

Supplementary Material

Causal association between depression and intracranial aneurysms: A bidirectional two-sample Mendelian randomization study

Authors: Jujiang Wu^{1†}, Hao Sun^{1†}, Junqiang Ma^{1,2*}

¹ Neurointensive Care Unit, the First Affiliated Hospital of Shantou University Medical College, Shantou, China.

² Department of Population Medicine, Shantou University Medical College, Shantou, China.

[†]*These authors contributed equally to this work and should be considered co-first authors.*

*** Correspondence:**

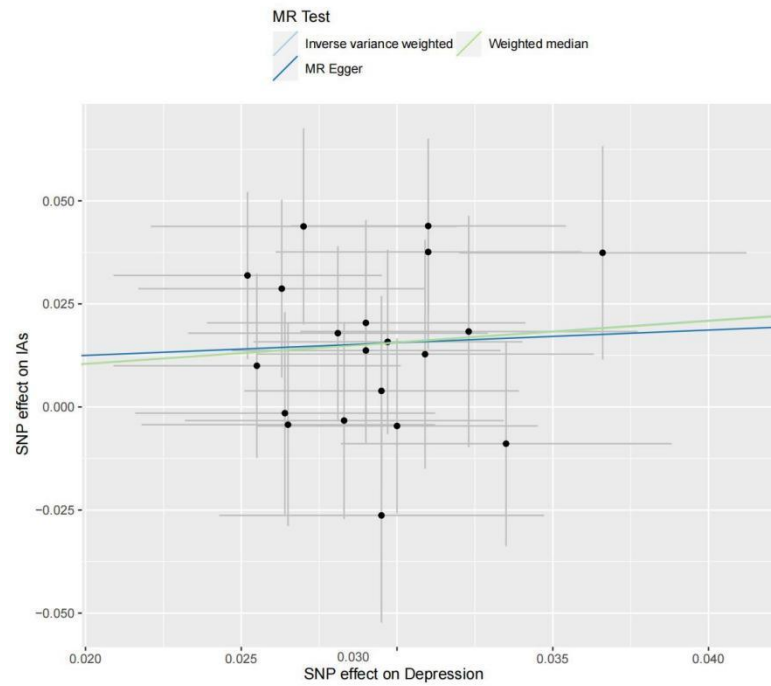
Junqiang Ma, M.D.,Ph.D.

Neurointensive Care Unit, the First Affiliated Hospital of Shantou University Medical College, Shantou, China.

Department of Population Medicine, Shantou University Medical College, Shantou, China. Tel: +86 13682867983; E-mail:
736247781@qq.com

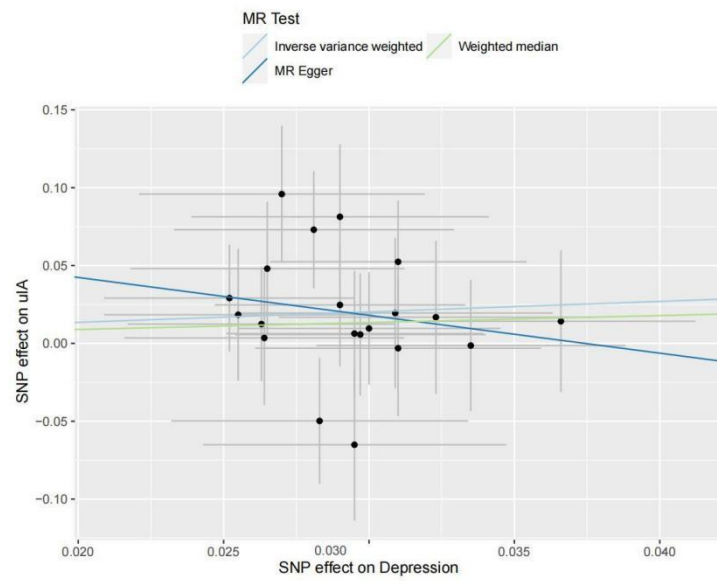
1. Supplementary Figures

1.1 Supplementary Figure 1a. Scatter plot for depression on IAs.



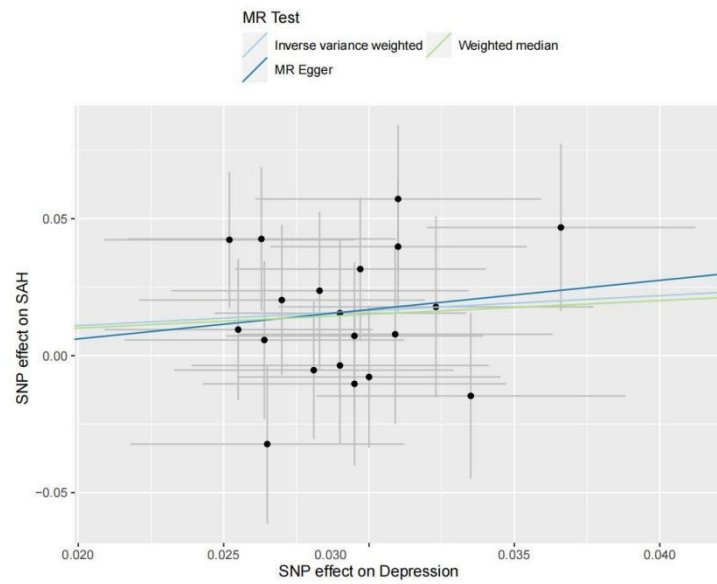
IAs, intracranial aneurysms; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

