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BRIEF COMMUNICATION

Genetically-Proxied Levels of Vitamin D and Risk of Intracerebral Hemorrhage

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BACKGROUND: The evidence linking vitamin D (VitD) levels and spontaneous intracerebral hemorrhage (ICH) remains inconclusive. We tested the hypothesis that lower genetically determined VitD levels are associated with higher risk of ICH.

METHODS AND RESULTS: We conducted a 2 sample Mendelian Randomization (MR) study using publicly available summary statistics from published genome-wide association studies of VitD levels (417 580 study participants) and ICH (1545 ICH cases and 1481 matched controls). We used the inverse-variance weighted approach to generate causal estimates and the MR Pleiotropy Residual Sum and Outlier and MR-Egger approaches to assess for horizontal pleiotropy. To account for known differences in their underlying mechanism, we implemented stratified analysis based on the location of the hemorrhage within the brain (lobar or nonlobar). Our primary analysis indicated that each SD decrease in genetically instrumented VitD levels was associated with a 60% increased risk of ICH (odds ratio [OR], 1.60; [95% CI, 1.05–2.43]; P=0.029). We found no evidence of horizontal pleiotropy (MR-Egger intercept and MR Pleiotropy Residual Sum and Outlier global test with P>0.05). Stratified analyses indicated that the association was stronger for nonlobar ICH (OR, 1.87; [95% CI, 1.18–2.97]; P=0.007) compared with lobar ICH (OR, 1.43; [95% CI, 0.86–2.38]; P=0.17).

CONCLUSIONS: Lower levels of genetically proxied VitD levels are associated with higher ICH risk. These results provide evidence for a causal role of VitD metabolism in ICH.

Key Words: intracerebral hemorrhage ■ mendelian randomization ■ vitamin D

Vitamin D (VitD) metabolism is an appealing target for preventive interventions in cerebrovascular disease, as it can be easily and safely intervened upon.[1] A number of studies have explored the role of VitD in ischemic stroke.[2,3] Two observational studies demonstrated that depleted levels of VitD were associated with increased mortality and worse outcome in this condition.[2,3] Additionally, Zhou et al found that lower VitD levels were related to a higher risk of ischemic stroke in a large meta-analysis.[4] Genetic studies have also examined the relationship between VitD levels and ischemic stroke. A Mendelian Randomization (MR) study evaluating the association between genetically determined VitD and ischemic stroke did not find an association between these 2 traits.[5] Despite the significant amount of research outlined above, the role of VitD metabolism in intracerebral hemorrhage (ICH) remains relatively unexplored. While ICH shares some biological features with ischemic stroke, the overall pathophysiology of these 2 types of cerebrovascular diseases is significantly different. We therefore aimed to use MR analyses to evaluate the role of circulating levels of VitD in ICH, hypothesizing that genetically reduced levels of VitD lead to higher risk of ICH.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from

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qualified researchers trained in human subject confidentiality protocols may be sent to dbGap. Institutional Review Board approval was not required for this study.

Study Design

We conducted a 2-sample MR study, a study design where the genetic information for the exposure (VitD levels) and the outcome (risk of ICH) come from different studies, using summary statistics from large genetic studies of these traits. Importantly, there was no overlap between both study populations.

Instruments

We used independent (r^2>0.1) single nucleotide polymorphisms (SNPs) associated with VitD levels at genome-wide levels ($P<5\times10^{-8}$)[6,7] from the largest GWAS (Genome-Wide Association Study) on VitD available to date.[7] Palindromic SNPs were excluded from all analyses. For the final list of VitD associated instruments, we abstracted effect estimates and standard errors from the largest GWAS of ICH conducted to date,[8] using proxy variants (r^2>0.9) where available. The average F-statistic for the genetic instrument was 216 and the median was 39. The I^2 for the genetic instrument was 0.99. In combination, these metrics suggest that the genetic instrument had sufficient strength. We did not adjust for ancestry in the MR analysis because both GWAS (for the exposure and for the outcome) conducted principal component analyses, a robust method to identify genetic ancestry, to identify study participants from European ancestry and exclude population outliers.

Statistical Analysis

Our primary MR analysis used the inverse-variance weighted method. We tested for horizontal pleiotropy (the possibility that the effect of the instrument on the outcome of interest is exerted through a pathway other than VitD levels) using the MR-Egger intercept and Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) global test. In sensitivity analyses, we implemented the weighted median method and calculated the MR-PRESSO outlier corrected estimate.

