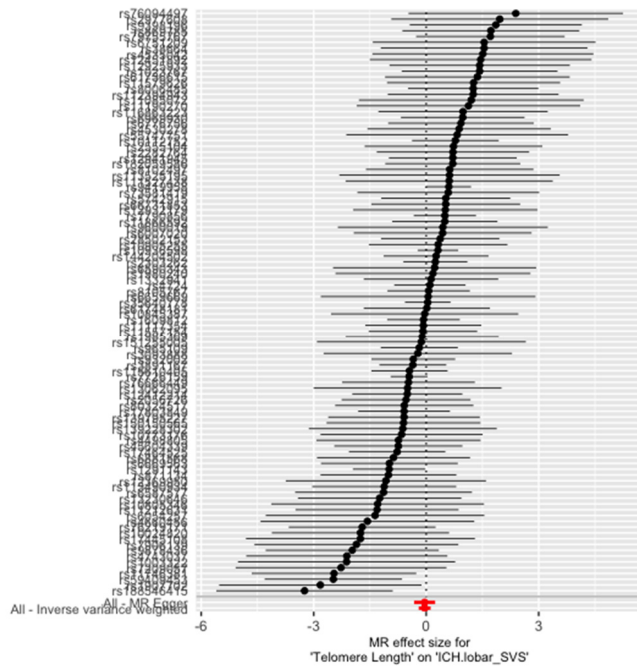
(b) Leave-one-out analysis



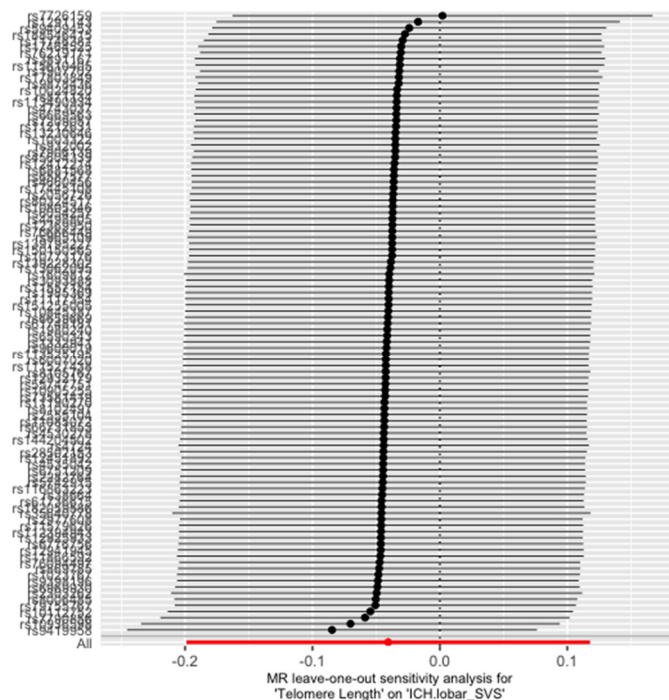
Supplement 2 Figure 9. The single SNP analysis and leave-one-out analysis for LTL on lobar ICH or SVS

(a) Forest plot of single SNP MR



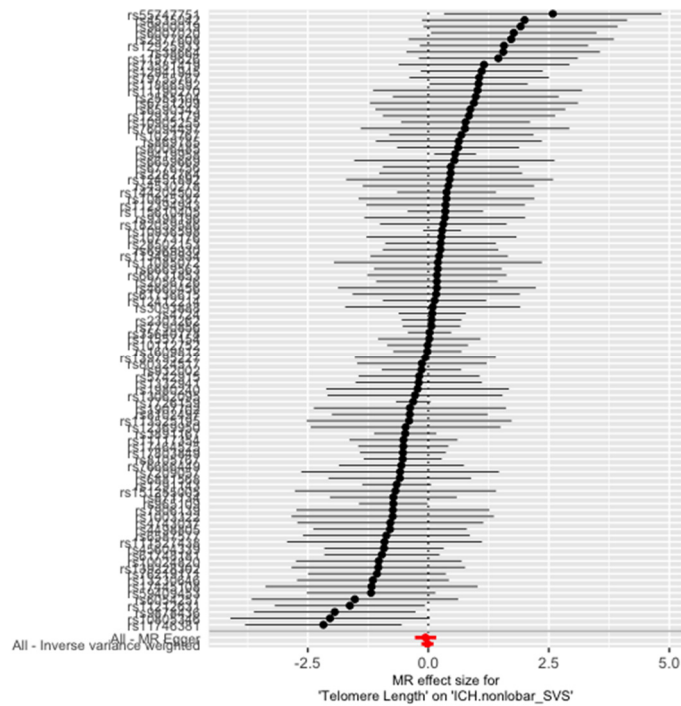


(b) Leave-one-out analysis

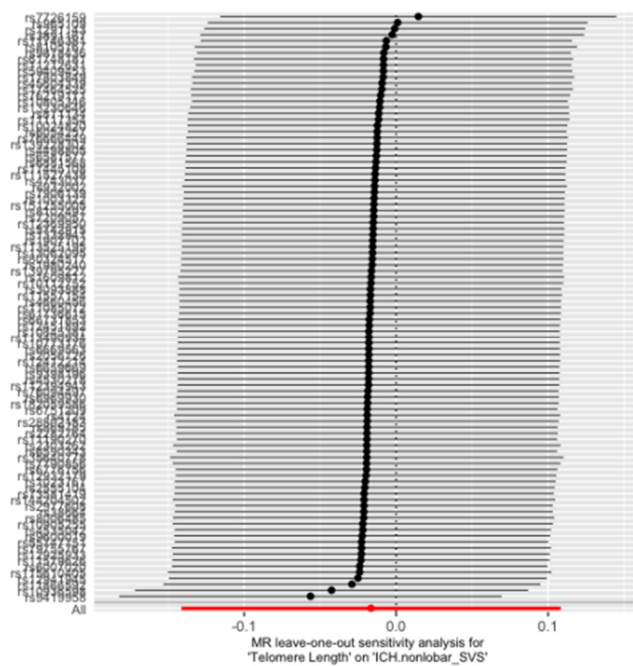


Supplement 2 Figure 10. The single SNP analysis and leave-one-out analysis for LTL on non-lobar ICH or SVS

(a) Forest plot of single SNP MR

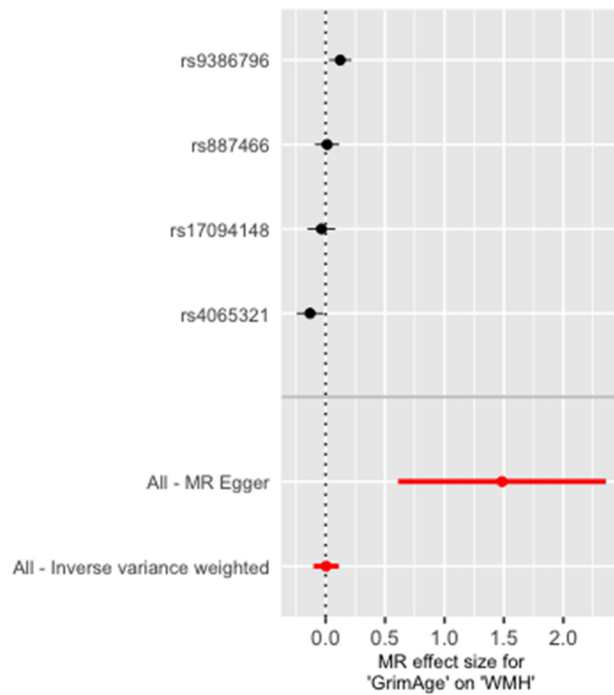


(b) Leave-one-out analysis

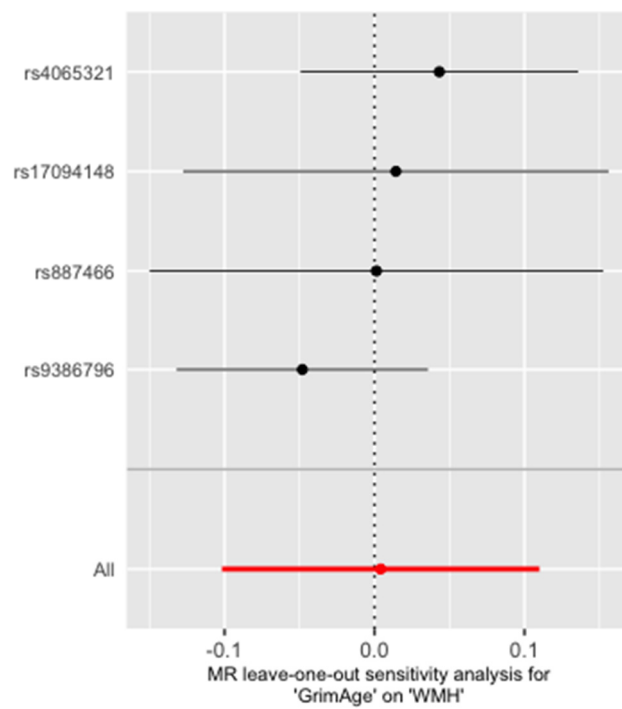


Supplement 2 Figure 11. The single SNP analysis and leave-one-out analysis for GrimAge on WMH volume

(a) Forest plot of single SNP MR

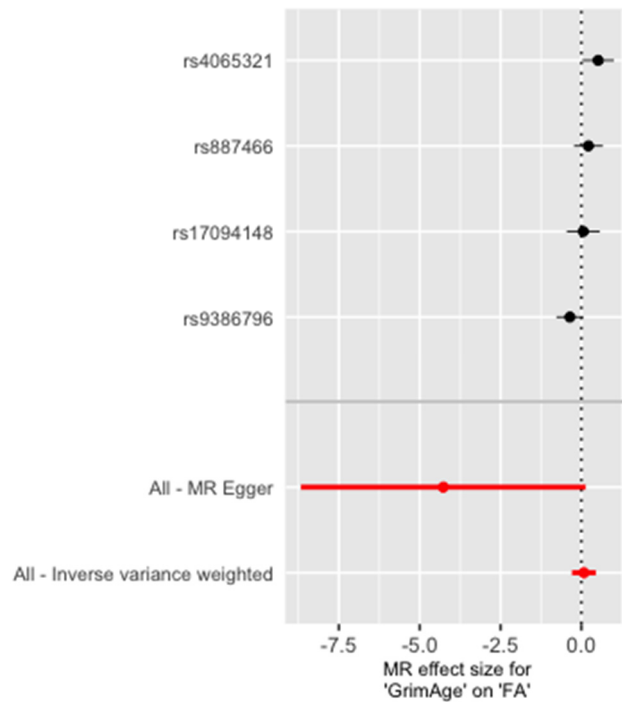


(b) Leave-one-out analysis

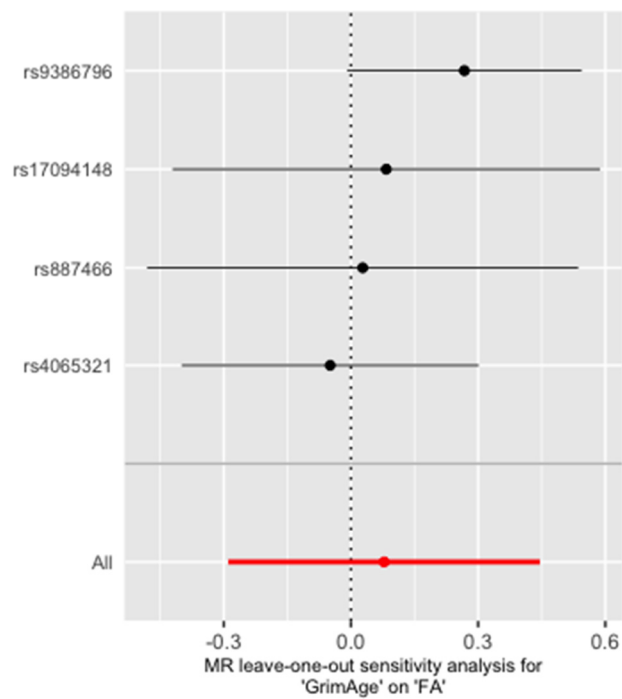


Supplement 2 Figure 12. The single SNP analysis and leave-one-out analysis for GrimAge on FA

(a) Forest plot of single SNP MR

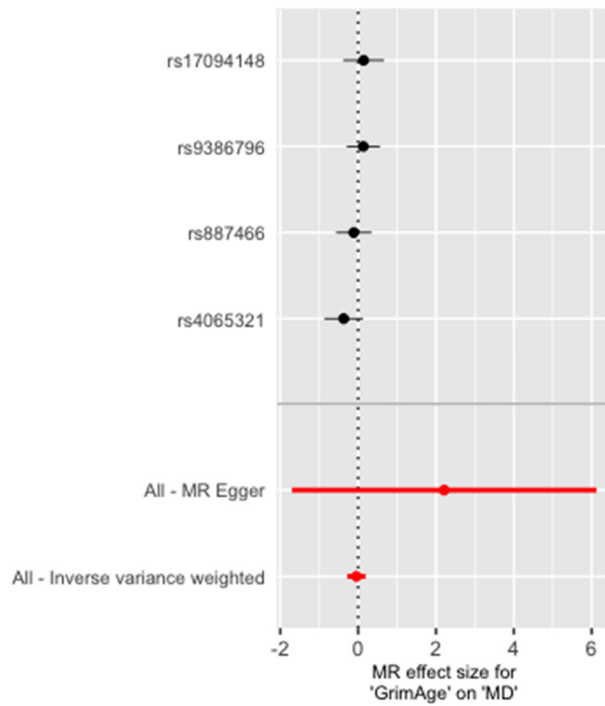


(b) Leave-one-out analysis

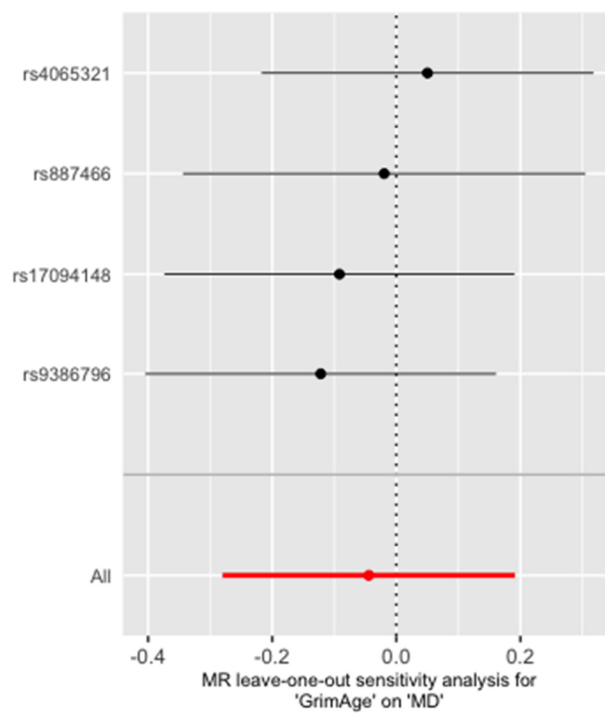


Supplement 2 Figure 13. The single SNP analysis and leave-one-out analysis for GrimAge on MD

(a) Forest plot of single SNP MR

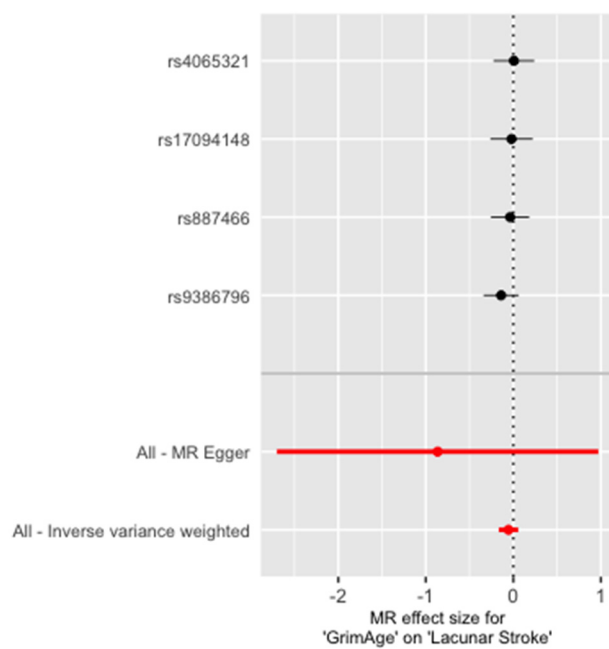


(b) Leave-one-out analysis

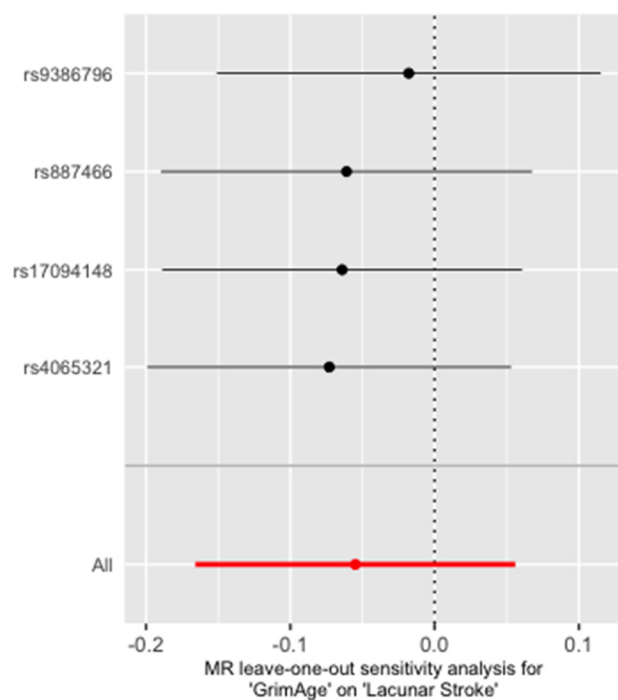


Supplement 2 Figure 14. The single SNP analysis and leave-one-out analysis for GrimAge on lacunar stroke