1.2 Supplementary Figure 1b. Scatter plot for depression on uIA.



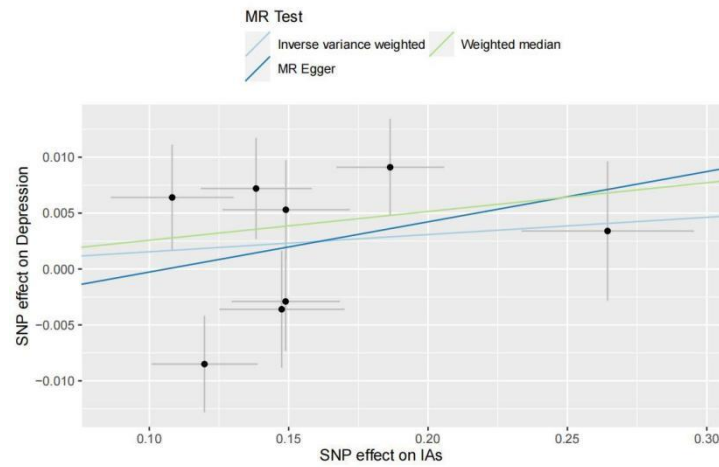
uIA, unruptured intracranial aneurysm; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

1.3 Supplementary Figure 1c. Scatter plot for depression on SAH.

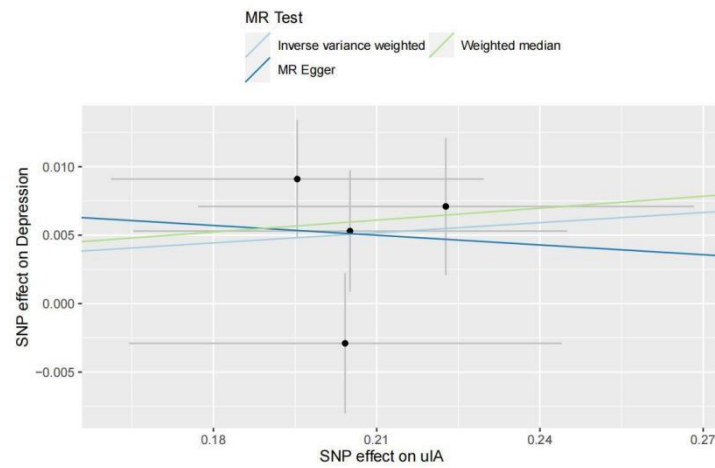


SAH, subarachnoid hemorrhage; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

1.4 Supplementary Figure 1d. Scatter plot for IAs on depression.

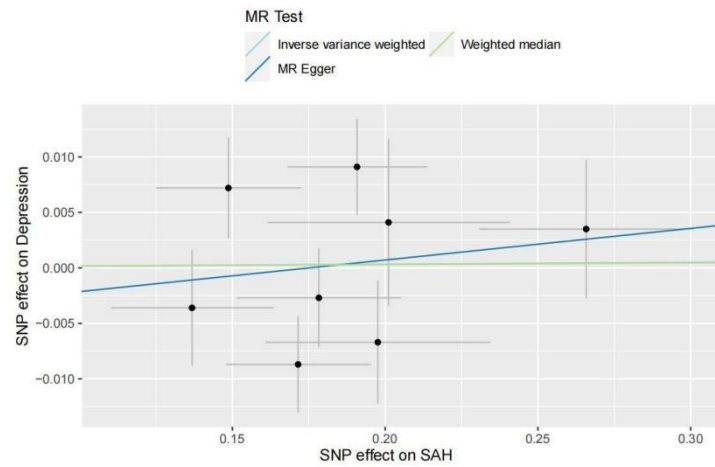


IAs, intracranial aneurysms; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