We also examined whether any of the instruments were potentially associated with known confounders of the association between VitD and ICH. To this end, we performed sensitivity analyses using Cook's distance, defining outlier instruments as those with a Cook's distance >4/number of SNPs. We also looked for evidence of SNP outliers with RadialMR. In addition, we performed sensitivity analyses using multivariable MR to adjust for the genetic contribution of VitD going through other pathways associated with ICH. Finally, we completed leave-one-out plots (Figures S1 through S3). We recalibrated the effect estimates to express the change in ICH risk associated with an SD decrease in genetically instrumented VitD levels. We declared statistical significance at $P<0.05$ (2-tailed) when testing the single primary hypothesis that lower genetically determined VitD levels are associated with higher risk of ICH. We used R (version 3.6.0)[9] and its TwoSampleMR and MR-PRESSO packages.

RESULTS

From a GWAS of VitD that analyzed data on 417 580 people of European ancestry, we identified 108 SNPs that met our criteria to select instruments for this trait (Table 1). Of these, 88 SNPs (Table S1) had available summary results in a GWAS of ICH that included 1545 ICH cases (664 lobar and 881 nonlobar ICH cases) and 1481 matched controls of European ancestry (Table 1). Our primary analysis using the inverse-variance weighted MR method indicated that each SD decrease in genetically instrumented VitD levels was associated with an 60% increased risk of ICH (odds ratio [OR], 1.60; [95% CI, 1.05–2.43]; P=0.029) (Figure). To rule out heterogeneity in estimates across SNPs, we calculated Cochran Q statistics, which did not reveal heterogeneity. For all ICH, Q was 105.01, with 87 degrees of freedom and P value of 0.09. For lobar ICH, Q was 89.43 with 87 degrees of freedom and P value of 0.41. For nonlobar ICH, Q was 88.77, with 88 degrees of freedom and P value of 0.46.

Table 1. Characteristics of GWAS of Vitamin D and Intracerebral Hemorrhage

Characteristic	GWAS of vitamin D	GWAS of intracerebral hemorrhage
Sample size	417 580	3026
Mean age, y	47–66 [0.34–14.12]	67 [SD, 10]
Female sex	51%	45%
Genotyping platform	UK Biobank Axiom Array	Affymetrix 6.0 Illumina HumanHap610
No. of SNPs evaluated	8 806 780	5 258 103
No. of genome-wide significant loci	143	2

GWAS indicates Genome-Wide Association Study; and SNP, single nucleotide polymorphism.