(a) Forest plot of single SNP MR

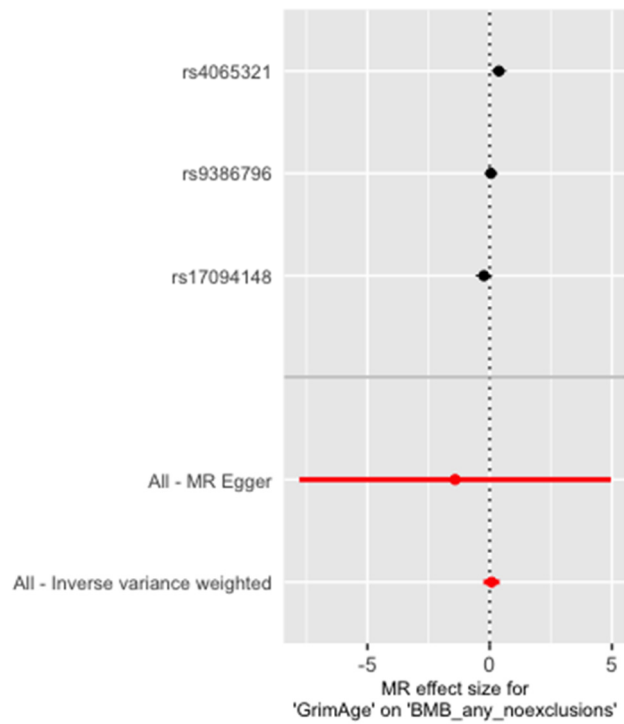


(b) Leave-one-out analysis

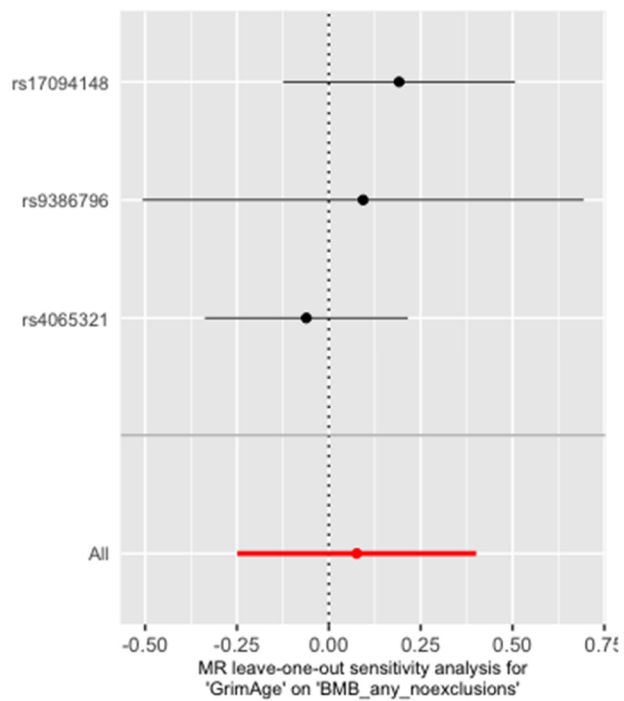


Supplement 2 Figure 15. The single SNP analysis and leave-one-out analysis for GrimAge on all location BMB

(a) Forest plot of single SNP MR

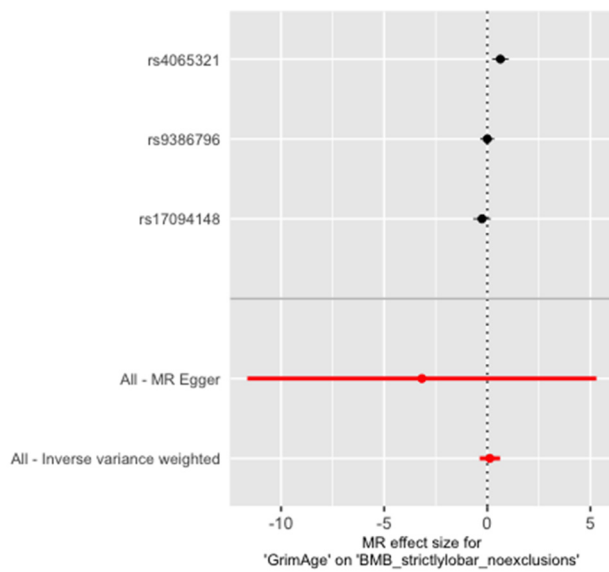


(b) Leave-one-out analysis

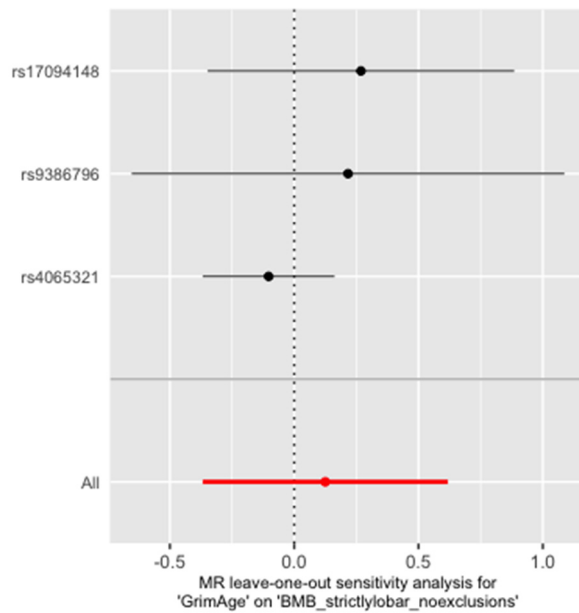


Supplement 2 Figure 16. The single SNP analysis and leave-one-out analysis for GrimAge on lobar BMB

(a) Forest plot of single SNP MR



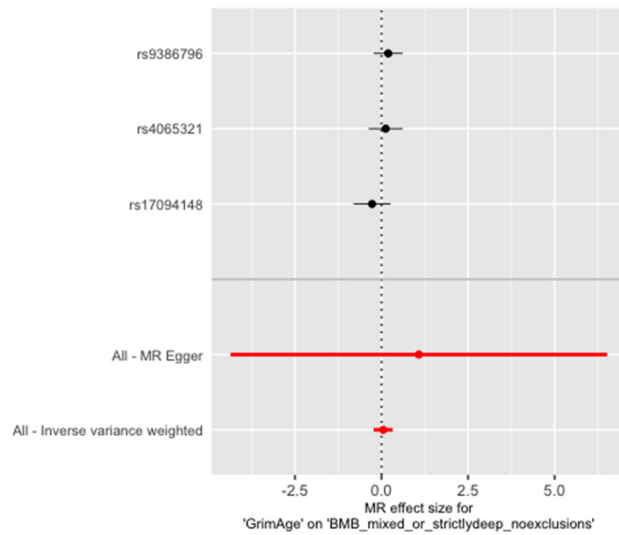
(b) Leave-one-out analysis



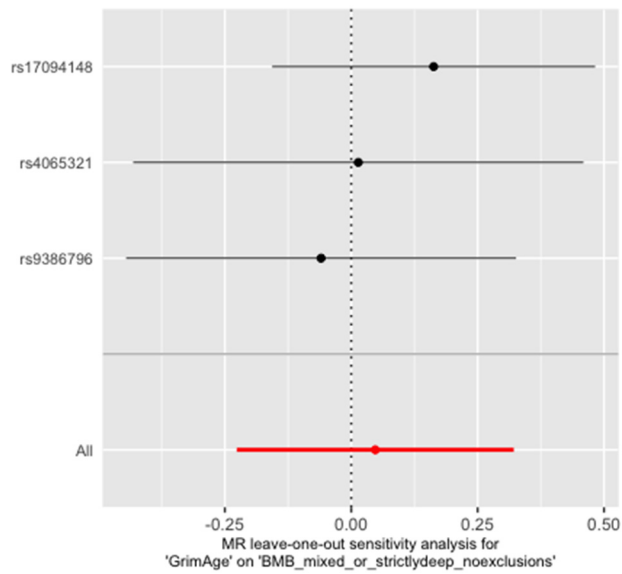
Supplement 2 Figure 17. The single SNP analysis and leave-one-out analysis for GrimAge on mixed or deep BMB

(a) Forest plot of single SNP MR



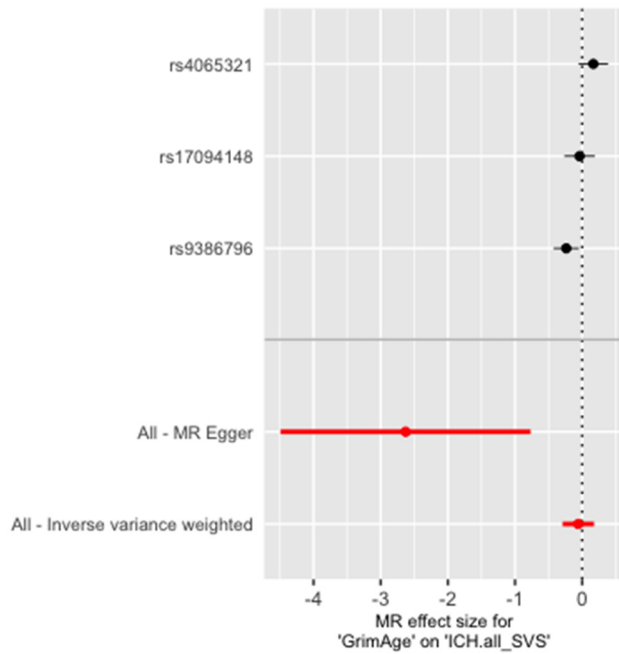


(b) Leave-one-out analysis

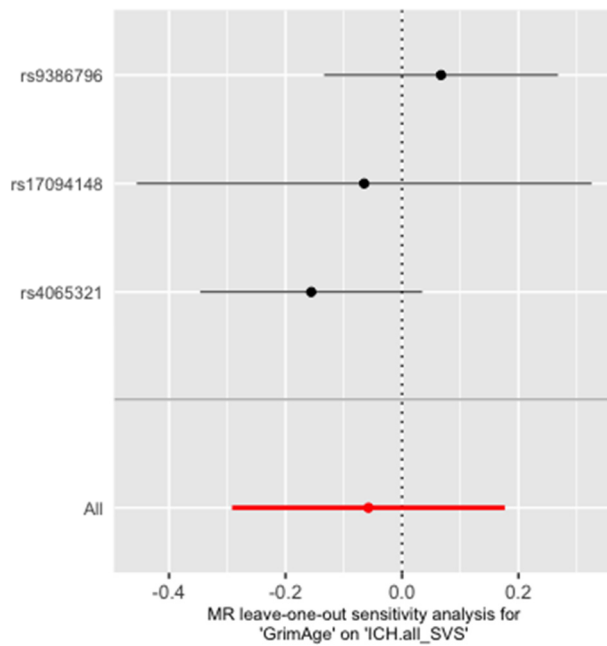


Supplement 2 Figure 18. The single SNP analysis and leave-one-out analysis for GrimAge on all location ICH or SVS

(a) Forest plot of single SNP MR

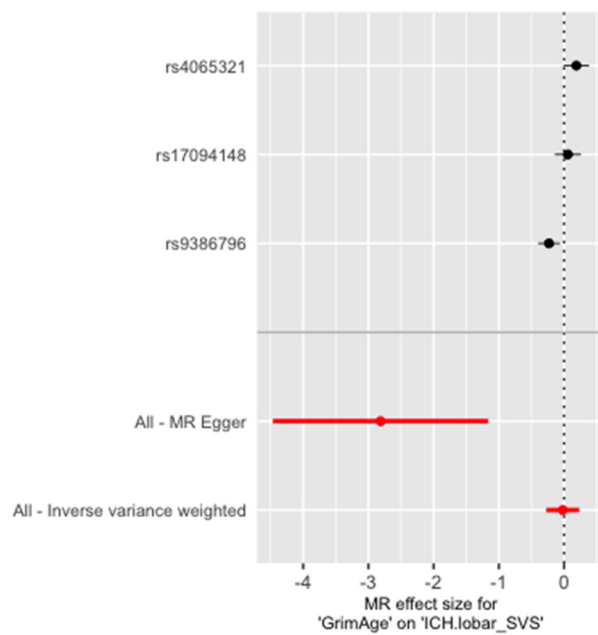


(b) Leave-one-out analysis

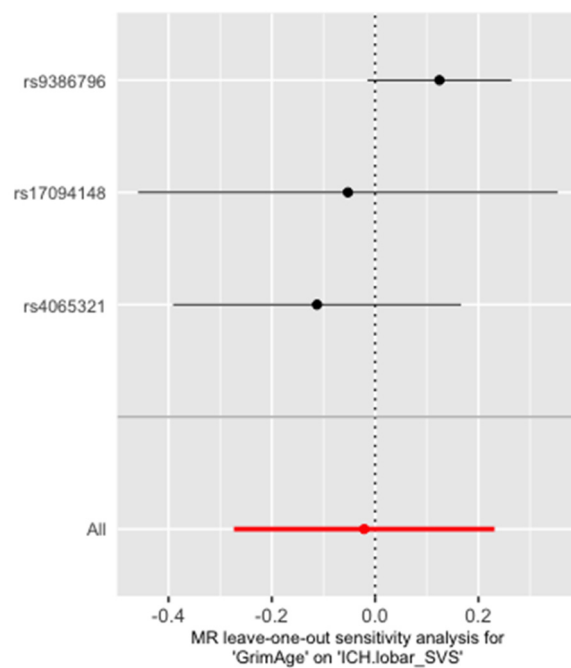


Supplement 2 Figure 19. The single SNP analysis and leave-one-out analysis for GrimAge on lobar ICH or SVS

(a) Forest plot of single SNP MR

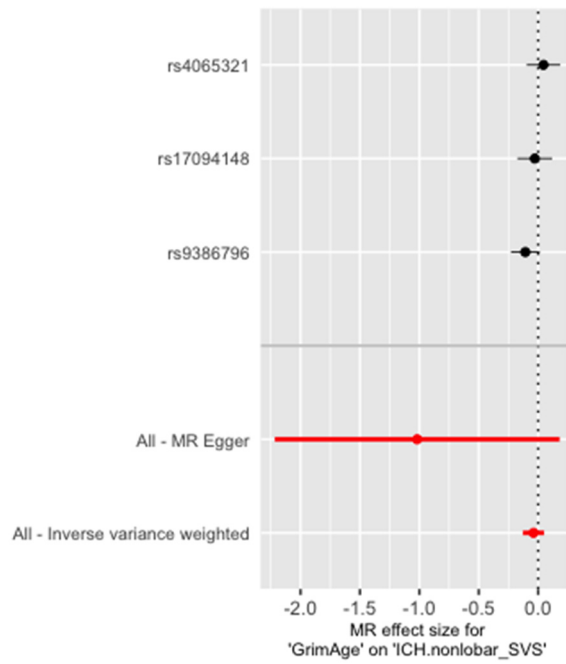


(b) Leave-one-out analysis

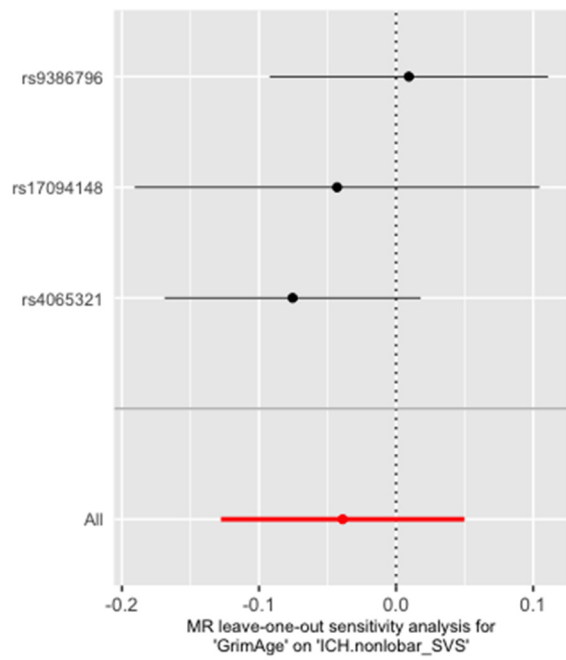


Supplement 2 Figure 20. The single SNP analysis and leave-one-out analysis for GrimAge on non-lobar ICH or SVS