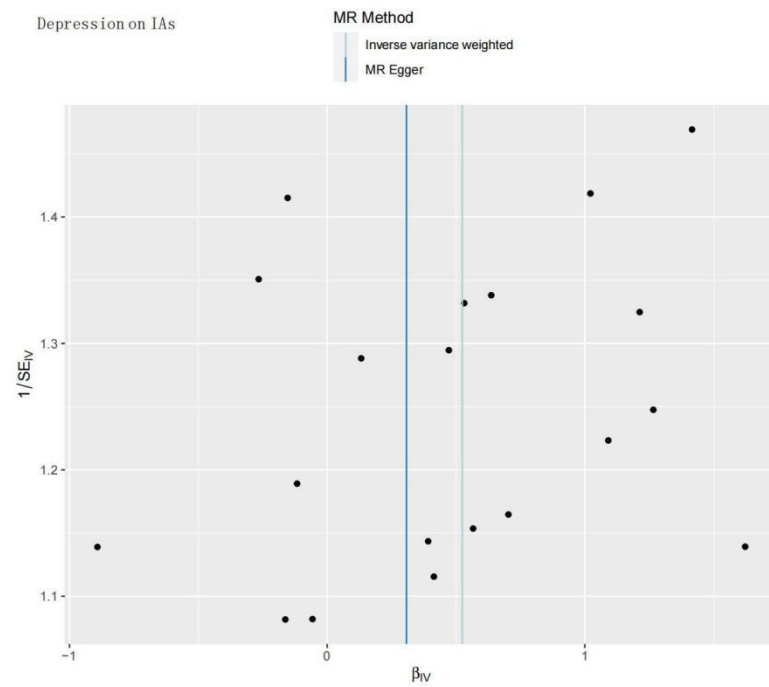
1.5 Supplementary Figure 1e. Scatter plot for uIA on depression.

uIA, unruptured intracranial aneurysm; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

1.6 **Supplementary Figure 1f.** Scatter plot for SAH on depression.

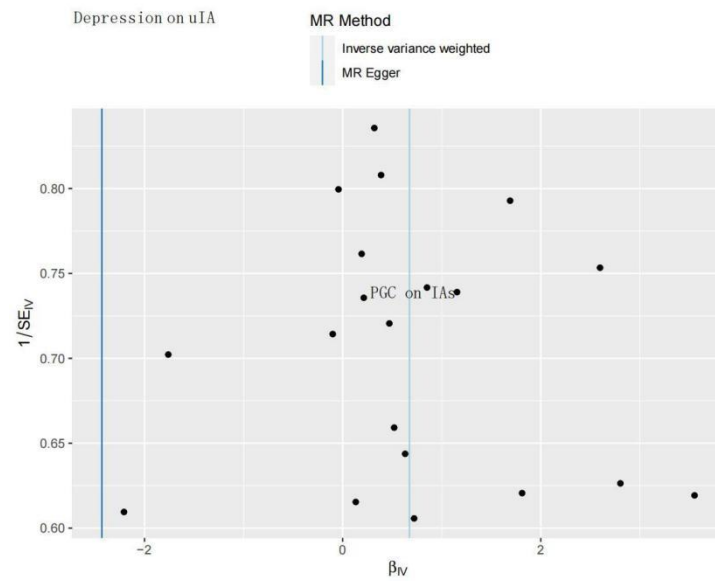


SAH, subarachnoid hemorrhage; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

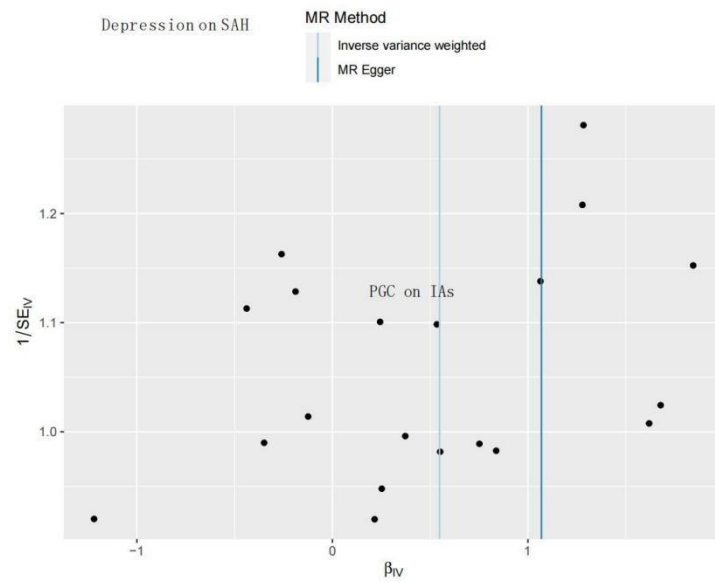
1.7 Supplementary Figure 2a. Funnel plot for depression on IAs.

IAs, intracranial aneurysms; MR, Mendelian randomization; IV, instrumental variable; SE, standard error.