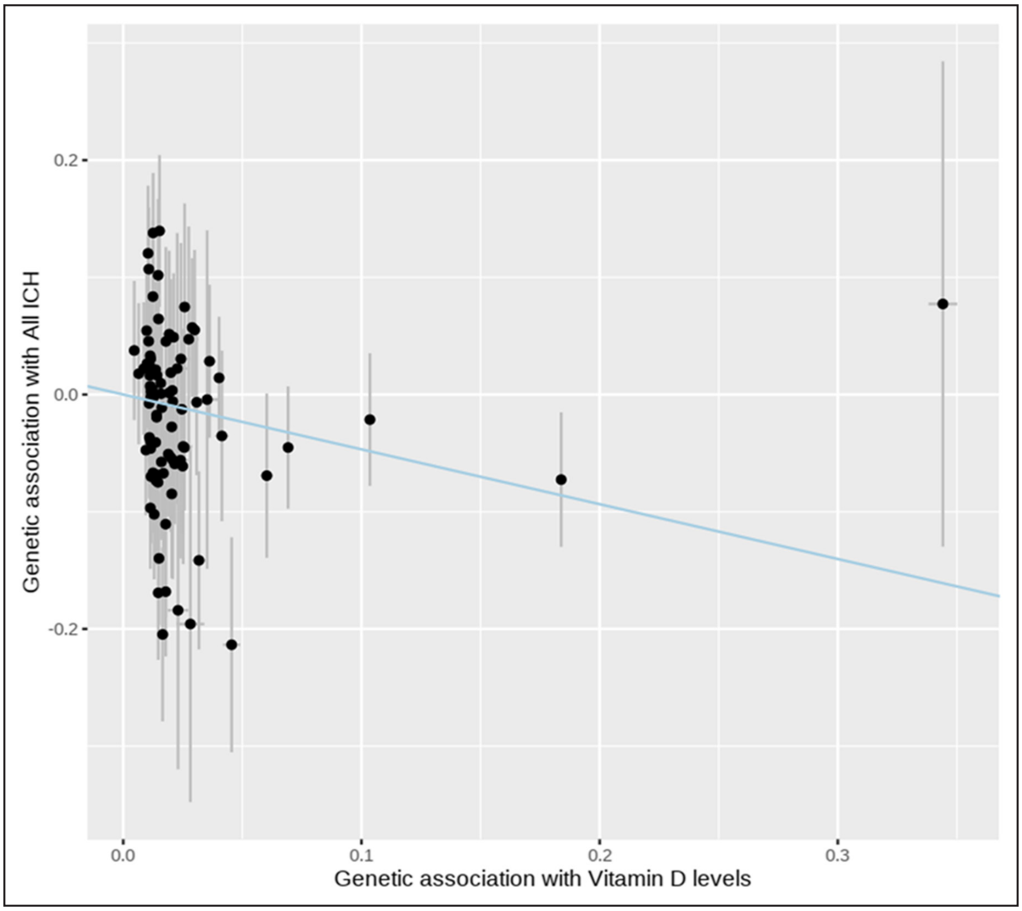

Figure. Mendelian randomization plot.
The plot presents the effect estimates of association tests between the single nucleotide polymorphisms and vitamin D levels (*X* axis) and risk of intracerebral hemorrhage (*Y* axis). The blue summary line corresponds to the slope of the inverse-variance weighted method. ICH indicates intracerebral hemorrhage.

There was no evidence of significant horizontal pleiotropy, as evidenced by the nonsignificant results of the MR-Egger intercept and MR-PRESSO Global tests (both P>0.05, Table 2). The direction and size of the effect were consistent in secondary analyses aimed at reducing the impact of any pleiotropy (Table 2). Summary statistics for analyses stratified by location were based on the analysis of 664 lobar and

Table 2. Results of Different Mendelian Randomization Analyses

Mendelian randomization method	All intracerebral hemorrhage		Lobar intracerebral hemorrhage		Nonlobar intracerebral hemorrhage	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Association tests						
Inverse-variance weighted	1.60 (1.05–2.43)	0.029	1.43 (0.86–2.38)	0.17	1.87 (1.18–2.97)	0.007
Weighted median	1.42 (0.81–2.50)	0.22	1.36 (0.66–2.79)	0.40	1.46 (0.76–2.80)	0.26
MR-Egger estimate	1.42 (0.82–2.46)	0.21	1.21 (0.62–2.36)	0.57	1.51 (0.83–2.73)	0.19
Weighted mode	1.37 (0.89–2.11)	0.15	1.11 (0.62–1.98)	0.73	1.45 (0.84–2.52)	0.19
Tests for horizontal pleiotropy*						
MR-Egger intercept	1.01 (0.99–1.02)	0.52	1.01 (0.99–1.03)	0.45	1.01 (0.99–1.03)	0.26
MR-PRESSO global test	…	0.11	…	0.44	…	0.48

IVW indicates inverse-variance weighted; MR, Mendelian Randomization; MR-PRESSO, Mendelian Randomization Pleiotropy Residual Sum and Outlier; and OR, odds ratio.
*Horizontal pleiotropy is absent if P>0.05.

881 nonlobar ICH cases (Table 1). In these stratified analyses according to location (Tables S2 and S3), the results remained significant for nonlobar ICH (OR, 1.87; [95% CI, 1.18–2.97]; *P*=0.007) but not for lobar ICH (OR, 1.43; [95% CI, 0.86–2.38]; *P*=0.17) (Table 2). For nonlobar ICH, there was no evidence of significant horizontal pleiotropy (*P*>0.05 for both the MR-Egger intercept and MR-PRESSO Global tests) and the direction and size of the effect were consistent in secondary analyses aimed at reducing pleiotropy (Table 2). The direction of effect for the MR-Egger estimate was consistent with other methods. For all ICH, the MR-Egger estimate was 1.42 (95% CI, 0.82–2.46; *P*=0.21). For nonlobar ICH, the MR-Egger estimate was 1.51 (95% CI, 0.83–2.73; *P*=0.19). For lobar ICH, the MR-Egger estimate was 1.21 (95% CI, 0.62–2.36; *P*=0.57). After performing Cook's distance, we found 2 outliers for all ICH, 1 outlier for lobar ICH and 3 outliers for nonlobar ICH. The Cook's distance plots can be found in Figures S4 through S6. After removing these outliers, the association remained significant for both all ICH (OR, 1.95; [95% CI, 1.08–3.55]; *P*=0.027) and nonlobar ICH (OR, 2.37; [95% CI, 1.20–4.67]; *P*=0.013).

In additional sensitivity analyses using multivariable MR to adjust for the genetic contribution of VitD to other pathways associated with ICH, we found that the association between VitD and both all and nonlobar ICH remained significant (Table S4). Finally, we have conducted a sensitivity analysis using an R^2 threshold of 0.001 for clumping, that resulted in the selection of 64 SNPs. Results were similar and consistent with the original analyses for all ICH (OR, 1.55; [95% C,I 1.01–2.40]; *P*=0.047), lobar ICH (OR, 1.47; [95% CI, 0.86–2.54]; *P*=0.16), and nonlobar ICH (OR, 1.78; [95% CI, 1.08–2.92]; *P*=0.02). Moreover, when testing for potential outliers with RadialMR, we did not detect any significant outliers for all ICH, lobar ICH, or nonlobar ICH using a Bonferroni-corrected threshold. Using a nominal threshold of 0.05, there were 9 outliers for all ICH, 6 outliers for lobar ICH, and 4 outliers for nonlobar ICH. The inverse-variance weighted MR remained significant for both all ICH (*P*=0.0467) and nonlobar ICH (*P*=0.016) after removing these outliers.