(a) Forest plot of single SNP MR

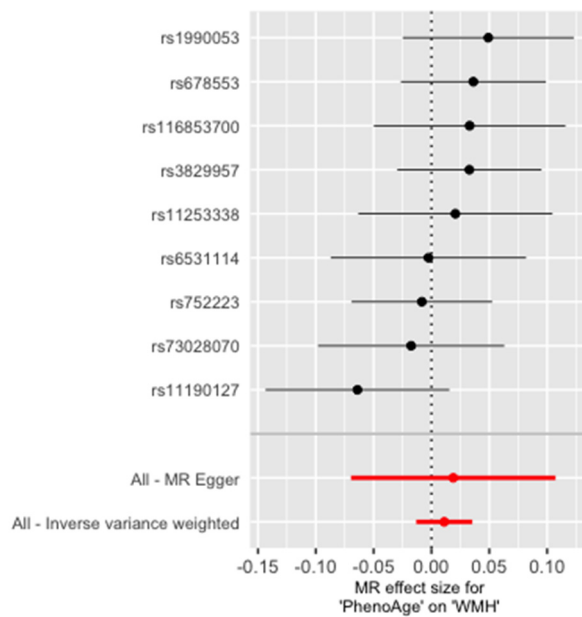


(b) Leave-one-out analysis

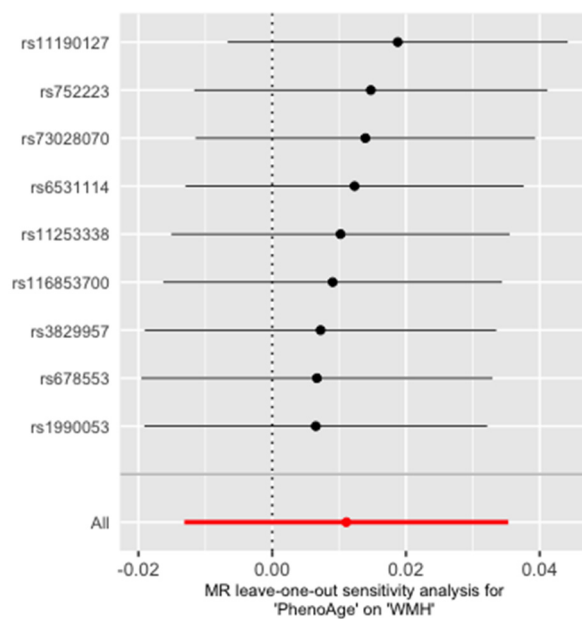


Supplement 2 Figure 21. The single SNP analysis and leave-one-out analysis for PhenoAge on WMH volume

(a) Forest plot of single SNP MR

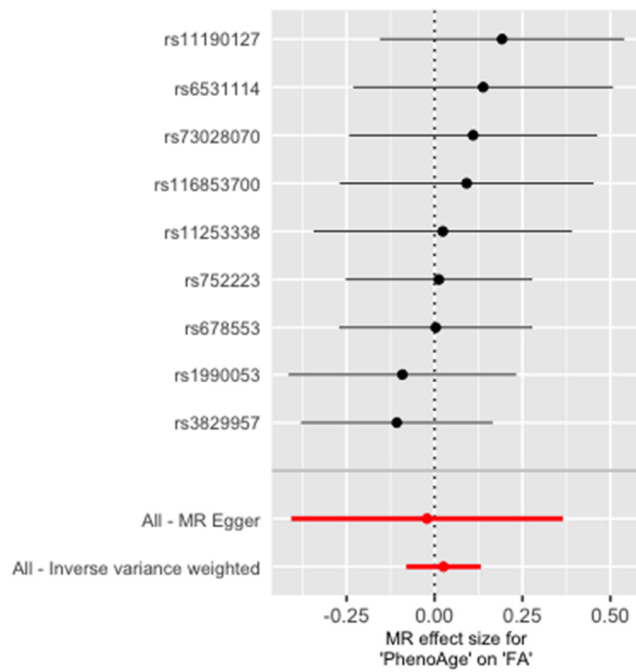


(b) Leave-one-out analysis

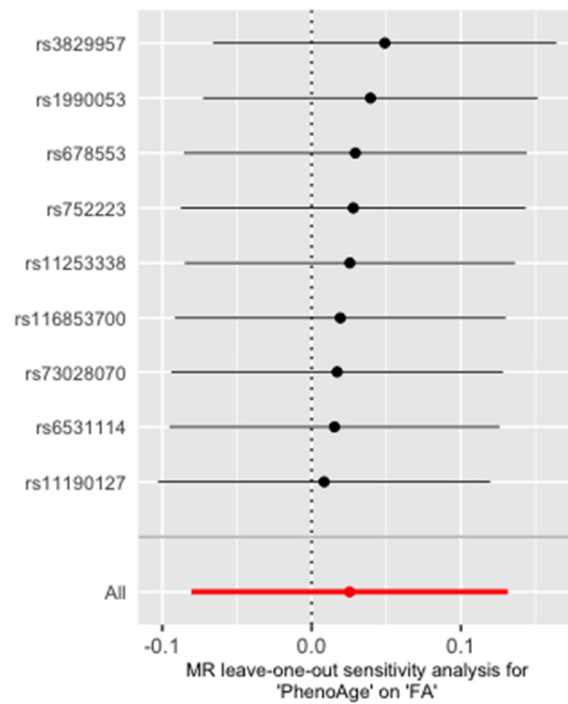


Supplement 2 Figure 22. The single SNP analysis and leave-one-out analysis for PhenoAge on FA

(a) Forest plot of single SNP MR

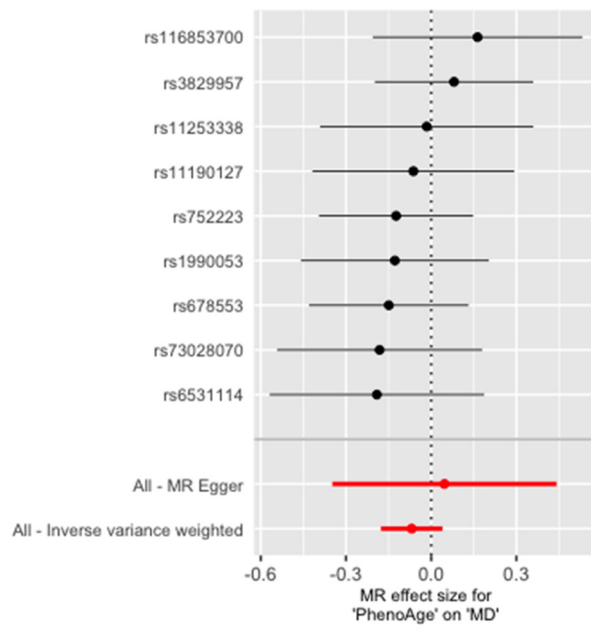


(b) Leave-one-out analysis

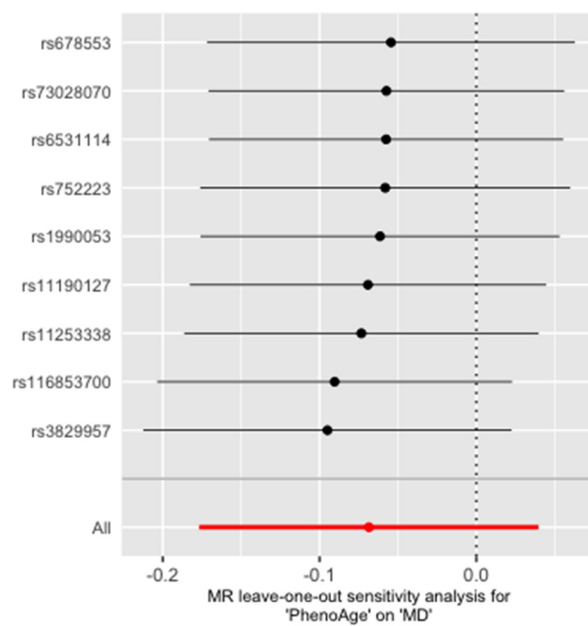


Supplement 2 Figure 23. The single SNP analysis and leave-one-out analysis for PhenoAge on MD

(a) Forest plot of single SNP MR

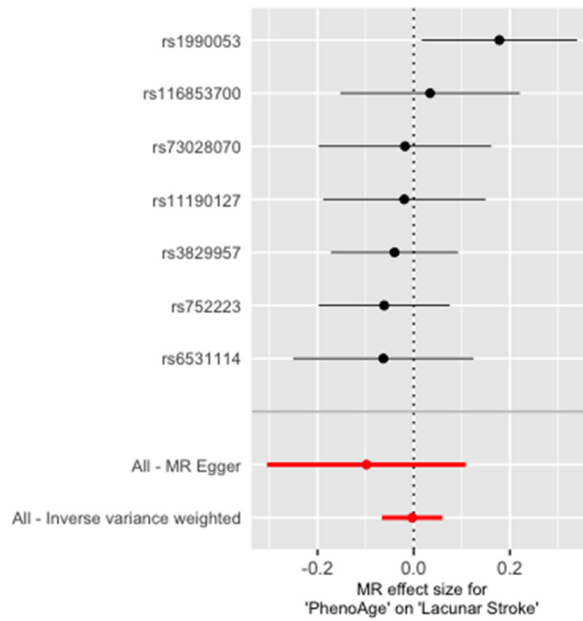


(b) Leave-one-out analysis

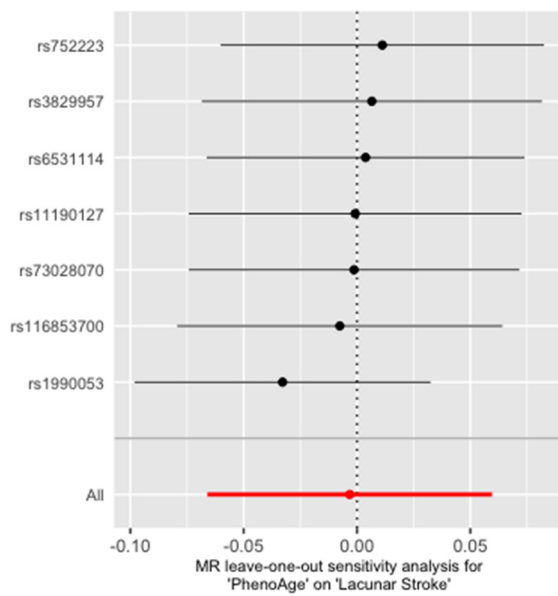


Supplement 2 Figure 24. The single SNP analysis and leave-one-out analysis for PhenoAge on lacunar stroke

(a) Forest plot of single SNP MR



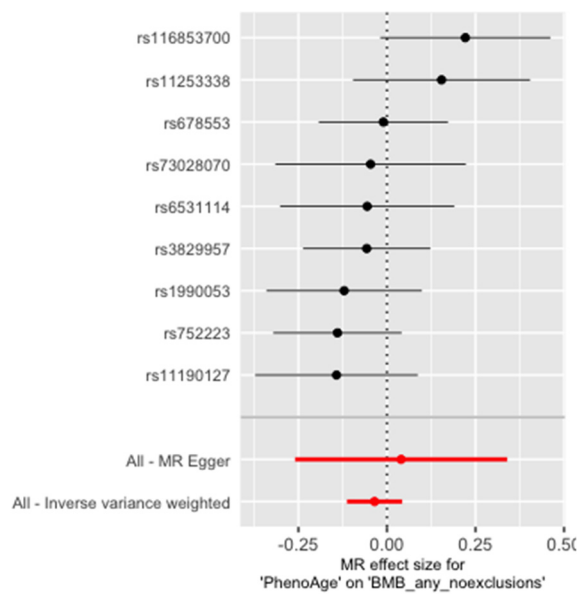
(b) Leave-one-out analysis



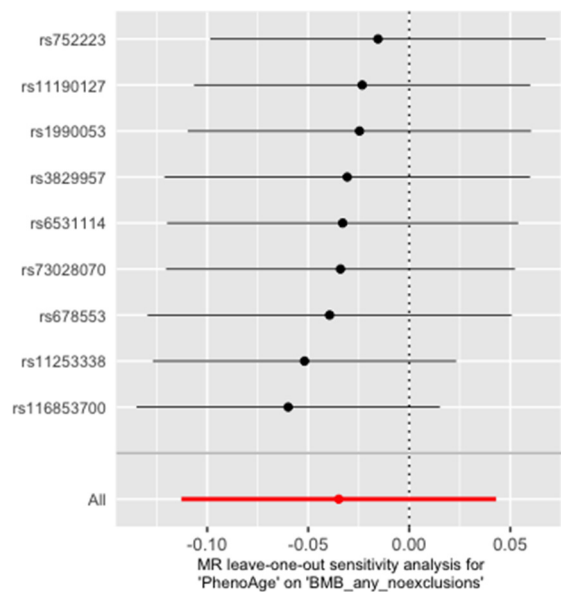
Supplement 2 Figure 25. The single SNP analysis and leave-one-out analysis for PhenoAge on all location BMB

(a) Forest plot of single SNP MR



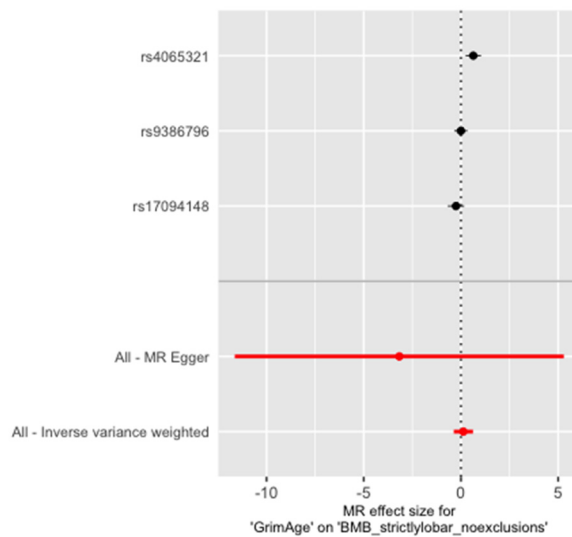


## (b) Leave-one-out analysis

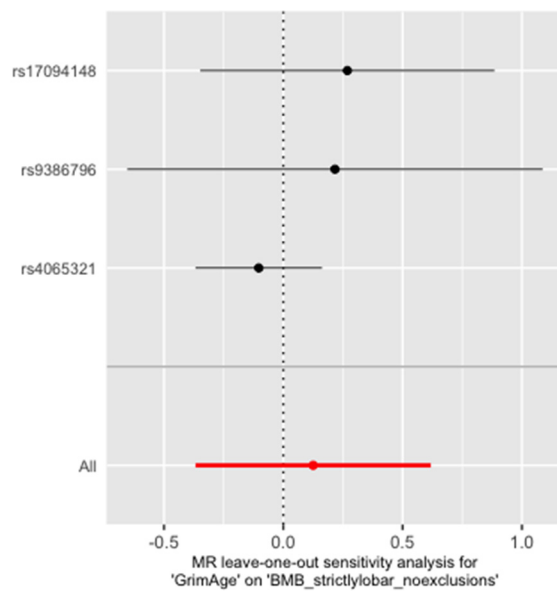


Supplement 2 Figure 26. The single SNP analysis and leave-one-out analysis for PhenoAge on lobar BMB

## (a) Forest plot of single SNP MR

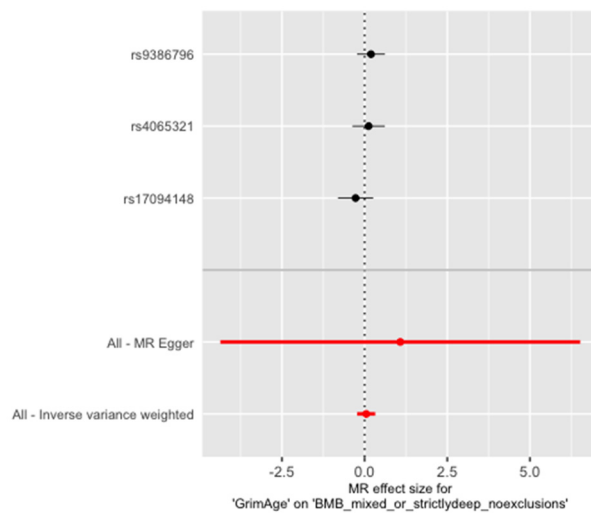


(b) Leave-one-out analysis

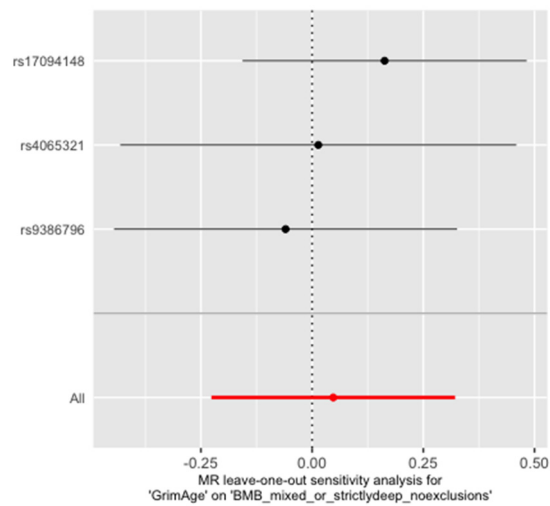


Supplement 2 Figure 27. The single SNP analysis and leave-one-out analysis for PhenoAge on mixed or deep BMB