1.8 Supplementary Figure 2b. Funnel plot for depression on uIA.

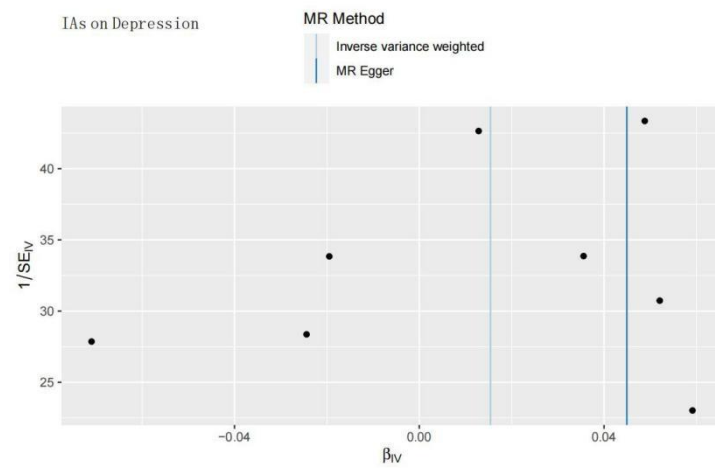


uIA, unruptured intracranial aneurysm; MR, Mendelian randomization; IV, instrumental variable; SE, standard error.

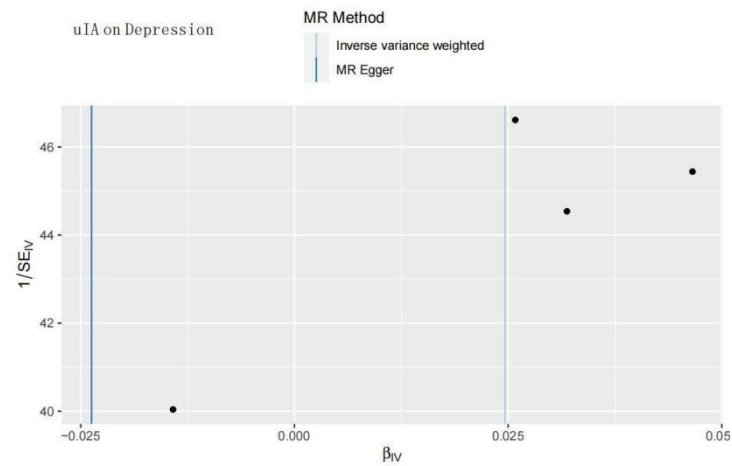
1.9 Supplementary Figure 2c. Funnel plot for depression on SAH.

SAH, subarachnoid hemorrhage; MR, Mendelian randomization; IV, instrumental variable; SE, standard error.

1.10 **Supplementary Figure 2d.** Funnel plot for IAs on depression.

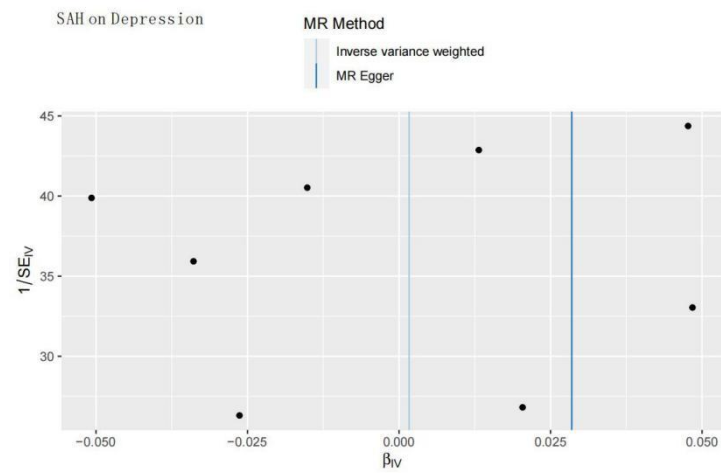


IAs, intracranial aneurysms; MR, Mendelian randomization; IV, instrumental variable; SE, standard error.

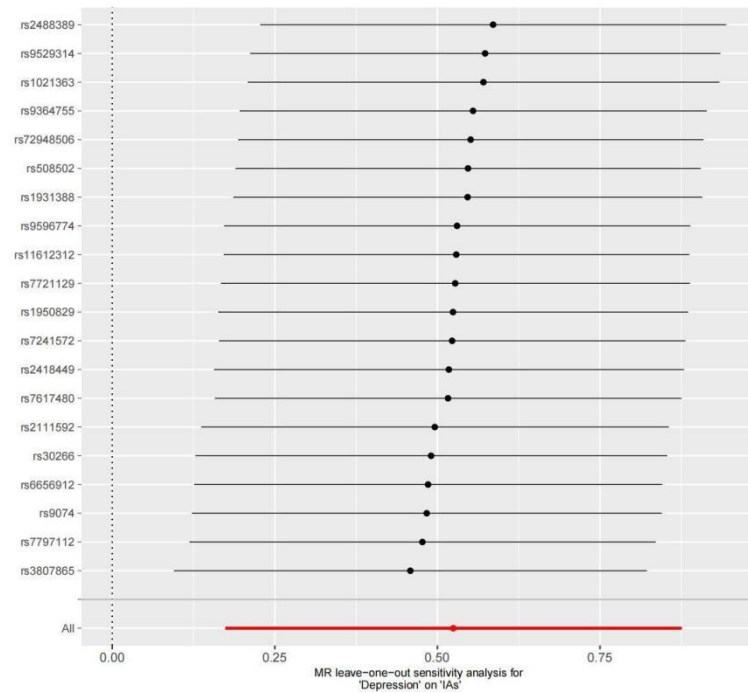
1.11 Supplementary Figure 2e. Funnel plot for uIA on depression.