DISCUSSION

We report the results of a 2-sample MR study that used summary level results to evaluate the relationship between genetically determined VitD levels and risk of ICH. We found that genetically reduced levels of VitD associated with a modest increase in the risk of ICH, without evidence of significant horizontal pleiotropy and consistent direction of effects in secondary, more conservative analyses. However, only substantial pleiotropic effects can be ruled out because of the limited statistical power of methods such as MR-Egger. Stratification by location indicated that these associations were predominantly driven by nonlobar ICH, where associations were stronger despite a significant reduction in sample size.

Prior studies investigated the link between VitD deficit and ischemic stroke. A systematic review and meta-analysis demonstrated a 62% higher risk of stroke among individuals in the lowest versus highest categories of VitD concentrations.[4] Importantly, a randomized controlled trial evaluating cardiovascular disease broadly failed to show a protective effect of VitD supplementation on stroke risk.[10] From a population genetics perspective, a prior MR study that evaluated the relationship between genetically instrumented VitD levels and risk of ischemic stroke failed to find a protective association.[11]

Our study adds important new evidence to the field of VitD metabolism and ICH, an area of research that remains relatively unexplored. A prior MR study examined causal associations between VitD levels and several cardiovascular traits, including myocardial infarction, ischemic heart disease, ischemic stroke, subarachnoid hemorrhage, and ICH among Chinese.[5] Importantly, the effect size for the association between genetically determined VitD levels and ICH risk observed in this study[5] was similar (hazard ratio, 1.09 [95% CI, 1.01–1.18] per 25 nmol/L higher plasma 25(OH)D) to that obtained in our study. Another study implemented MR analyses using data from the China Kadoorie Biobank, the Copenhagen City Heart Study, and the Copenhagen General Population Study, and did not find any significant associations. However, the study only considered VitD-related variants in the *CYP2R1* and *DCHR7* genes. In contrast, the present study used a more powerful approach using several dozen genetic risk variants known to modify VitD levels. In addition, by focusing on a single outcome, we increase our discovery power by reducing multiple testing.

There are several possible pathophysiological mechanisms that could mediate the inverse association between VitD and ICH. First, VitD plays an important role in the occurrence of various cardiometabolic traits that predispose to ICH, including diabetes,[12] metabolic syndrome,[13] and renin-angiotensin system activation.[14] Another potential mechanism involves an upregulation of inflammatory pathways, as VitD inhibits the production of various inflammation factors.[15]

In conclusion, our results point to an inverse association between genetically determined VitD levels and risk of ICH. This association was driven by nonlobar (also known as deep) hemorrhages. Further research is needed to confirm these findings, extend these results to non-Europeans, and identify the putative mechanisms behind this association.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Tables S1–S4
Figures S1–S6