(a) Forest plot of single SNP MR

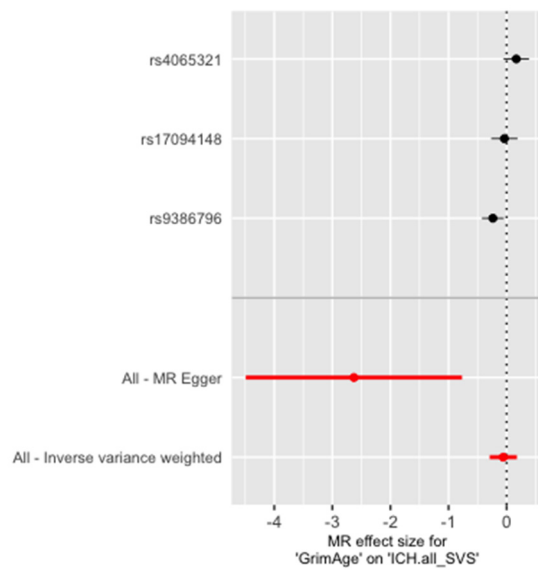


(b) Leave-one-out analysis

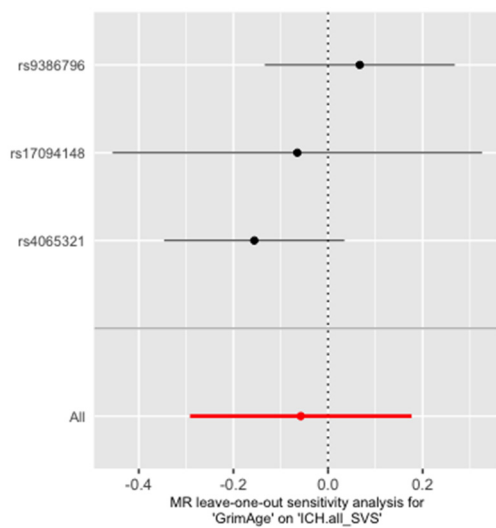


Supplement 2 Figure 28. The single SNP analysis and leave-one-out analysis for PhenoAge on all location ICH or SVS

(a) Forest plot of single SNP MR

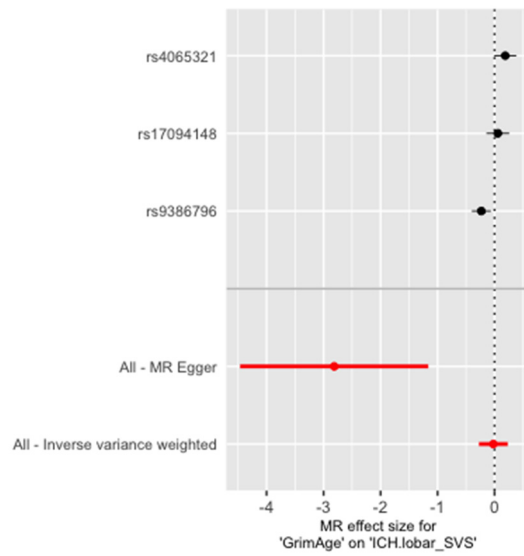


(b) Leave-one-out analysis

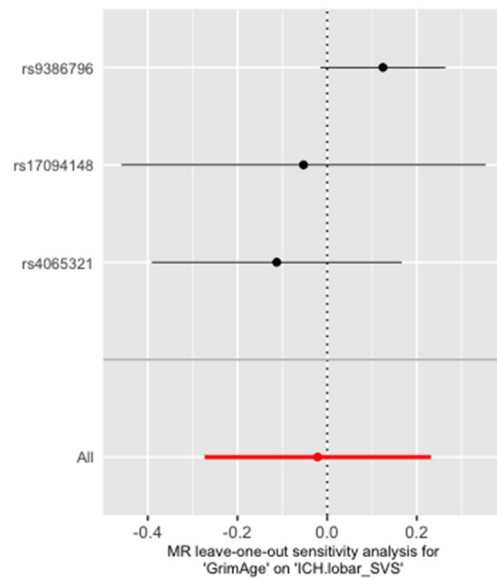


Supplement 2 Figure 29. The single SNP analysis and leave-one-out analysis for PhenoAge on lobar ICH or SVS

(a) Forest plot of single SNP MR

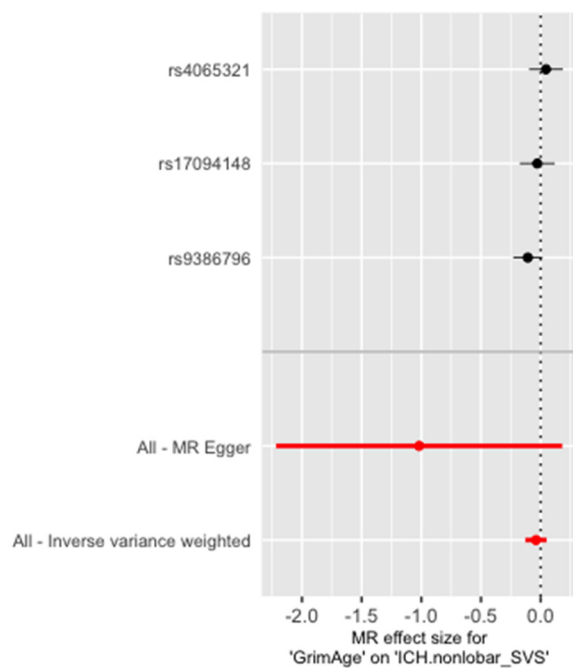


(b) Leave-one-out analysis

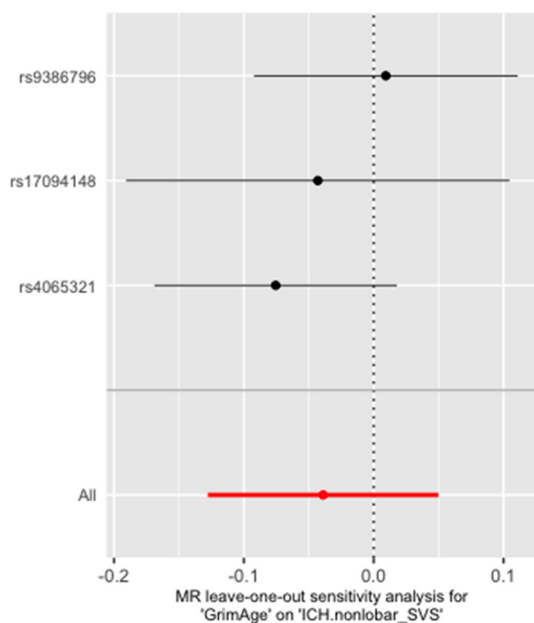


Supplement 2 Figure 30. The single SNP analysis and leave-one-out analysis for PhenoAge on non-lobar ICH or SVS

(a) Forest plot of single SNP MR

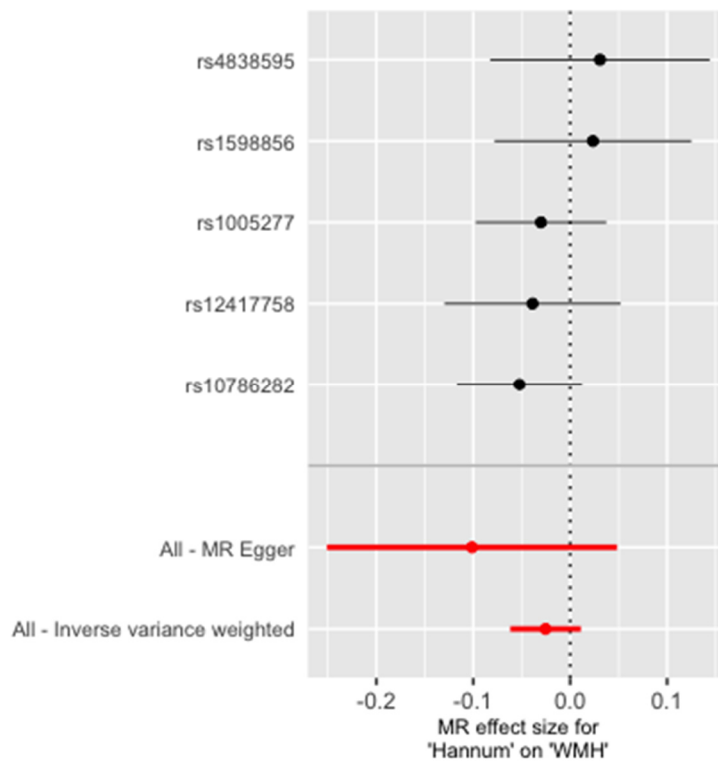


(b) Leave-one-out analysis

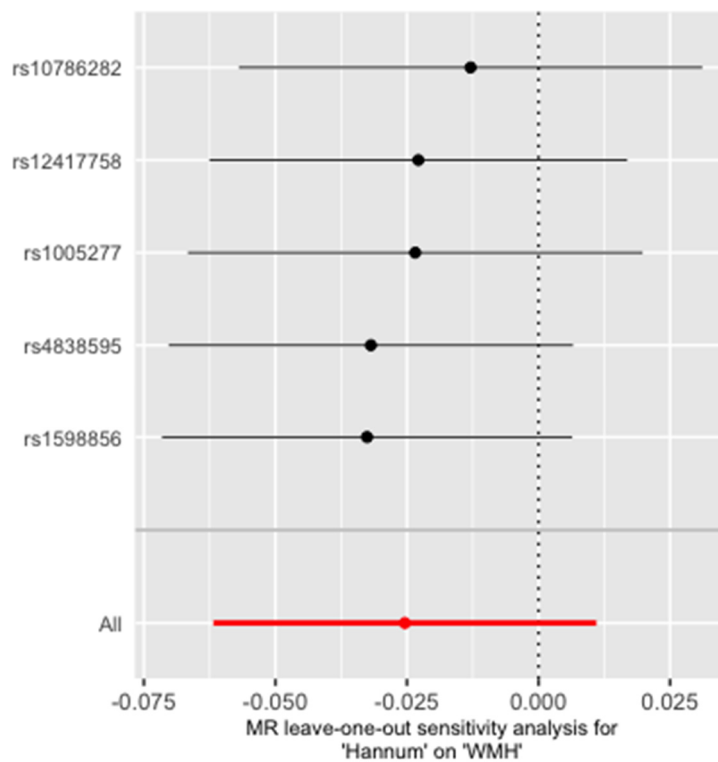


Supplement 2 Figure 31. The single SNP analysis and leave-one-out analysis for HannumAge on WMH volume

(a) Forest plot of single SNP MR

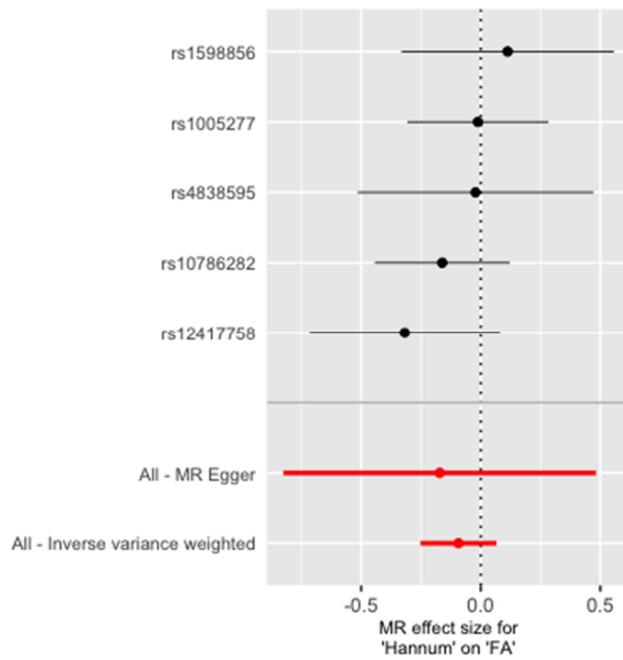


(b) Leave-one-out analysis

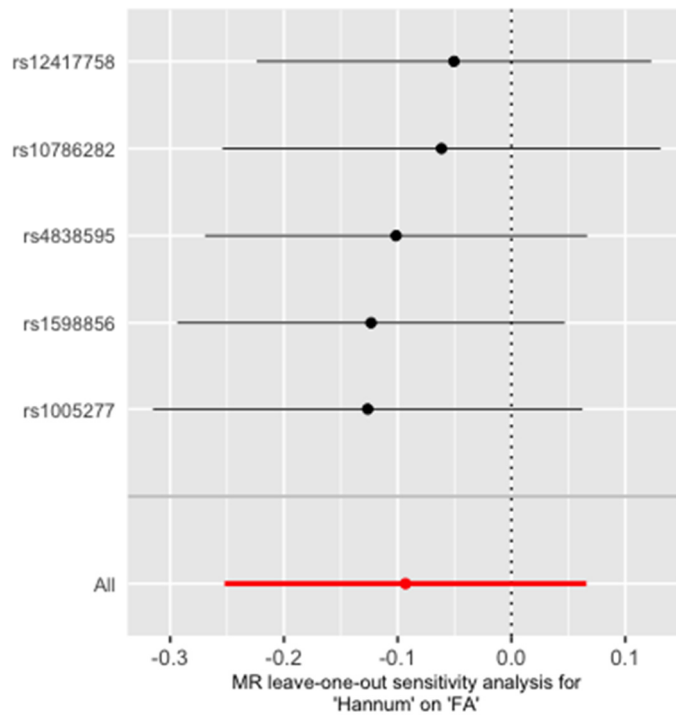


Supplement 2 Figure 32. The single SNP analysis and leave-one-out analysis for HannumAge on FA

(a) Forest plot of single SNP MR



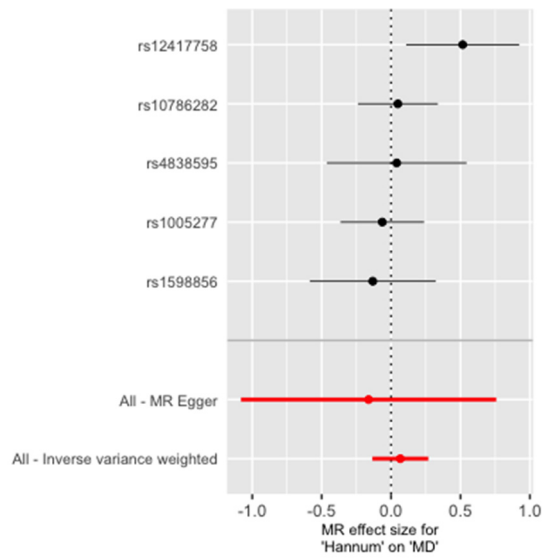
(b) Leave-one-out analysis



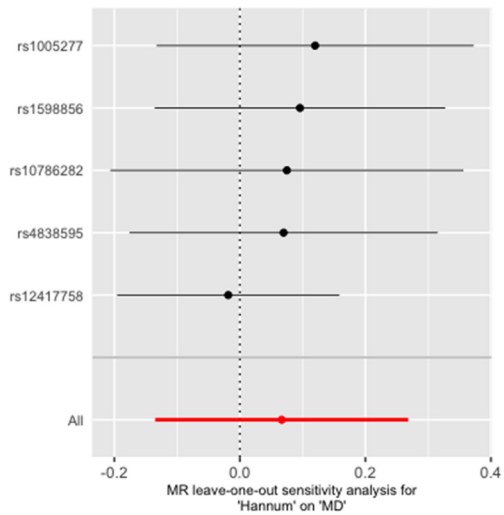
Supplement 2 Figure 33. The single SNP analysis and leave-one-out analysis for HannumAge on MD