uIA, unruptured intracranial aneurysm; MR, Mendelian randomization; IV, instrumental variable; SE, standard error.

1.12 **Supplementary Figure 2f.** Funnel plot for SAH on depression.

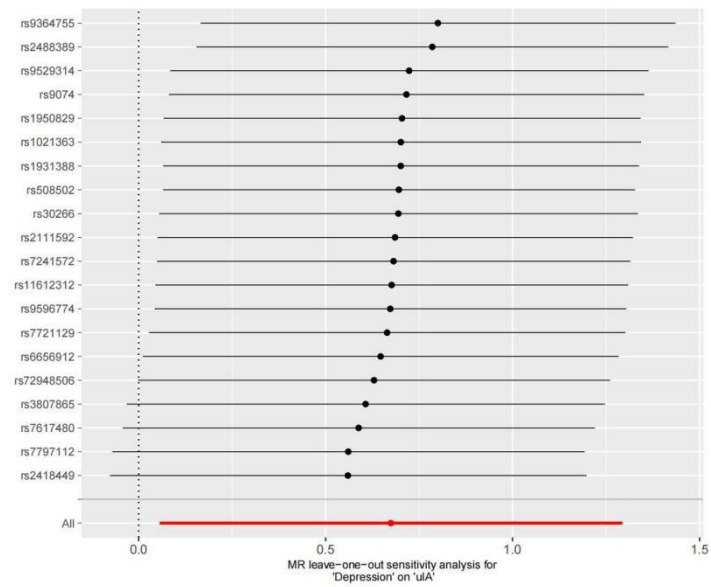


SAH, subarachnoid hemorrhage; MR, Mendelian randomization; IV, instrumental variable; SE, standard error.

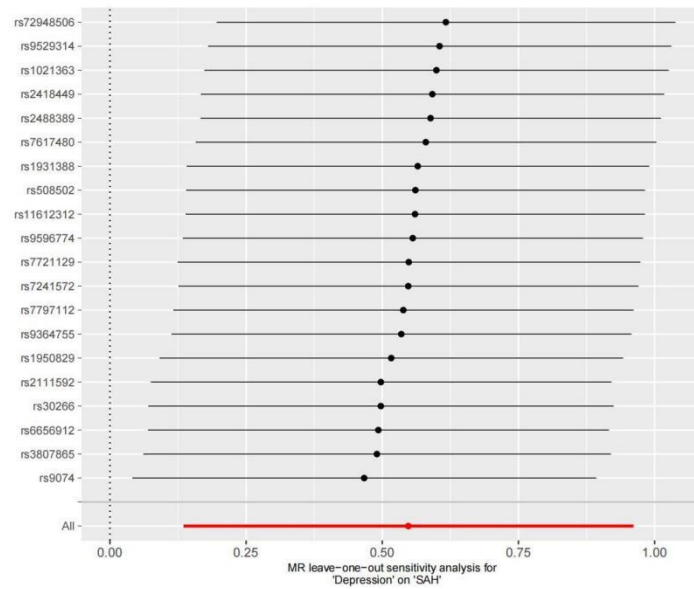
1.13 Supplementary Figure 3a. Leave-one-out graph for depression on IAs.

IAs, intracranial aneurysms; MR, Mendelian randomization.

1.14 **Supplementary Figure 3b.** Leave-one-out graph for depression on uIA.

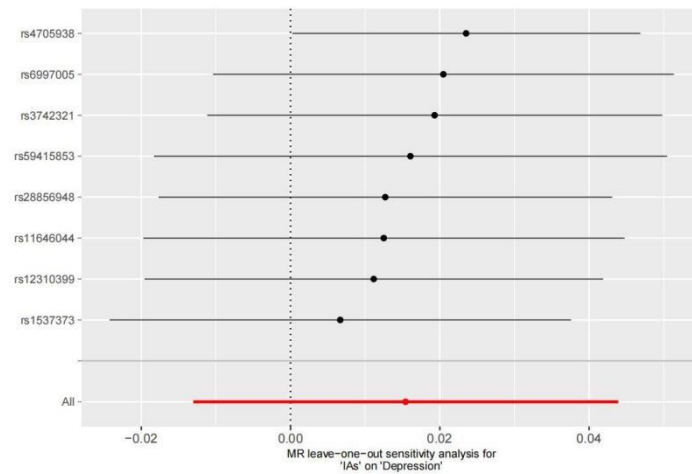


uIA, unruptured intracranial aneurysm; MR, Mendelian randomization.