REFERENCES

1. Ma L, Wang S, Chen H, Cui L, Liu X, Yang H, Li G, Liu S, Qi T, Tian H. Diminished 25-OH vitamin D(3) levels and vitamin D receptor variants are associated with susceptibility to type 2 diabetes with coronary artery diseases. *J Clin Lab Anal*. 2020;34:e23137. doi: 10.1002/jcla.23137
2. Wajda J, Świat M, Owczarek AJ, Brzozowska A, Olszanecka-Glinianowicz M, Chudek J. Severity of vitamin D deficiency predicts mortality in ischemic stroke patients. *Dis Markers*. 2019;2019:3652894. doi: 10.1155/2019/3652894
3. Chen H, Liu Y, Huang G, Zhu J, Feng W, He J. Association between vitamin D status and cognitive impairment in acute ischemic stroke patients: A prospective cohort study. *Clin Interv Aging*. 2018;13:2503–2509. doi: 10.2147/cia.S187142
4. Zhou R, Wang M, Huang H, Li W, Hu Y, Wu T. Lower vitamin D status is associated with an increased risk of ischemic stroke: A systematic review and meta-analysis. *Nutrients*. 2018;10:1–12. doi: 10.3390/nu10030277
5. Huang T, Afzal S, Yu C, Guo Y, Bian Z, Yang L, Millwood IY, Walters RG, Chen Y, Chen N, et al. Vitamin D and cause-specific vascular disease and mortality: A mendelian randomisation study involving 99,012 Chinese and 106,911 European adults. *BMC Med*. 2019;17:160. doi: 10.1186/s12916-019-1401-y
6. Jiang X, O'Reilly PF, Aschard H, Hsu YH, Richards JB, Dupuis J, Ingelsson E, Karasik D, Pilz S, Berry D, et al. Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. *Nat Commun*. 2018;9:260. doi: 10.1038/s41467-017-02662-2
7. Revez JA, Lin T, Qiao Z, Xue A, Holtz Y, Zhu Z, Zeng J, Wang H, Sidorenko J, Kemper KE, et al. Genome-wide association study identifies 143 loci associated with 25 hydroxyvitamin D concentration. *Nat Commun*. 2020;11:1647. doi: 10.1038/s41467-020-15421-7
8. Woo D, Falcone GJ, Devan WJ, Brown WM, Biffi A, Howard TD, Anderson CD, Brouwers HB, Valant V, Battey TWK, et al. Meta-analysis of genome-wide association studies identifies 1q22 as a susceptibility locus for intracerebral hemorrhage. *Am J Hum Genet*. 2014;94:511–521. doi: 10.1016/j.ajhg.2014.02.012
9. Team RC. *R: A Language and Environment for Statistical Computing*. Viena, Austria: R Foundation for Statistical Computing; 2018. Available from: http://www.r-project.org/.
10. Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, Murphy J, Khaw KT, Camargo CA Jr. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessment study: A randomized clinical trial. *JAMA Cardiol*. 2017;2:608–616. doi: 10.1001/jamacardio.2017.0175
11. Larsson SC, Traylor M, Mishra A, Howson JMM, Michaëlsson K, Markus HS. Serum 25-hydroxyvitamin D concentrations and ischemic stroke and its subtypes. *Stroke*. 2018;49:2508–2511. doi: 10.1161/strokeaha.118.022242
12. Dadrass A, Mohamadzadeh Salamat K, Hamidi K, Azizbeigi K. Anti-inflammatory effects of vitamin D and resistance training in men with type 2 diabetes mellitus and vitamin D deficiency: A randomized, double-blinded, placebo-controlled clinical trial. *J Diabetes Metab Disord*. 2019;18:323–331. doi: 10.1007/s40200-019-00416-z
13. Park JE, Pichiah PBT, Cha YS. Vitamin D and metabolic diseases: Growing roles of vitamin D. *J Obes Metab Syndr*. 2018;27:223–232. doi: 10.7570/jomes.2018.27.4.223
14. Cui C, Xu P, Li G, Qiao Y, Han W, Geng C, Liao D, Yang M, Chen D, Jiang P. Vitamin D receptor activation regulates microglia polarization and oxidative stress in spontaneously hypertensive rats and angiotensin II-exposed microglial cells: Role of renin-angiotensin system. *Redox Biol*. 2019;26:101295. doi: 10.1016/j.redox.2019.101295
15. Krivoy A, Satz J, Hornfeld SH, Bar L, Gaughran F, Shoval G, Hochman E, Weizman A, Taler M. Low levels of serum vitamin D in clozapine-treated schizophrenia patients are associated with high levels of the proinflammatory cytokine IL-6. *Int Clin Psychopharmacol*. 2020;35:208–213. doi: 10.1097/yic.0000000000000303

SUPPLEMENTAL MATERIAL

Table S1. List of single nucleotide polymorphisms used in the study (all ICH).