(a) Forest plot of single SNP MR



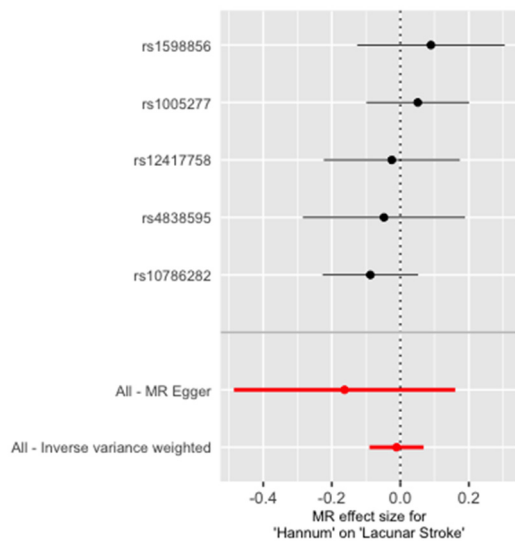


(b) Leave-one-out analysis

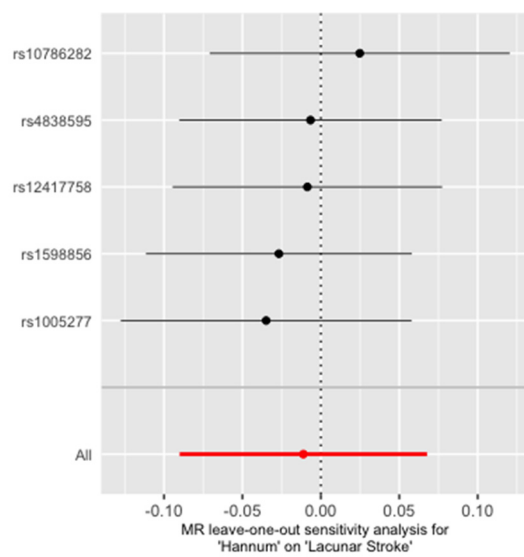


Supplement 2 Figure 34. The single SNP analysis and leave-one-out analysis for HannumAge on lacunar stroke

(a) Forest plot of single SNP MR

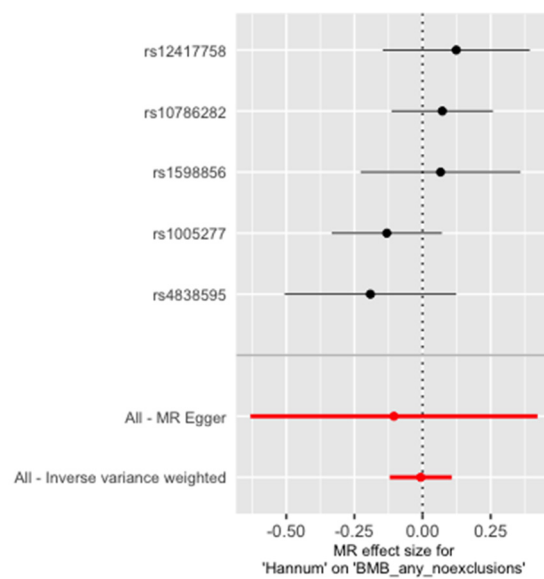


(b) Leave-one-out analysis

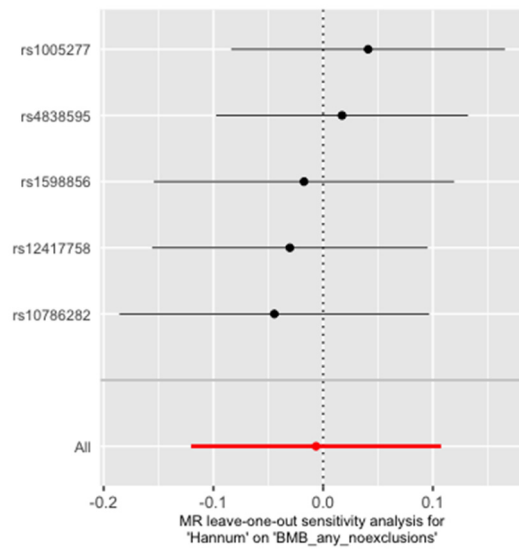


Supplement 2 Figure 35. The single SNP analysis and leave-one-out analysis for HannumAge on all location BMB

(a) Forest plot of single SNP MR

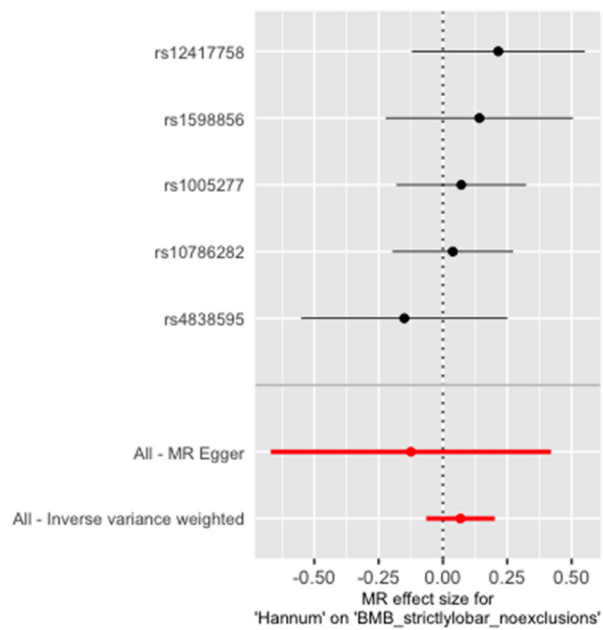


(b) Leave-one-out analysis

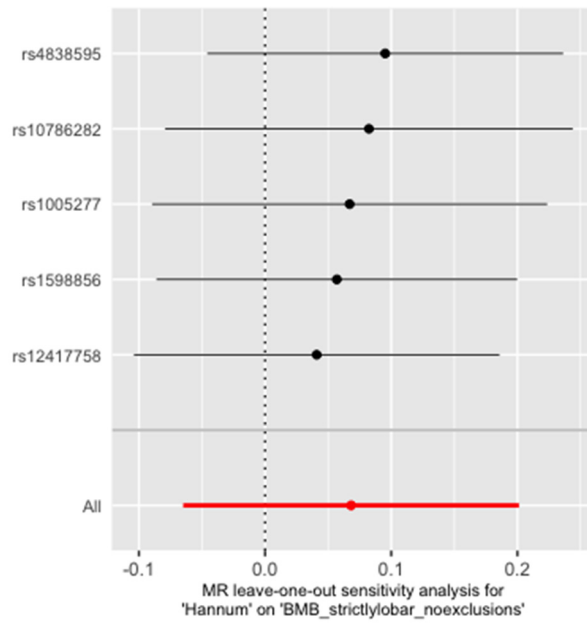


Supplement 2 Figure 36. The single SNP analysis and leave-one-out analysis for HannumAge on lobar BMB

(a) Forest plot of single SNP MR

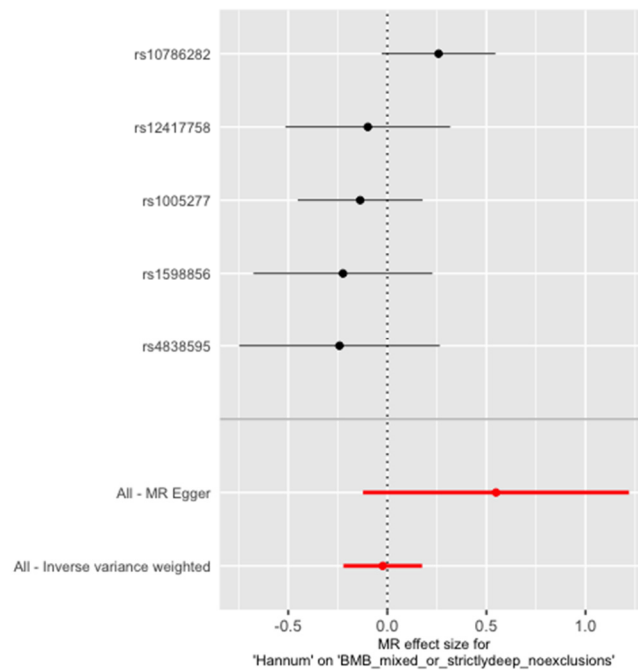


(b) Leave-one-out analysis

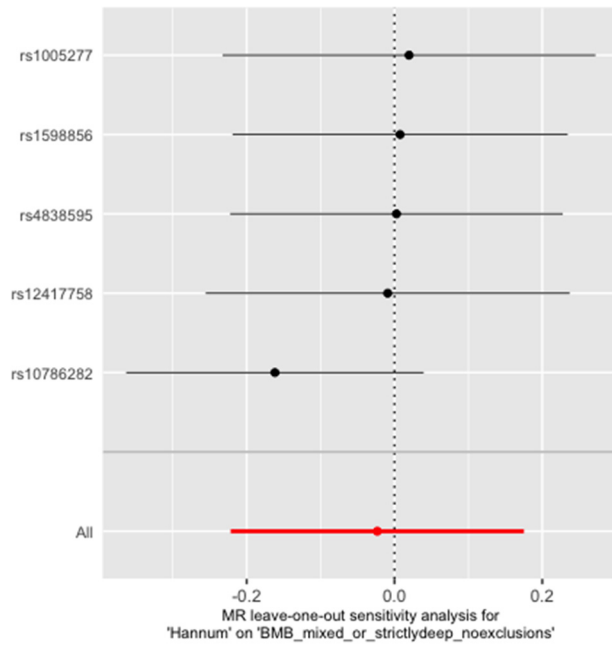


Supplement 2 Figure 37. The single SNP analysis and leave-one-out analysis for HannumAge on mixed or deep BMB

(a) Forest plot of single SNP MR

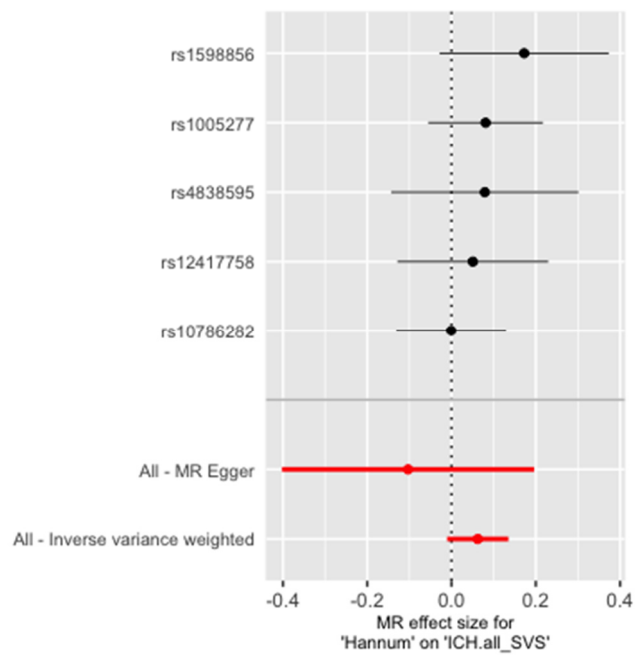


(b) Leave-one-out analysis

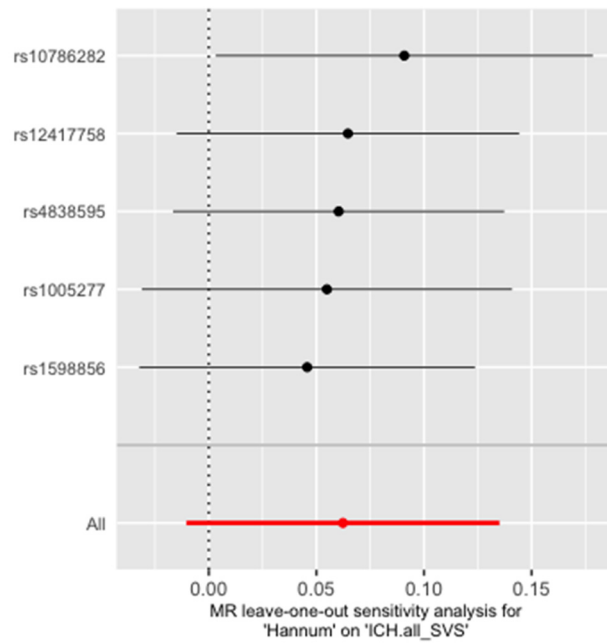


Supplement 2 Figure 38. The single SNP analysis and leave-one-out analysis for HannumAge on all location ICH or SVS

(a) Forest plot of single SNP MR

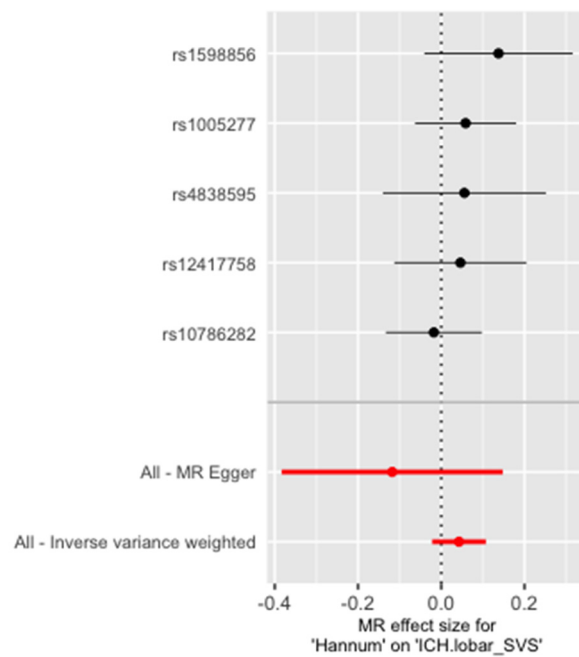


(b) Leave-one-out analysis

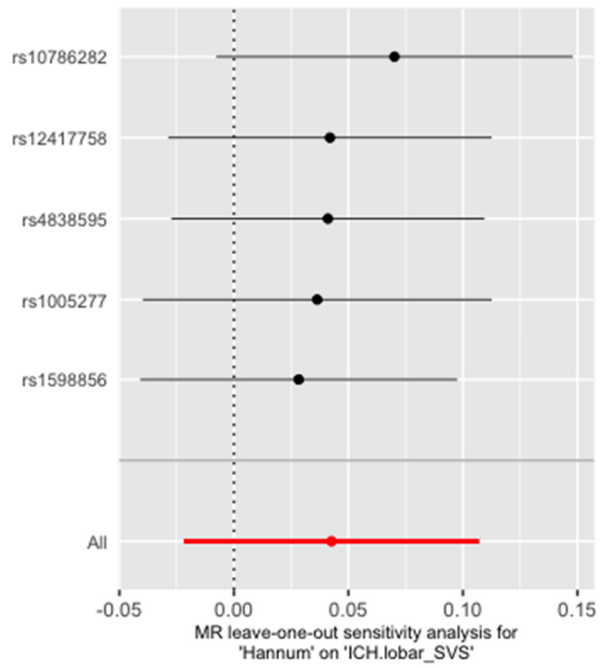


Supplement 2 Figure 39. The single SNP analysis and leave-one-out analysis for HannumAge on lobar ICH or SVS

(a) Forest plot of single SNP MR

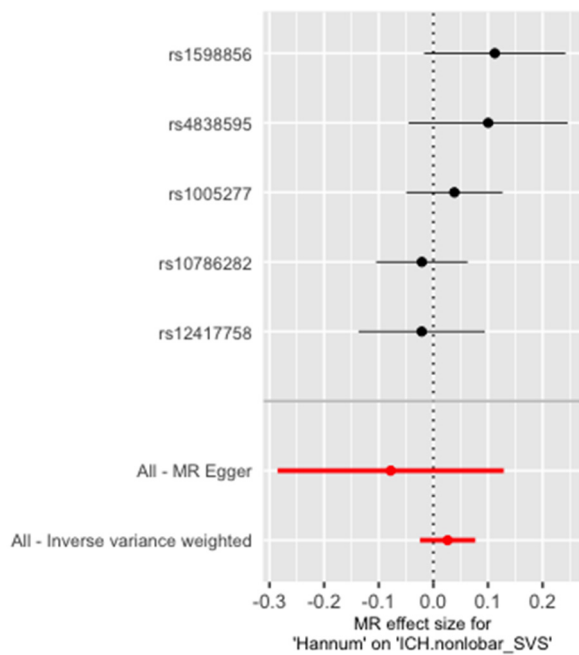


(b) Leave-one-out analysis

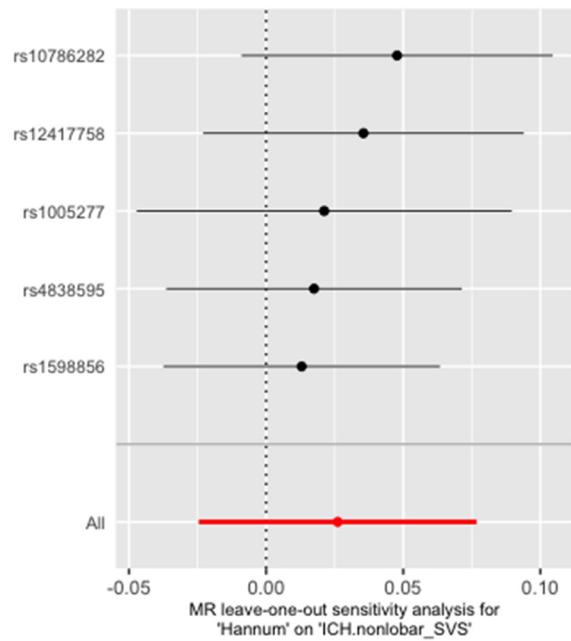


Supplement 2 Figure 40. The single SNP analysis and leave-one-out analysis for HannumAge on non-lobar ICH or SVS