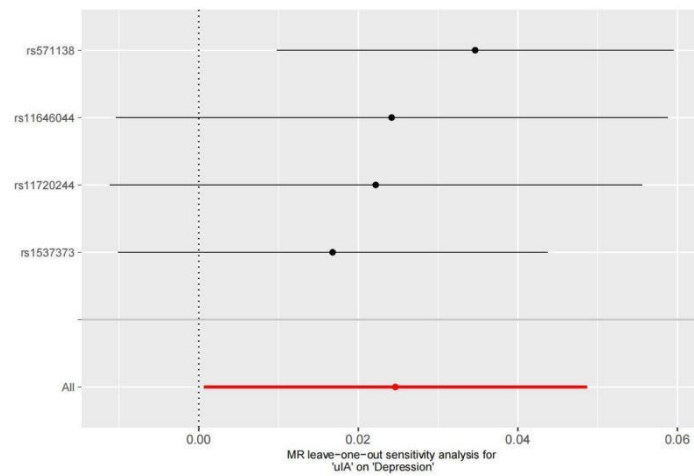
1.15 Supplementary Figure 3c. Leave-one-out graph for depression on SAH.

SAH, subarachnoid hemorrhage; MR, Mendelian randomization.

1.16 **Supplementary Figure 3d.** Leave-one-out graph for IAs on depression.

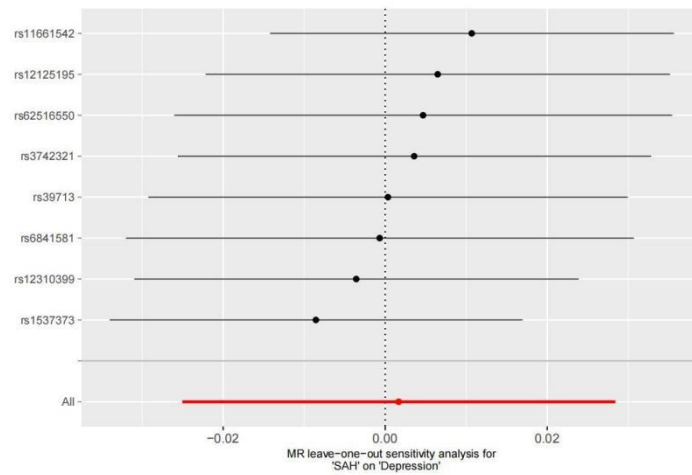


IAs, intracranial aneurysms; MR, Mendelian randomization.

1.17 Supplementary Figure 3e. Leave-one-out graph for uIA on depression.

uIA, unruptured intracranial aneurysm; MR, Mendelian randomization.

1.18 **Supplementary Figure 3f.** Leave-one-out graph for SAH on depression.



SAH, subarachnoid hemorrhage; MR, Mendelian randomization.

2. Supplementary Tables

2.1 Supplementary Table 1: Confounders/outcomes-related SNPs excluded from IVs that were screened based on the genome-wide significance threshold ($p < 1e-5$).

rait	PMID	SNP	EA	OA	Beta	SE	P-value
Body mass index	25673413	rs843812	G	A	0.0185	0.0038	1.13E-06
Body mass index	28443625	rs2568958	A	G	0.0434	0.0076	1.09E-08
Body mass index	UKBB	rs7152906	C	T	0.00862	0.001859	3.55E-06
Body mass index	UKBB	rs12631196	A	G	-0.01311	0.002443	8.00E-08
Body mass index	28892062	rs72841270	G	T	0.02319	0.004009	7.29E-09
Body mass index	28892062	rs79780963	C	T	-0.02522	0.004242	2.77E-09
Body mass index	28443625	rs10519203	A	G	0.0353	0.0071	7.22E-07
Alcohol intake frequency	UKBB	rs3099439	T	C	0.02025	0.003586	1.63E-08

Alcohol intake frequency	UKBB	rs4938021	C	T	0.01844	0.003659	4.65E-07
Alcohol intake frequency	UKBB	rs12967855	A	G	-0.007759	0.001658	2.86E-06
Alcohol intake frequency	UKBB	rs66511648	C	T	0.01811	0.003952	4.62E-06
smoking	20418888	rs7551758	G	T	NA	NA	1.60E-06
smoking	UKBB	rs12967855	A	G	0.006941	0.001411	8.74E-07
smoking	UKBB	rs67981811	C	G	-0.02246	0.004914	4.88E-06
smoking	20418890	rs10519203	A	G	-0.9817	0.0847	4.89E-31

SNP, single nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error.