SNP	Chr	Position	Effect allele	Other allele	Beta exposure	SE exposure	Beta outcome	SE outcome	EAF
rs10070734	5	87940026	T	C	-0.0104228	0.00216827	-0.1205	0.0577	0.290475
rs10085881	7	21577960	T	C	0.0141794	0.00220864	0.0164	0.0618	0.717835
rs1038165	12	68665940	C	T	-0.0113988	0.00199136	0.0968	0.052	0.416644
rs10426	19	51517798	G	A	-0.0245957	0.00239857	0.0126	0.0612	0.786581
rs10454087	17	40735641	C	T	0.0116466	0.00217735	-0.07	0.0569	0.715204
rs10859995	12	96375682	T	C	0.0402233	0.00199365	0.0142	0.0522	0.41738
rs10887718	10	82042624	C	T	0.0114771	0.00197171	-0.0461	0.051	0.471793
rs10908419	1	154567699	G	A	0.0113875	0.0019657	-0.0397	0.0508	0.510028
rs10908465	1	155389688	C	T	-0.0157145	0.0022193	-0.0097	0.0581	0.732654
rs11127186	2	28881407	T	C	-0.0110975	0.00200676	-0.0244	0.0523	0.504215
rs11182428	12	38526387	T	C	0.0118222	0.00196738	0.0191	0.0512	0.479988
rs11264322	1	155087933	G	A	0.00983463	0.00199554	0.0545	0.0529	0.570174
rs1149605	11	76485216	T	C	-0.0203649	0.00262634	0.0276	0.0704	0.829642
rs116970203	11	14876718	G	A	0.344103	0.00604043	0.0773	0.2071	0.972854
rs11732896	4	88287993	G	A	0.015001	0.00214451	-0.1398	0.0568	0.701193
rs12056768	8	116988527	T	G	0.0216054	0.0019971	-0.0592	0.0514	0.417109
rs12317268	12	21352541	A	G	0.0192946	0.00274768	0.0515	0.0712	0.849004
rs12372115	12	97982701	G	T	0.0207748	0.00382803	-0.0558	0.1016	0.929278
rs1260326	2	27730940	T	C	-0.0205984	0.00200946	-0.0035	0.0519	0.393449
rs12794714	11	14913575	G	A	0.0692066	0.00198946	-0.0452	0.0522	0.578149
rs12803256	11	71132868	A	G	-0.103558	0.0023682	0.0214	0.0566	0.223276
rs12881545	14	101176212	G	C	-0.00951387	0.00210312	0.0474	0.0556	0.326518
rs13060130	3	84440527	C	T	0.0135967	0.00283432	0.0212	0.0751	0.860343
rs13104260	4	70348090	G	A	-0.00648517	0.00225343	-0.0178	0.0602	0.743081
rs13284054	9	107669073	T	C	-0.0178056	0.00309215	0.1106	0.0792	0.882245
rs1352846	4	72617775	A	G	0.183861	0.00216171	-0.0726	0.0574	0.708555

rs1660839	11	71094232	G	A	-0.0289517	0.00227489	-0.0572	0.0592	0.751121
rs17216707	20	52732362	T	C	0.0362329	0.00260201	0.0284	0.0653	0.817326
rs17231506	16	56994528	C	T	0.0178297	0.00210314	-0.1682	0.0553	0.676898
rs1800588	15	58723675	C	T	0.0308346	0.00238954	-0.0066	0.0623	0.784792
rs2012736	2	234622379	C	A	0.0455066	0.00361616	-0.2135	0.0917	0.919152
rs2037511	18	61366207	G	A	-0.0168582	0.00264423	0.0672	0.068	0.834022
rs2074735	22	31535872	G	C	-0.0275007	0.00401718	-0.0472	0.0962	0.935944
rs212100	19	48376995	T	C	0.0602544	0.00265433	-0.0692	0.0701	0.164003
rs2131925	1	63025942	G	T	0.0211261	0.00205682	0.0489	0.0546	0.356411
rs2229742	21	16339172	G	C	0.0240457	0.00322702	-0.056	0.0839	0.896533
rs2248551	6	131924689	G	A	0.0203669	0.00264676	-0.0848	0.0718	0.834819
rs2346264	7	133536351	A	C	0.0142533	0.00240377	-0.0685	0.0629	0.217301
rs261291	15	58680178	T	C	0.0256413	0.00205788	-0.0452	0.0537	0.644799
rs2710651	2	63166379	G	A	0.0113064	0.00196984	0.0072	0.0516	0.471888
rs2725371	8	30854033	A	G	-0.00861253	0.00215382	-0.0221	0.0567	0.302285
rs28692966	8	25892919	G	A	-0.0140087	0.00226945	0.0194	0.0588	0.747024
rs2952289	17	66464414	C	T	-0.0159269	0.00245912	-0.0007	0.0636	0.201966
rs31612	5	108996643	T	C	0.0124544	0.00261401	0.0836	0.0649	0.825572
rs325384	15	100229761	C	T	0.0126665	0.00218846	-0.0025	0.0594	0.715856
rs34290760	8	9185179	C	G	0.0281839	0.00585264	-0.1958	0.152	0.970879
rs35408430	1	17560195	C	T	0.0207679	0.00207182	-0.0059	0.0544	0.657829
rs3849374	2	101443397	G	C	0.0159963	0.00258093	-0.0575	0.0665	0.82199
rs3925446	10	91495322	G	A	-0.0147869	0.002463	-0.0645	0.0653	0.800891
rs4121823	18	47144223	T	A	0.0165318	0.00274098	-0.2047	0.0742	0.154674
rs4327060	16	72807438	C	T	0.0226633	0.00433397	0.0222	0.1156	0.945604
rs4418728	10	94839724	G	T	-0.0111594	0.00197359	-0.0163	0.0517	0.54832
rs4575545	16	79755446	G	A	0.0145918	0.00214424	-0.0749	0.0555	0.695191
rs4616820	4	57745481	C	T	0.012479	0.00199079	-0.0668	0.0511	0.535048