(a) Forest plot of single SNP MR

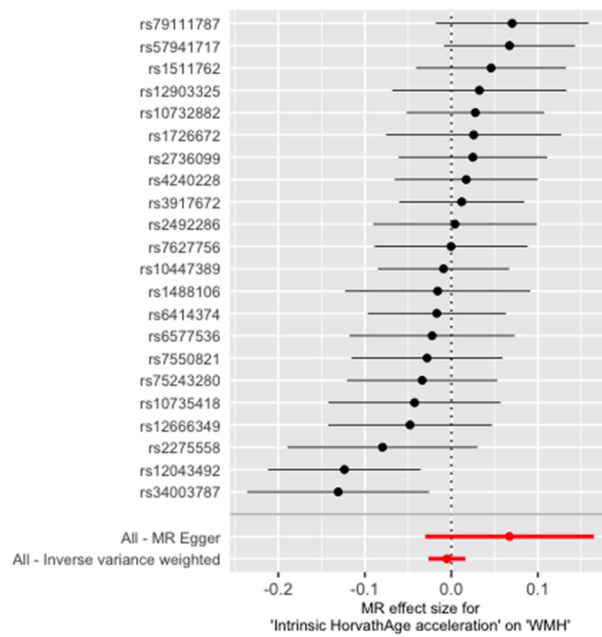


(b) Leave-one-out analysis



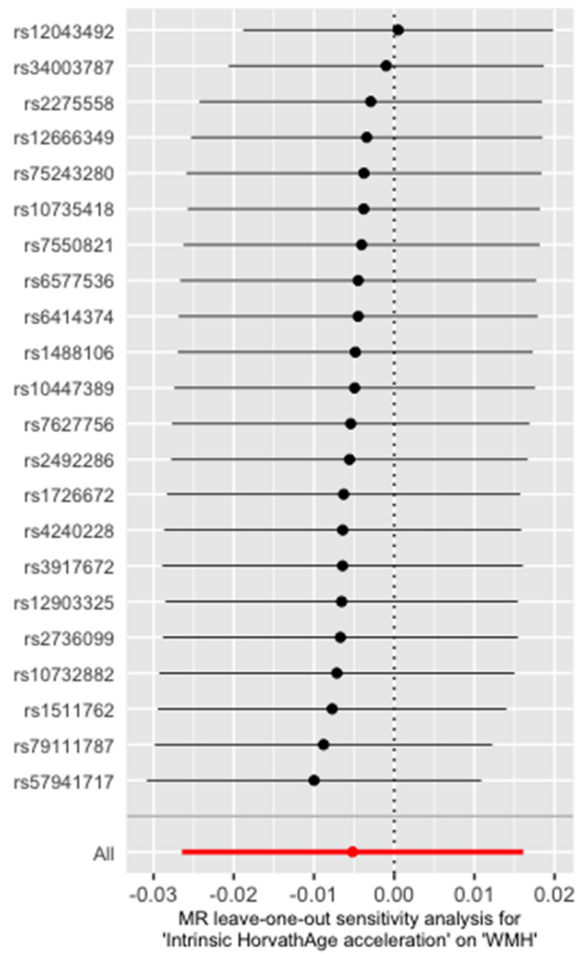
Supplement 2 Figure 41. The single SNP analysis and leave-one-out analysis for Intrinsic HorvathAge acceleration on WMH volume

(a) Forest plot of single SNP MR



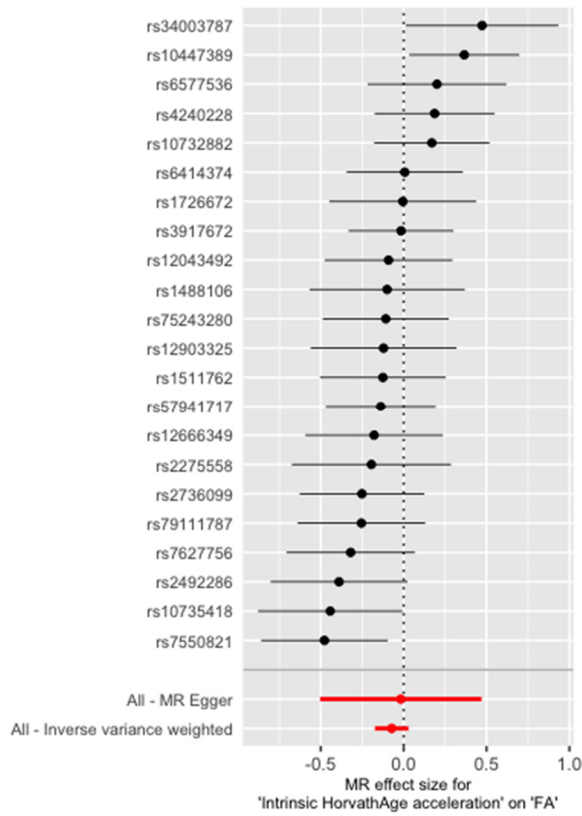
(b) Leave-one-out analysis



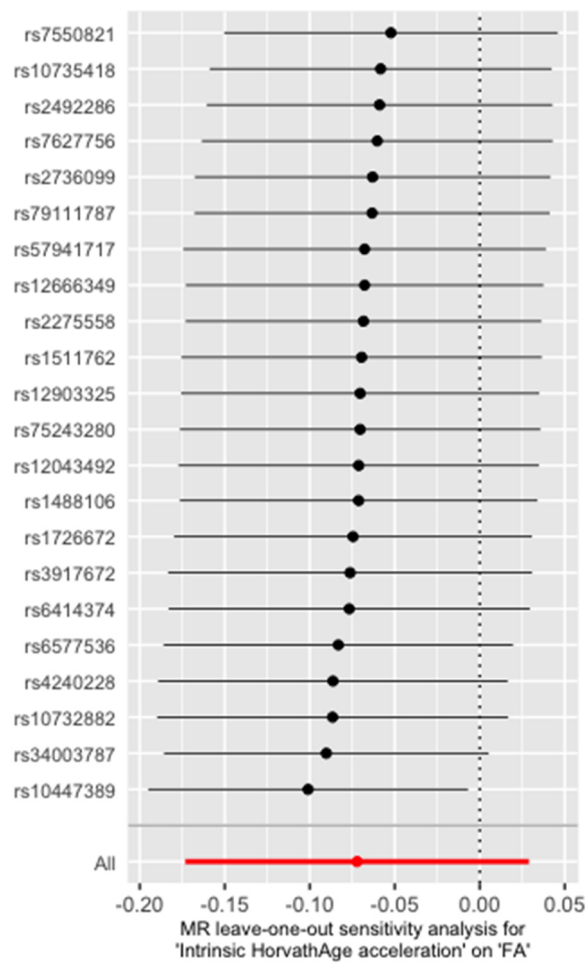


Supplement 2 Figure 42. The single SNP analysis and leave-one-out analysis for Intrinsic HorvathAge acceleration on FA

(a) Forest plot of single SNP MR

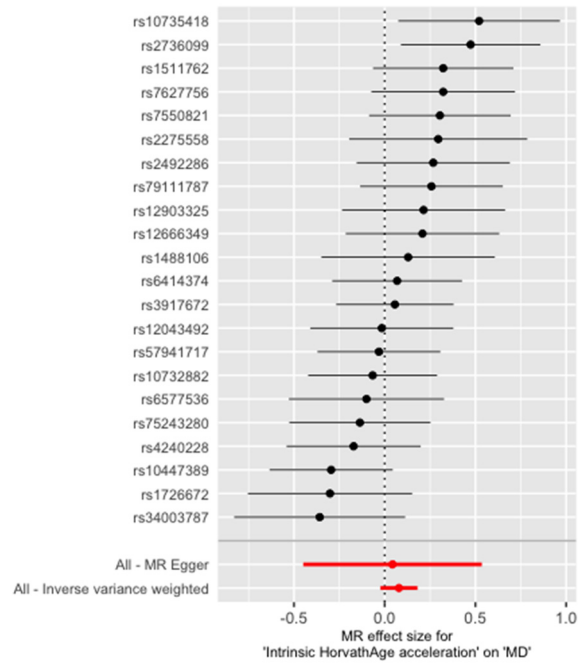


(b) Leave-one-out analysis

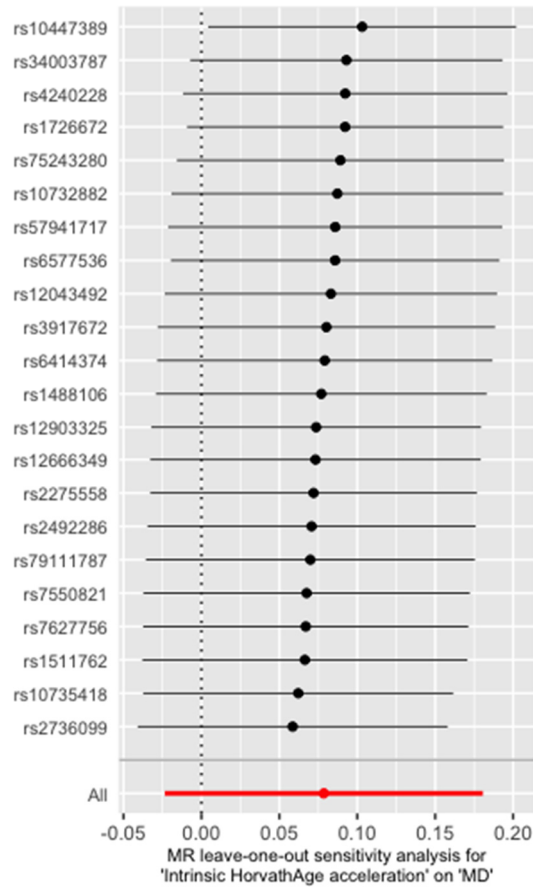


Supplement 2 Figure 43. The single SNP analysis and leave-one-out analysis for Intrinsic HorvathAge acceleration on MD

(a) Forest plot of single SNP MR

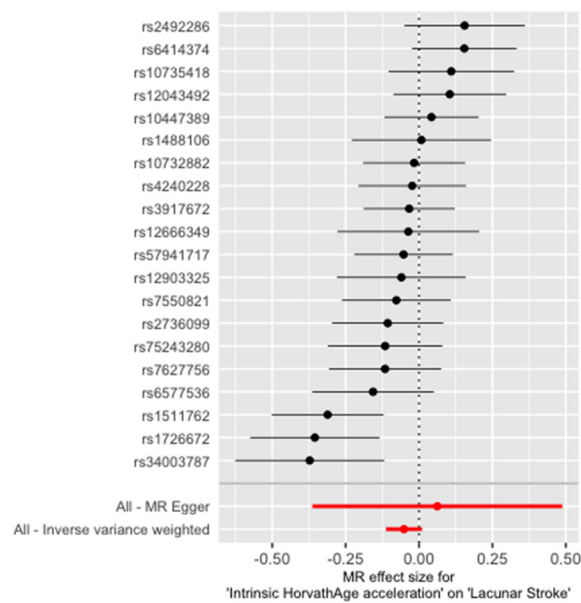


(b) Leave-one-out analysis

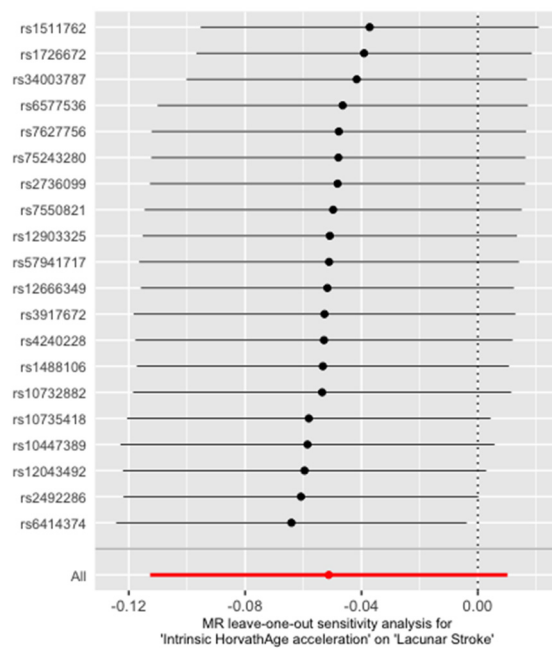


Supplement 2 Figure 44. The single SNP analysis and leave-one-out analysis for Intrinsic HorvathAge acceleration on lacunar stroke

(a) Forest plot of single SNP MR

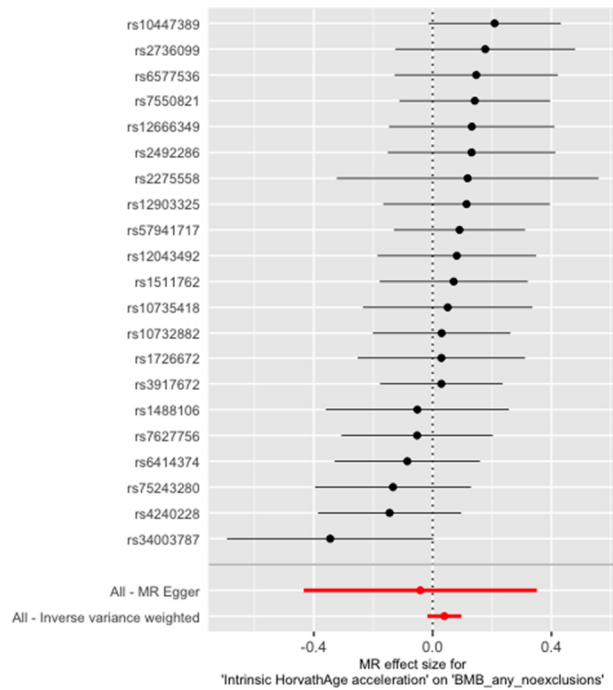


(b) Leave-one-out analysis

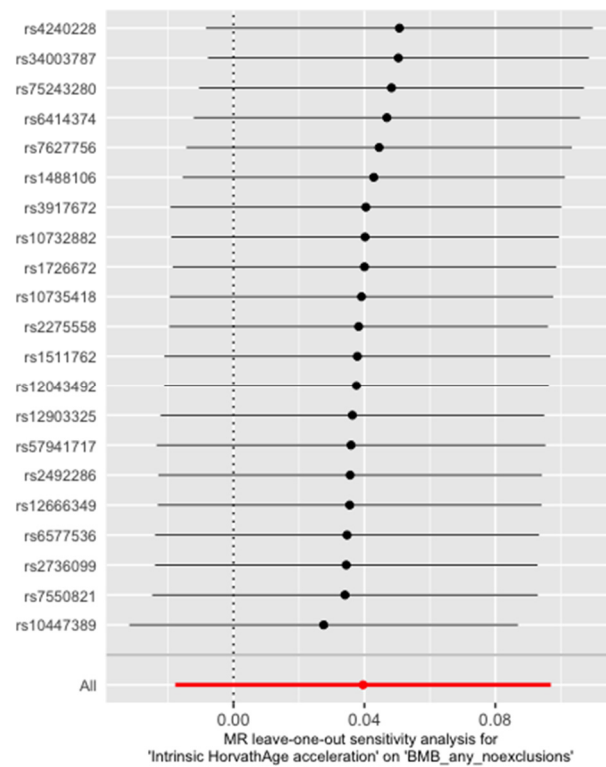


Supplement 2 Figure 45. The single SNP analysis and leave-one-out analysis for Intrinsic HorvathAge acceleration on all location BMB

(a) Forest plot of single SNP MR

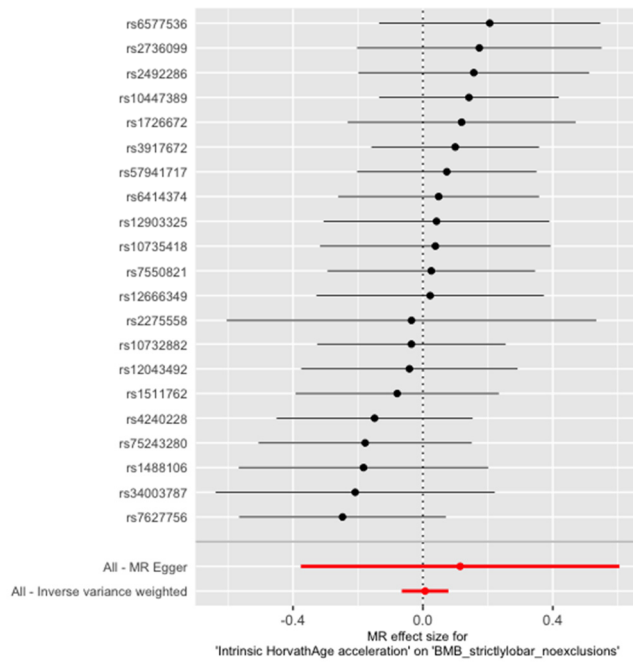


## (b) Leave-one-out analysis

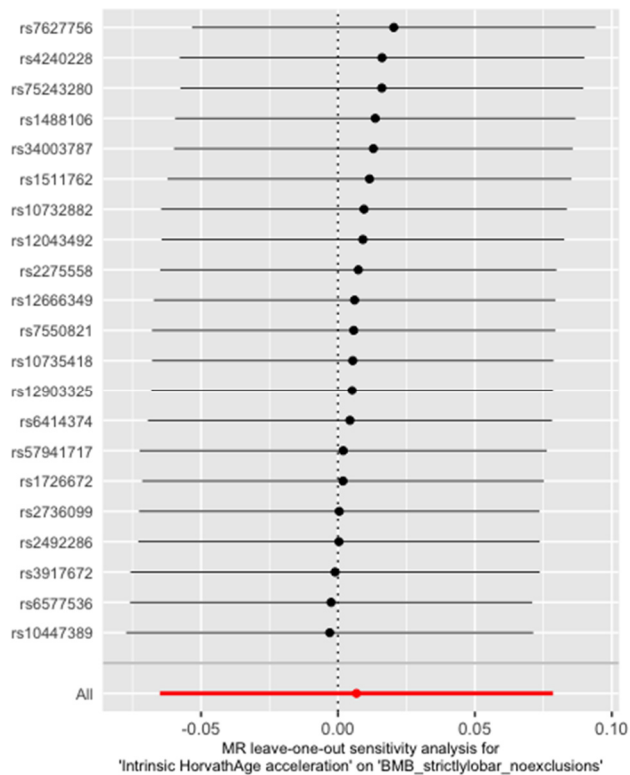


Supplement 2 Figure 46. The single SNP analysis and leave-one-out analysis for Intrinsic HorvathAge acceleration on lobar BMB