2.2 **Supplementary Table 2:** Instrumental variables for depression ($p < 5e-08$).

SNP	Effect/Other	Beta(SE)	R ²	F statistics	p value	mr-keep	IAs		uIA		SAH	
							Beta (SE)	p value	Beta (SE)	p value	Beta (SE)	p value
rs1021363	A/G	0.03 (0.0045)	8.88E-05	44.44426674	2.62E-11	YES	-0.0046 (0.0212)	0.8295	0.0096 (0.0359)	0.7899	-0.0078 (0.0258)	0.7635
rs11612312	T/C	-0.0309 (0.0054)	6.55E-05	32.74369624	1.05E-08	YES	-0.0128 (0.0277)	0.6423	-0.0195 (0.048)	0.6848	-0.0078 (0.0326)	0.8119
rs1931388	A/G	0.0295 (0.0044)	8.99E-05	44.95075002	2.02E-11	YES	0.0039 (0.0229)	0.8652	0.0063 (0.0401)	0.8749	0.0072 (0.0268)	0.7873

rs195082 9	A/G	0.0297 (0.0043)	9.54E-05	47.706137	4.95 E-12	YES	0.0158 (0.0223)	0.478 3	0.0057 (0.039)	0.883 5	0.0316 (0.0261)	0.227 1
rs211159 2	A/G	0.0263 (0.0046)	6.53E-05	32.688432 62	1.08 E-08	YES	0.0287 (0.0215)	0.182 7	0.0124 (0.0365)	0.733	0.0426 (0.0261)	0.102 3
rs241844 9	T/C	0.0281 (0.0048)	6.85E-05	34.271130 33	4.79 E-09	YES	0.0179 (0.021)	0.394 4	0.073 (0.0373)	0.050 26	-0.0053 (0.0417)	0.831 7
rs248838 9	A/G	-0.02959 (0.0052)	6.43E-05	32.183673 09	1.40 E-08	YES	0.0263 (0.0259)	0.310 2	0.0651 (0.0484)	0.178 8	0.0103 (0.0321)	0.730 6
rs30266	A/G	0.0366 (0.0046)	0.0001265 46	63.305985 06	1.77 E-15	YES	0.0374 (0.0258)	0.146 5	0.0142 (0.0453)	0.753 2	0.0468 (0.0246)	0.122 7
rs380786 5	A/G	0.031 (0.0044)	9.92E-05	49.638231 28	1.85 E-12	YES	0.0439 (0.0211)	0.037 22	0.0524 (0.0391)	0.180 1	0.0398 (0.0287)	0.101 1

rs508502	T/C	-0.0264 (0.0048)	6.05E-05	30.249879 05	3.80 E-08	YES	0.0015 (0.0244)	0.950 3	-0.0035 (0.0429)	0.934 6	-0.0057 (0.0329)	0.842 4
rs665691 2	T/C	-0.0252 (0.0043)	6.87E-05	34.344914 05	4.62 E-09	YES	-0.0319 (0.0202)	0.114 5	0.048 (0.0341)	0.394 4	-0.0423 (0.0246)	0.084 85
rs724157 2	A/G	0.0323 (0.0054)	7.15E-05	35.777977 66	2.21 E-09	YES	0.0183 (0.028)	0.512 7	0.0813 (0.049)	0.732 3	0.0178 (0.0392)	0.587 6
rs729485 06	A/G	0.0265 (0.0047)	6.36E-05	31.790275 79	1.72 E-08	YES	-0.0043 (0.0245)	0.860 1	0.0247 (0.0427)	0.261 8	-0.0323 (0.0288)	0.262 5
rs761748 0	A/C	0.029 (0.0051)	6.46E-05	32.333588 52	1.30 E-08	YES	0.0204 (0.0249)	0.413	0.0959 (0.0463)	0.078 98	-0.0036 (0.0286)	0.899 6
rs772112 9	A/G	0.029 (0.0043)	9.09E-05	45.483863 57	1.54 E-11	YES	0.0137 (0.0224)	0.542 6	-0.0031 (0.0391)	0.527 8	0.0155 (0.0264)	0.558 3

rs779711 2	T/C	0.027 (0.0049)	6.07E-05	30.362227 62	3.58 E-08	YES	0.0438 (0.0237)	0.064 66	0.0498 (0.0436)	0.027 97	0.0203 (0.0273)	0.457 5
rs9074	A/G	0.031 (0.0049)	8.00E-05	40.024829 55	2.51 E-10	YES	0.0376 (0.0234)	0.107 7	0.0014 (0.0434)	0.943 7	0.0572 (0.0269)	0.033 27
rs936475 5	A/G	-0.0283 (0.0051)	6.16E-05	30.791495 49	2.87 E-08	YES	0.0033 (0.0238)	0.888 2	0.0184 (0.0403)	0.216	-0.0237 (0.0288)	0.411
rs952931 4	A/G	-0.0335 (0.0053)	7.99E-05	39.951780 45	2.60 E-10	YES	0.0089 (0.0248)	0.718 5	0.0096 (0.0419)	0.973 9	0.0147 (0.0301)	0.625 7
rs959677 4	T/C	0.0255 (0.0046)	6.14E-05	30.730028 36	2.97 E-08	YES	0.01 (0.0223)	0.653 5	-0.0195 (0.0421)	0.661 5	0.0095 (0.0256)	0.710 9

SNP, single nucleotide polymorphism; SE, standard error; IAs, intracranial aneurysms; uIA, unruptured intracranial aneurysm; SAH, subarachnoid hemorrhage.