rs4738684	8	59393273	A	G	-0.00994588	0.00208683	-0.0263	0.0548	0.334508
rs541041	2	21294975	G	A	0.0152241	0.00255168	0.1396	0.0648	0.180809
rs55829990	15	63790642	T	C	0.0191915	0.00207492	0.0014	0.0534	0.655979
rs590215	18	57904088	C	T	0.00462051	0.00222766	0.0376	0.0594	0.734097
rs6003456	22	23356100	T	A	0.0122883	0.00233244	0.0044	0.0621	0.765364
rs613808	11	116710968	A	G	-0.024948	0.00220937	0.0611	0.0568	0.279985
rs61891388	11	66079818	T	G	-0.0115084	0.00198127	-0.0305	0.0512	0.544054
rs62007299	15	77711719	G	A	0.0116231	0.00217065	0.0026	0.0561	0.287451
rs6672758	1	230303512	C	T	-0.0146302	0.0024755	-0.1018	0.0652	0.199137
rs6782190	3	85639672	G	A	0.0189106	0.00205644	-0.0508	0.0535	0.352497
rs6966728	7	104618318	C	T	0.0113076	0.00201049	0.0331	0.0513	0.537355
rs705117	4	72608115	C	T	0.0317739	0.00276853	-0.1415	0.076	0.147721
rs7149014	14	29802911	T	C	0.0107334	0.0020584	0.107	0.0527	0.370816
rs727857	2	58981967	G	A	0.0109766	0.00203429	-0.0366	0.0521	0.388495
rs72834856	6	22801858	T	G	0.0251376	0.00379985	-0.0443	0.1004	0.927943
rs72997623	11	75488054	C	A	-0.0257654	0.00353337	-0.0747	0.0884	0.915323
rs7522116	1	41835685	C	T	0.012542	0.00199858	0.1379	0.0512	0.433716
rs7528419	1	109817192	A	G	-0.019866	0.00235556	0.0535	0.0635	0.775305
rs7569755	2	118648261	G	A	-0.0135962	0.00218248	0.0408	0.0566	0.709372
rs75741381	7	100809458	C	G	0.0137731	0.00278718	-0.0734	0.0719	0.852317
rs7604788	2	21190024	C	T	-0.0352194	0.0054801	0.0043	0.1444	0.966596
rs77532868	10	88081438	C	T	-0.0230071	0.0043429	0.1841	0.1357	0.945978
rs7784802	7	64015379	A	T	-0.0129774	0.00204446	0.1022	0.0555	0.639012
rs78151190	6	25619007	A	C	0.0179172	0.00293406	0.0453	0.0806	0.871246
rs78649910	4	3482213	T	A	0.019983	0.00320891	0.0187	0.0798	0.893826
rs8018720	14	39556185	G	C	0.0299593	0.0025742	0.0551	0.0683	0.176691
rs804281	8	11611865	A	G	-0.0161836	0.00199452	0.0112	0.052	0.416402
rs8091117	18	28919794	C	A	0.0241938	0.0039757	0.0304	0.0989	0.934736

rs8113404	19	53065579	C	T	-0.0115758	0.00214261	0.0021	0.0557	0.695417
rs867772	1	220972343	A	G	0.0147054	0.00212274	-0.1692	0.0572	0.315533
rs9476310	6	57767576	C	T	-0.0108729	0.00197437	0.0076	0.0509	0.488661
rs9490317	6	121859499	T	C	-0.0106658	0.00198507	-0.0455	0.0514	0.554066
rs964184	11	116648917	G	C	-0.0414009	0.00290504	0.0353	0.0728	0.131625
rs9861009	3	141654685	T	C	-0.0139778	0.00222312	0.0175	0.0566	0.272456