## (a) Forest plot of single SNP MR

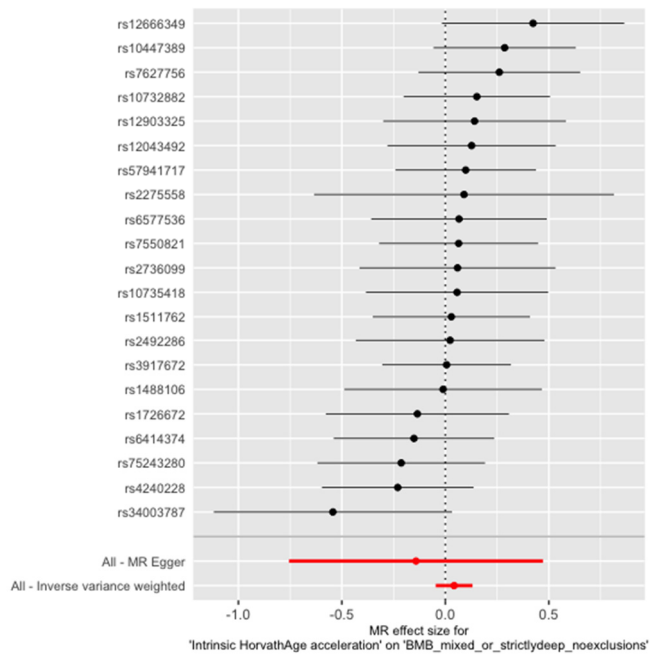


(b) Leave-one-out analysis

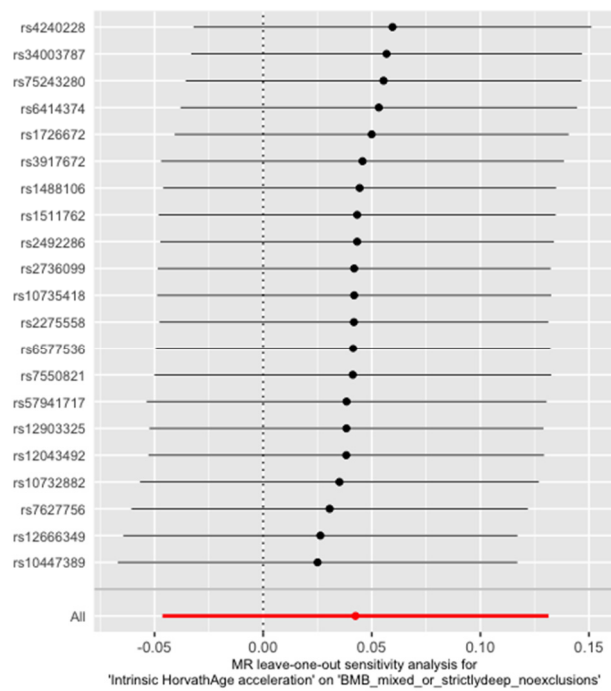


Supplement 2 Figure 47. The single SNP analysis and leave-one-out analysis for Intrinsic HorvathAge acceleration on mixed or deep BMB

(a) Forest plot of single SNP MR

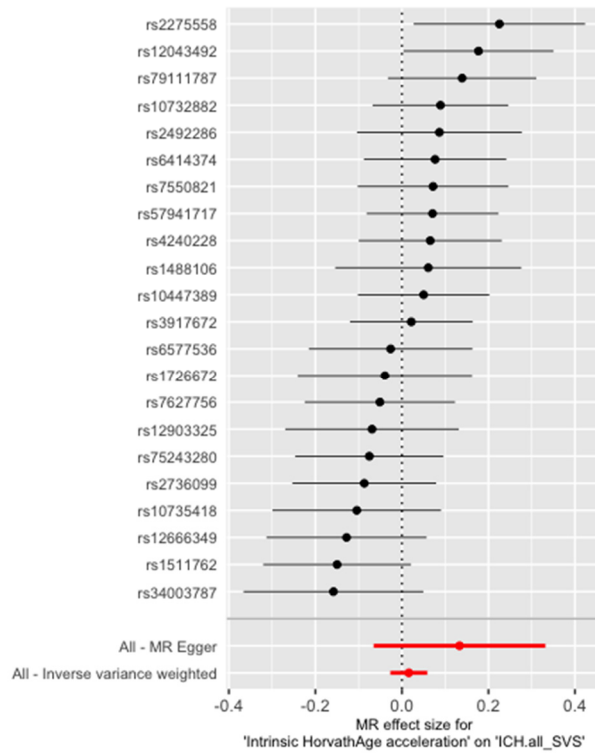


### (b) Leave-one-out analysis

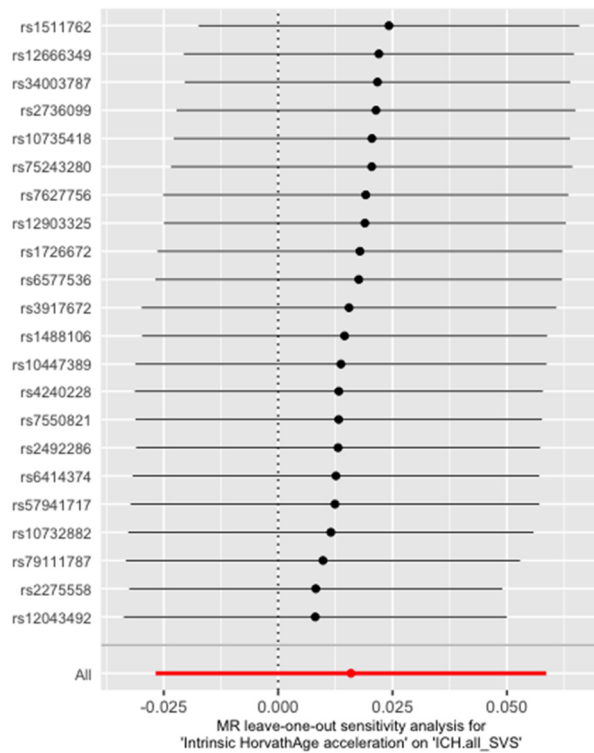


Supplement 2 Figure 48. The single SNP analysis and leave-one-out analysis for Intrinsic HorvathAge acceleration on all location ICH or SVS

### (a) Forest plot of single SNP MR



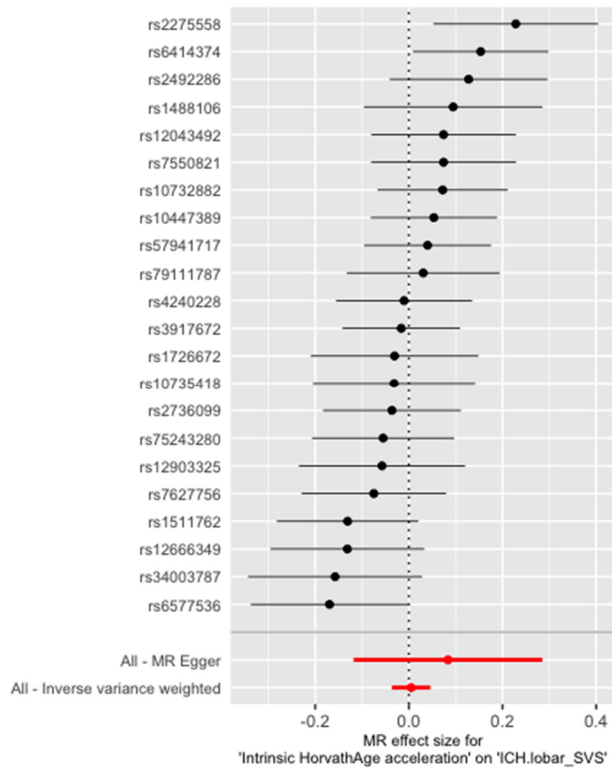
(b) Leave-one-out analysis



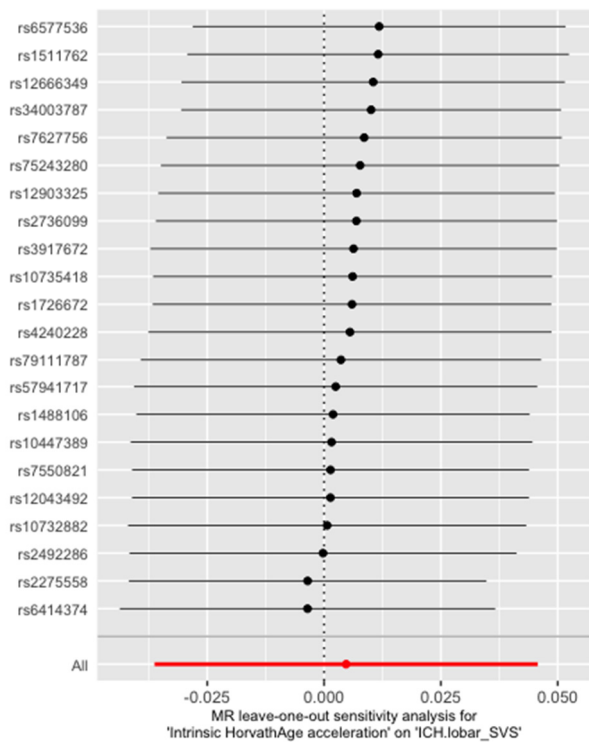
Supplement 2 Figure 49. The single SNP analysis and leave-one-out analysis for Intrinsic HorvathAge acceleration on lobar ICH or SVS

(a) Forest plot of single SNP MR



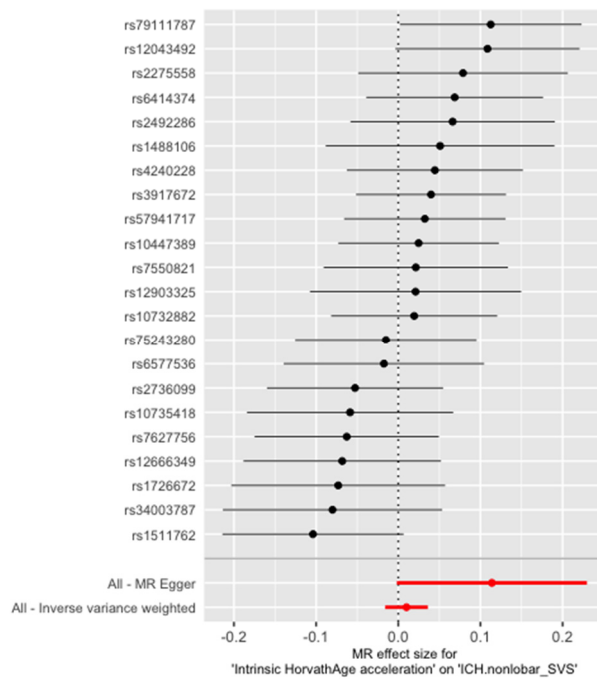


(b) Leave-one-out analysis

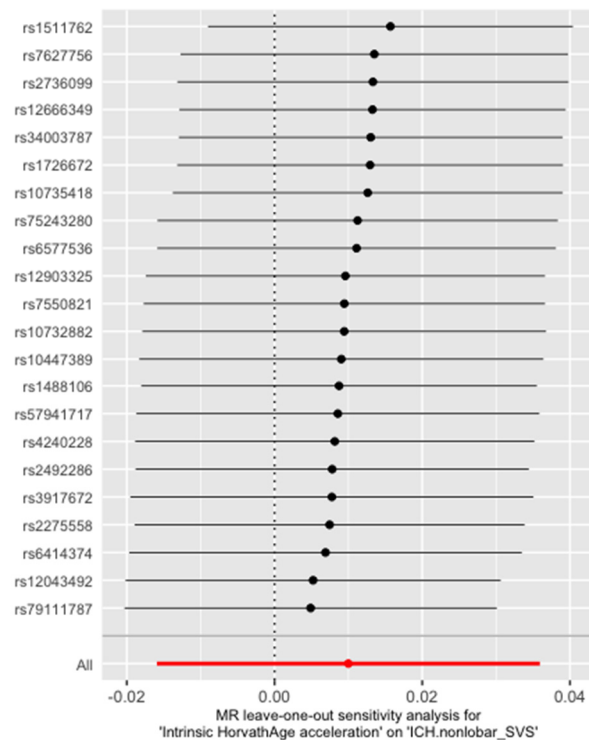


Supplement 2 Figure 50. The single SNP analysis and leave-one-out analysis for Intrinsic HorvathAge acceleration on non-lobar ICH or SVS

(a) Forest plot of single SNP MR



### (b) Leave-one-out analysis



## Supplement 3. Results of other four MR methods for causal effect of exposures on outcomes

Supplement 3 Table 1. Results of other four MR methods for causal effect of LTL on CSVD

TL on CSVD	No.of SNPs	Method	OR	[95%CI]	P
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WMH volume	119	MR Egger	1.07	[0.93, 1.24]	0.32
		Weighted median	1.00	[0.88, 1.15]	0.94
		Simple mode	1.07	[0.80, 1.44]	0.64
		Weighted mode	1.01	[0.84, 1.20]	0.95
FA	119	MR Egger	0.41	[0.21, 0.81]	0.01
		Weighted median	0.76	[0.43, 1.36]	0.36
		Simple mode	0.77	[0.26, 2.24]	0.63
		Weighted mode	0.70	[0.37, 1.34]	0.29
MD	118	MR Egger	1.57	[0.79, 3.11]	0.20
		Weighted median	1.64	[0.91, 2.95]	0.10
		Simple mode	1.61	[0.51, 5.14]	0.42
		Weighted mode	1.61	[0.82, 3.16]	0.17
lacunar stroke	98	MR Egger	0.76	[0.50, 1.14]	0.19
		Weighted median	0.99	[0.74, 1.33]	0.96
		Simple mode	0.80	[0.46, 1.37]	0.41
		Weighted mode	0.98	[0.69, 1.39]	0.92
all location BMB	94	MR Egger	0.82	[0.48, 1.40]	0.46
		Weighted median	1.01	[0.66, 1.55]	0.97
		Simple mode	1.06	[0.48, 2.32]	0.89
		Weighted mode	1.03	[0.64, 1.65]	0.91
lobar BMB	94	MR Egger	0.97	[0.49, 1.92]	0.94
		Weighted median	0.91	[0.54, 1.53]	0.72
		Simple mode	1.04	[0.38, 2.79]	0.95
		Weighted mode	0.88	[0.50, 1.56]	0.66
mixed or deep BMB	89	MR Egger	0.69	[0.27, 1.72]	0.42
		Weighted median	1.36	[0.67, 2.77]	0.40
		Simple mode	1.89	[0.52, 6.87]	0.34
		Weighted mode	1.53	[0.68, 3.44]	0.31
all location ICH or SVS	98	MR Egger	0.92	[0.65, 1.31]	0.66
		Weighted median	1.09	[0.83, 1.44]	0.53
		Simple mode	1.12	[0.62, 2.01]	0.70
		Weighted mode	1.14	[0.76, 1.72]	0.52
lobar ICH or SVS	101	MR Egger	0.96	[0.73, 1.27]	0.77
		Weighted median	1.04	[0.81, 1.35]	0.74
		Simple mode	1.42	[0.84, 2.39]	0.20
		Weighted mode	1.11	[0.81, 1.52]	0.52
non-lobar ICH or SVS	97	MR Egger	0.95	[0.76, 1.18]	0.62
		Weighted median	1.04	[0.85, 1.26]	0.72
		Simple mode	1.19	[0.79, 1.79]	0.42

		Weighted mode	1.07	[0.81, 1.40]	0.63
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Supplement 3 Table 2. Results of other four MR methods for causal effect of GrimAge on CSVD