2.3 **Supplementary Table 3:** Instrumental variables for IAs ($p < 1e-06$).

SNP	Effect/Other	Beta(SE)	R ²	F statistics	p value	mr-keep	PGC	
							Beta (SE)	p value
rs11646044	T/G	-0.149 (0.0227)	0.000542133	43.08339185	5.24E-11	YES	-0.0053 (0.0044)	0.229

rs12310399	T/C	-0.1383 (0.0198)	0.000613858	48.78687989	2.85E-12	YES	-0.0072 (0.0045)	0.1072
rs1537373	T/G	-0.1864 (0.0192)	0.00118521	94.24936288	2.78E-22	YES	-0.0091 (0.0043)	0.03362
rs3742321	T/C	-0.1475 (0.0223)	0.000307223	24.40930176	3.73E-11	YES	0.0036 (0.0052)	0.4796
rs39713	T/C	0.1823 (0.0332)	0.000550498	43.74852135	4.00E-08	YES	0.0041 (0.0075)	0.5808
rs4705938	T/C	0.1198 (0.0189)	0.000505582	40.17714683	2.32E-10	YES	-0.0085 (0.0043)	0.04871
rs59415853	A/G	-0.2644 (0.0308)	0.000926914	73.69033538	9.13E-18	YES	-0.0034 (0.0062)	0.5858
rs6997005	A/G	0.1489 (0.0193)	0.000748808	59.520126	1.21E-14	YES	-0.0029 (0.0044)	0.5042

SNP, single nucleotide polymorphism; SE, standard error; IAs, intracranial aneurysms.

2.4 **Supplementary Table 4:** Instrumental variables for uIA ($p < 1e-06$).

SNP	Effect/Other	Beta(SE)	R ²	F statistics	p value	mr-keep	PGC	
							Beta (SE)	p value
rs571138	A/C	-0.2042 (0.0397)	0.000357372	26.45566757	2.56E-07	YES	-0.0053 (0.0044)	0.229
rs11646044	T/G	-0.2051 (0.0398)	0.000358719	26.55543619	9.86E-07	YES	-0.0071 (0.005)	0.1533
rs11720244	T/C	-0.2227 (0.0455)	0.00032361	23.95553661	1.11E-08	YES	-0.00919 (0.0043)	0.03362
rs1537373	T/G	-0.1954 (0.0342)	0.00044091	32.64263203	2.85E-06	YES	-0.0113 (0.0168)	0.5009

SNP, single nucleotide polymorphism; SE, standard error; uIA, unruptured intracranial aneurysm.

2.5 **Supplementary Table 5:** Instrumental variables for SAH ($p < 1 \times 10^{-6}$).

SNP	Effect/Other	Beta(SE)	R ²	F statistics	p value	mr-keep	PGC	
							Beta (SE)	p value
rs11661542	A/C	-0.1715 (0.0235)	0.000748808	59.520126	2.92E-13	YES	0.0087 (0.0043)	0.04397
rs12125195	T/C	0.1976 (0.0367)	0.000690533	53.25755868	7.28E-08	YES	-0.0067 (0.0055)	0.2268
rs12310399	T/C	-0.1487 (0.0236)	0.000375985	28.98881631	2.96E-10	YES	-0.0072 (0.0045)	0.1072
rs1537373	T/G	-0.1908 (0.0227)	0.000514833	39.69964849	4.27E-17	YES	-0.0091 (0.0043)	0.03362

rs3742321	T/C	-0.1368 (0.0265)	0.000915797	70.64700525	2.44E-07	YES	0.0036 (0.0052)	0.4796
rs39713	T/C	0.2011 (0.0395)	0.000345639	26.64827965	3.56E-07	YES	0.0041 (0.0075)	0.5808
rs62516550	T/C	0.1783 (0.0268)	0.000336183	25.91902617	2.87E-11	YES	-0.0027 (0.0044)	0.5493
rs6841581	A/G	-0.2658 (0.0351)	0.000573952	44.26106184	3.66E-14	YES	-0.0035 (0.0062)	0.5703

SNP, single nucleotide polymorphism; SE, standard error; SAH, subarachnoid hemorrhage.