GrimAge on CSVD	No.of SNPs	Method	OR	[95%CI]	P
WMH volume	4	MR Egger	4.41	[1.84, 10.57]	0.08
		Weighted median	1.00	[0.92, 1.08]	0.98
		Simple mode	0.98	[0.85, 1.13]	0.81
		Weighted mode	1.00	[0.87, 1.15]	0.99
FA	4	MR Egger	0.01	[0.00, 1.14]	0.20
		Weighted median	1.12	[0.83, 1.53]	0.45
		Simple mode	1.21	[0.69, 2.11]	0.55
		Weighted mode	1.20	[0.68, 2.11]	0.57
MD	4	MR Egger	9.12	[0.18, 455.84]	0.38
		Weighted median	1.01	[0.76, 1.36]	0.93
		Simple mode	1.12	[0.72, 1.73]	0.65
		Weighted mode	1.12	[0.75, 1.66]	0.63
lacunar stroke	4	MR Egger	0.42	[0.07, 2.64]	0.45
		Weighted median	0.97	[0.85, 1.10]	0.62
		Simple mode	0.98	[0.82, 1.18]	0.84
		Weighted mode	0.98	[0.80, 1.19]	0.84
all location BMB	3	MR Egger	0.24	[0.00, 142.24]	0.74
		Weighted median	1.06	[0.82, 1.37]	0.65
		Simple mode	1.02	[0.70, 1.48]	0.94
		Weighted mode	1.05	[0.75, 1.45]	0.81
lobar BMB	3	MR Egger	0.04	[8.86E-6, 198.45]	0.60
		Weighted median	0.99	[7.23E-1, 1.35]	0.95
		Simple mode	0.89	[6.02E-1, 1.31]	0.61
		Weighted mode	0.92	[6.50E-1, 1.31]	0.70
mixed or deep BMB	3	MR Egger	2.94	[0.01, 679.25]	0.76
		Weighted median	1.14	[0.82, 1.60]	0.42
		Simple mode	1.17	[0.79, 1.74]	0.52
		Weighted mode	1.18	[0.79, 1.75]	0.50
all location ICH or SVS	3	MR Egger	0.07	[0.01, 0.46]	0.22
		Weighted median	0.94	[0.78, 1.13]	0.50
		Simple mode	0.95	[0.71, 1.28]	0.78
		Weighted mode	0.89	[0.67, 1.20]	0.53
lobar ICH or SVS	3	MR Egger	0.06	[0.01, 0.31]	0.19

non-lobar ICH or SVS	3	Weighted median	1.02	[0.87, 1.20]	0.79
		Simple mode	1.12	[0.88, 1.41]	0.46
		Weighted mode	1.11	[0.85, 1.45]	0.52
		MR Egger	0.36	[0.11, 1.20]	0.34
		Weighted median	0.96	[0.87, 1.06]	0.44
		Simple mode	0.98	[0.85, 1.13]	0.79
		Weighted mode	0.94	[0.82, 1.08]	0.48

Supplement 3 Table 3. Results of other four MR methods for causal effect of PhenoAge on CSVD.

PhenoAge on CSVD	No.of SNPs	Method	OR	[95%CI]	P
WMH volume	9	MR Egger	1.02	[0.93, 1.11]	0.69
		Weighted median	1.02	[0.99, 1.06]	0.15
		Simple mode	1.03	[0.98, 1.08]	0.31
		Weighted mode	1.03	[0.98, 1.08]	0.25
FA	9	MR Egger	0.98	[0.67, 1.44]	0.92
		Weighted median	1.01	[0.89, 1.16]	0.84
		Simple mode	1.06	[0.85, 1.31]	0.64
		Weighted mode	1.02	[0.83, 1.25]	0.86
MD	9	MR Egger	1.05	[0.71, 1.55]	0.82
		Weighted median	0.88	[0.77, 1.01]	0.08
		Simple mode	0.87	[0.68, 1.09]	0.26
		Weighted mode	0.87	[0.71, 1.07]	0.23
lacunar stroke	7	MR Egger	0.91	[0.74, 1.05]	0.39
		Weighted median	0.97	[0.90, 1.05]	0.48
		Simple mode	0.96	[0.87, 1.07]	0.52
		Weighted mode	0.96	[0.87, 1.07]	0.48
all location BMB	9	MR Egger	1.04	[0.77, 1.40]	0.80
		Weighted median	0.95	[0.86, 1.04]	0.26
		Simple mode	0.93	[0.81, 1.06]	0.29
		Weighted mode	0.93	[0.82, 1.05]	0.27
lobar BMB	9	MR Egger	1.09	[0.78, 1.52]	0.64
		Weighted median	0.98	[0.87, 1.10]	0.70
		Simple mode	0.99	[0.83, 1.19]	0.94
		Weighted mode	0.93	[0.79, 1.10]	0.43
mixed or deep BMB	9	MR Egger	0.93	[0.59, 1.44]	0.75
		Weighted median	0.90	[0.78, 1.03]	0.13
		Simple mode	0.85	[0.69, 1.06]	0.18
		Weighted mode	0.87	[0.72, 1.06]	0.20

all location ICH or SVS	9	MR Egger	0.98	[0.82, 1.17]	0.80
		Weighted median	0.98	[0.92, 1.03]	0.40
		Simple mode	0.96	[0.87, 1.06]	0.49
		Weighted mode	0.96	[0.88, 1.05]	0.38
lobar ICH or SVS	9	MR Egger	1.04	[0.89, 1.22]	0.62
		Weighted median	0.98	[0.93, 1.04]	0.51
		Simple mode	0.98	[0.90, 1.06]	0.58
		Weighted mode	0.98	[0.90, 1.06]	0.57
non-lobar ICH or SVS	9	MR Egger	0.93	[0.81, 1.07]	0.36
		Weighted median	0.97	[0.93, 1.01]	0.19
		Simple mode	0.97	[0.91, 1.03]	0.38
		Weighted mode	0.97	[0.91, 1.02]	0.29

Supplement 3 Table 4. Results of other four MR methods for causal effect of HannumAge on CSVD

HannumAge on CSVD	No.of SNPs	Method	OR	[95%CI]	P
WMH volume	5	MR Egger	0.90	[0.78, 1.05]	0.28
		Weighted median	0.97	[0.92, 1.01]	0.13
		Simple mode	0.96	[0.90, 1.02]	0.27
		Weighted mode	0.96	[0.91, 1.01]	0.22
FA	5	MR Egger	0.84	[0.44, 1.62]	0.64
		Weighted median	0.96	[0.79, 1.17]	0.71
		Simple mode	0.98	[0.75, 1.28]	0.90
		Weighted mode	0.94	[0.73, 1.22]	0.68
MD	5	MR Egger	0.85	[0.34, 2.13]	0.75
		Weighted median	1.04	[0.85, 1.28]	0.70
		Simple mode	0.98	[0.76, 1.27]	0.90
		Weighted mode	0.99	[0.78, 1.25]	0.94
lacunar stroke	5	MR Egger	0.85	[0.62, 1.17]	0.40
		Weighted median	0.97	[0.88, 1.08]	0.60
		Simple mode	0.96	[0.83, 1.11]	0.58
		Weighted mode	0.94	[0.81, 1.09]	0.48
all location BMB	5	MR Egger	0.90	[0.53, 1.52]	0.72
		Weighted median	1.07	[0.94, 1.22]	0.32
		Simple mode	1.09	[0.88, 1.34]	0.47
		Weighted mode	1.08	[0.89, 1.32]	0.46
lobar BMB	5	MR Egger	0.88	[0.51, 1.52]	0.68
		Weighted median	1.07	[0.91, 1.25]	0.44
		Simple mode	1.10	[0.89, 1.35]	0.42

mixed or deep BMB	5	Weighted mode	1.07	[0.88, 1.30]	0.53
		MR Egger	1.73	[0.88, 3.38]	0.21
		Weighted median	0.89	[0.71, 1.11]	0.31
		Simple mode	0.84	[0.60, 1.16]	0.35
all location ICH or SVS	5	Weighted mode	0.86	[0.58, 1.26]	0.48
		MR Egger	0.90	[0.67, 1.22]	0.55
		Weighted median	1.07	[0.98, 1.18]	0.12
		Simple mode	1.07	[0.95, 1.22]	0.34
lobar ICH or SVS	5	Weighted mode	1.07	[0.96, 1.21]	0.29
		MR Egger	0.89	[0.68, 1.16]	0.45
		Weighted median	1.05	[0.97, 1.14]	0.19
		Simple mode	1.05	[0.93, 1.19]	0.44
non-lobar ICH or SVS	5	Weighted mode	1.06	[0.95, 1.17]	0.36
		MR Egger	0.92	[0.75, 1.14]	0.51
		Weighted median	1.01	[0.96, 1.07]	0.66
		Simple mode	1.00	[0.91, 1.09]	0.95
		Weighted mode	1.00	[0.92, 1.08]	0.95

Supplement 3 Table 5. Results of other four MR methods for causal effect of Intrinsic HorvathAge acceleration on CSVD

Intrinsic HorvathAge acceleration on CSVD	No.of SNPs	Method	OR	[95%CI]	P
WMH volume	22	MR Egger	1.07	[0.97, 1.18]	0.19
		Weighted median	1.00	[0.97, 1.03]	0.92
		Simple mode	1.00	[0.95, 1.05]	0.94
		Weighted mode	1.00	[0.96, 1.05]	0.85
FA	22	MR Egger	0.98	[0.60, 1.60]	0.95
		Weighted median	0.90	[0.79, 1.02]	0.09
		Simple mode	0.88	[0.69, 1.12]	0.32
		Weighted mode	0.89	[0.71, 1.12]	0.34
MD	22	MR Egger	1.04	[0.64, 1.71]	0.87
		Weighted median	1.06	[0.93, 1.21]	0.35
		Simple mode	1.28	[0.96, 1.69]	0.10
		Weighted mode	1.00	[0.77, 1.30]	0.99
lacunar stroke	20	MR Egger	1.06	[0.70, 1.63]	0.78
		Weighted median	0.97	[0.91, 1.03]	0.28
		Simple mode	0.95	[0.85, 1.06]	0.38

all location BMB	21	Weighted mode	0.95	[0.86, 1.06]	0.37
		MR Egger	0.96	[0.65, 1.42]	0.84
		Weighted median	1.06	[0.98, 1.15]	0.12
		Simple mode	1.11	[0.97, 1.28]	0.16
lobar BMB	21	Weighted mode	1.09	[0.94, 1.26]	0.26
		MR Egger	1.12	[0.69, 1.83]	0.65
		Weighted median	1.04	[0.94, 1.14]	0.46
		Simple mode	1.05	[0.87, 1.26]	0.61
mixed or deep BMB	21	Weighted mode	1.06	[0.90, 1.26]	0.48
		MR Egger	0.87	[0.47, 1.60]	0.66
		Weighted median	1.06	[0.94, 1.20]	0.33
		Simple mode	1.07	[0.86, 1.33]	0.58
all location ICH or SVS	22	Weighted mode	1.06	[0.85, 1.33]	0.60
		MR Egger	1.14	[0.94, 1.39]	0.20
		Weighted median	1.05	[0.99, 1.10]	0.09
		Simple mode	1.07	[0.96, 1.19]	0.25
lobar ICH or SVS	22	Weighted mode	1.07	[0.96, 1.18]	0.23
		MR Egger	1.09	[0.89, 1.33]	0.43
		Weighted median	0.99	[0.94, 1.04]	0.67
		Simple mode	0.99	[0.89, 1.09]	0.80
non-lobar ICH or SVS	22	Weighted mode	1.00	[0.92, 1.09]	0.95
		MR Egger	1.12	[1.00, 1.26]	0.07
		Weighted median	1.02	[0.99, 1.06]	0.21
		Simple mode	1.04	[0.97, 1.11]	0.31
		Weighted mode	1.04	[0.97, 1.10]	0.27

#### Supplement 4. Results of sensitivity analysis

Supplement 4 Table 1. Results of sensitivity analysis of LTL on CSVD

LTL on CSVD	Heterogeneity test (Cochran's Q)		Pleiotropy test	MR PRESSO		F
	P (MR Egger)	P(IVW)	P (MR Egger)	P(Global test)	Outlier	
WMH volume	0.40	0.41	0.58	0.18	NA	36.87
FA	0.06	0.03	0.02	0.09	NA	36.87
MD	0.22	0.24	0.58	0.28	NA	35.62
lacunar stroke	0.003	0.002	0.08	0.003	3	39.06
all location	0.25	0.22	0.16	0.18	NA	44.21



BMB						
lobar BMB	0.26	0.29	0.83	0.27	NA	44.21
mixed or deep BMB	0.07	0.048	0.09	0.04	NA	46.31
all location ICH or SVS	0.01	0.01	0.89	0.008	NA	38.06
lobar ICH or SVS	0.19	0.21	0.99	0.17	NA	37.23
non-lobar ICH or SVS	0.03	0.04	0.68	0.02	NA	38.44

Supplement 4 Table 2. Results of sensitivity analysis of GrimAge on CSVD

GrimAge on CSVD	Heterogeneity test (Cochran's Q)		Pleiotropy test		MR PRESSO		F
	P (MR Egger)	P (IVW)	P (MR Egger)	P (Global test)	Outlier		
WMH volume	0.59	0.01	0.08	0.04	2		17.58
FA	0.27	0.05	0.19	0.11	NA		17.58
MD	0.45	0.41	0.38	0.48	NA		17.58
lacunar stroke	0.86	0.79	0.48	0.78	NA		17.58
all location BMB	0.02	0.03	0.73	-	-		17.34
lobar BMB	0.01	0.01	0.58	-	-		17.34
mixed or deep BMB	0.19	0.38	0.77	-	-		17.34
all location ICH or SVS	0.71	0.02	0.22	-	-		17.34
lobar ICH or SVS	0.81	0.003	0.87	-	-		17.34
non-lobar ICH or SVS	0.87	0.27	0.35	-	-		17.34

- means MR PRESSO is not suitable to carry out

Supplement 4 Table 3. Results of sensitivity analysis of PhenoAge on CSVD

PhenoAge on CSVD	Heterogeneity test (Cochran's Q)		Pleiotropy test		MR PRESSO		F
	P (MR Egger)	P (IVW)	P (MR Egger)	P (Global test)	Outlier		
WMH volume	0.45	0.55	0.86	0.62	NA		14.17
FA	0.89	0.93	0.81	0.93	NA		14.17

MD	0.81	0.85	0.57	0.87	NA	14.17
lacunar stroke	0.36	0.37	0.39	0.46	NA	12.92
all location BMB	0.24	0.31	0.63	0.45	NA	14.17
lobar BMB	0.51	0.58	0.57	0.65	NA	14.17
mixed or deep BMB	0.88	0.93	0.93	0.98	NA	14.17
all location ICH or SVS	0.64	0.73	0.93	0.67	NA	14.17
lobar ICH or SVS	0.81	0.85	0.60	0.89	NA	14.17
non-lobar ICH or SVS	0.18	0.20	0.45	0.17	NA	14.17

Supplement 4 Table 4. Results of sensitivity analysis of HannumAge on CSVD

HannumAge on CSVD	Heterogeneity test (Cochran's Q)		Pleiotropy test		MR PRESSO		F
	P (MR Egger)	P (IVW)	P (MR Egger)	P (Global test)	Outlier		
WMH volume	0.67	0.63	0.38	0.54	NA		23.62
FA	0.46	0.62	0.82	0.50	NA		23.62
MD	0.13	0.19	0.65	0.05	NA		23.62
lacunar stroke	0.60	0.60	0.41	0.59	NA		23.62
all location BMB	0.22	0.33	0.73	0.53	NA		23.62
lobar BMB	0.66	0.72	0.53	0.84	NA		23.62
mixed or deep BMB	0.42	0.21	0.18	0.26	NA		23.62
all location ICH or SVS	0.82	0.71	0.35	0.32	NA		23.62
lobar ICH or SVS	0.87	0.69	0.31	0.62	NA		23.62
non-lobar ICH or SVS	0.33	0.32	0.38	0.33	NA		23.62

Supplement 4 Table 5. Results of sensitivity analysis of Intrinsic HorvathAge acceleration on CSVD

Intrinsic HorvathAge acceleration on CSVD	Heterogeneity test (Cochran's Q)		Pleiotropy test		MR PRESSO		F
	P (MR Egger)	P (IVW)	P (MR Egger)	P (Global test)	Outlier		

WMH						
volume	0.24	0.18	0.15	0.23	NA	18.84
FA	0.05	0.07	0.82	0.11	NA	18.84
MD	0.06	0.08	0.89	0.08	NA	18.84
lacunar stroke	0.004	0.005	0.60	0.003	NA	20.00
all location						
BMB	0.65	0.70	0.69	0.80	NA	19.61
lobar BMB	0.89	0.92	0.67	0.74	NA	19.61
mixed or						
deep BMB	0.67	0.70	0.56	0.75	NA	19.61
all location						
ICH or SVS	0.18	0.16	0.25	0.21	NA	18.39
lobar ICH or						
SVS	0.05	0.06	0.44	0.09	NA	18.39
non-lobar						
ICH or SVS	0.40	0.28	0.09	0.29	NA	18.39