Table S2. **List of single nucleotide polymorphisms used in the study (Non-Lobar ICH).**									
SNP	chr	pos	effect_allele	other_allele	beta.exposure	se.exposure	beta.outcome	se.outcome	eaf
rs10070734	5	87940026	T	C	-0.0104228	0.00216827	-0.0818	0.0681	0.290475
rs10085881	7	21577960	T	C	0.0141794	0.00220864	-0.0331	0.0728	0.717835
rs1038165	12	68665940	C	T	-0.0113988	0.00199136	0.1259	0.0612	0.416644
rs10426	19	51517798	G	A	-0.0245957	0.00239857	-0.0196	0.0721	0.786581
rs10454087	17	40735641	C	T	0.0116466	0.00217735	-0.0748	0.0675	0.715204
rs10859995	12	96375682	T	C	0.0402233	0.00199365	-0.0138	0.0622	0.41738
rs10887718	10	82042624	C	T	0.0114771	0.00197171	-0.0427	0.0605	0.471793
rs10908419	1	154567699	G	A	0.0113875	0.0019657	-0.0076	0.0603	0.510028
rs10908465	1	155389688	C	T	-0.0157145	0.0022193	-0.055	0.0687	0.732654
rs11127186	2	28881407	T	C	-0.0110975	0.00200676	0.0285	0.0629	0.504215
rs11182428	12	38526387	T	C	0.0118222	0.00196738	-0.049	0.061	0.479988
rs11264322	1	155087933	G	A	0.00983463	0.00199554	0.0807	0.0626	0.570174
rs1149605	11	76485216	T	C	-0.0203649	0.00262634	-0.0901	0.0817	0.829642
rs116970203	11	14876718	G	A	0.344103	0.00604043	-0.0823	0.2469	0.972854
rs11732896	4	88287993	G	A	0.015001	0.00214451	-0.1184	0.0682	0.701193
rs12056768	8	116988527	T	G	0.0216054	0.0019971	-0.0869	0.0613	0.417109
rs12317268	12	21352541	A	G	0.0192946	0.00274768	0.0683	0.0823	0.849004
rs12372115	12	97982701	G	T	0.0207748	0.00382803	-0.0514	0.1195	0.929278
rs1260326	2	27730940	T	C	-0.0205984	0.00200946	0.0164	0.0615	0.393449
rs12794714	11	14913575	G	A	0.0692066	0.00198946	-0.0873	0.0618	0.578149
rs12803256	11	71132868	A	G	-0.103558	0.0023682	0.0076	0.0671	0.223276
rs12881545	14	101176212	G	C	-0.00951387	0.00210312	0.0026	0.0656	0.326518
rs13060130	3	84440527	C	T	0.0135967	0.00283432	-0.0437	0.0885	0.860343
rs13104260	4	70348090	G	A	-0.00648517	0.00225343	0.0077	0.0708	0.743081
rs13284054	9	107669073	T	C	-0.0178056	0.00309215	0.1024	0.094	0.882245
rs1352846	4	72617775	A	G	0.183861	0.00216171	-0.0736	0.0691	0.708555

rs1660839	11	71094232	G	A	-0.0289517	0.00227489	-0.0853	0.07	0.751121
rs17216707	20	52732362	T	C	0.0362329	0.00260201	0.0227	0.077	0.817326
rs17231506	16	56994528	C	T	0.0178297	0.00210314	-0.1847	0.0658	0.676898
rs1800588	15	58723675	C	T	0.0308346	0.00238954	0.0271	0.0744	0.784792
rs2012736	2	234622379	C	A	0.0455066	0.00361616	-0.201	0.1103	0.919152
rs2037511	18	61366207	G	A	-0.0168582	0.00264423	0.0927	0.0815	0.834022
rs2074735	22	31535872	G	C	-0.0275007	0.00401718	-0.0833	0.1136	0.935944
rs212100	19	48376995	T	C	0.0602544	0.00265433	-0.1506	0.0841	0.164003
rs2131925	1	63025942	G	T	0.0211261	0.00205682	0.0128	0.0652	0.356411
rs2229742	21	16339172	G	C	0.0240457	0.00322702	-0.0779	0.0993	0.896533
rs2248551	6	131924689	G	A	0.0203669	0.00264676	-0.0899	0.0851	0.834819
rs2346264	7	133536351	A	C	0.0142533	0.00240377	-0.0387	0.0743	0.217301
rs261291	15	58680178	T	C	0.0256413	0.00205788	-0.0694	0.063	0.644799
rs2710651	2	63166379	G	A	0.0113064	0.00196984	0.0107	0.0617	0.471888
rs2725371	8	30854033	A	G	-0.00861253	0.00215382	-0.0085	0.0669	0.302285
rs28692966	8	25892919	G	A	-0.0140087	0.00226945	0.0011	0.0695	0.747024
rs2952289	17	66464414	C	T	-0.0159269	0.00245912	-0.0651	0.0764	0.201966
rs31612	5	108996643	T	C	0.0124544	0.00261401	0.0423	0.077	0.825572
rs325384	15	100229761	C	T	0.0126665	0.00218846	0.066	0.0707	0.715856
rs34290760	8	9185179	C	G	0.0281839	0.00585264	-0.3061	0.1803	0.970879
rs35408430	1	17560195	C	T	0.0207679	0.00207182	-0.0172	0.0647	0.657829
rs3849374	2	101443397	G	C	0.0159963	0.00258093	-0.0952	0.0795	0.82199
rs3925446	10	91495322	G	A	-0.0147869	0.002463	-0.0539	0.0772	0.800891
rs4121823	18	47144223	T	A	0.0165318	0.00274098	-0.1955	0.0873	0.154674
rs4327060	16	72807438	C	T	0.0226633	0.00433397	0.0176	0.1381	0.945604
rs4418728	10	94839724	G	T	-0.0111594	0.00197359	0.0501	0.0615	0.54832
rs4575545	16	79755446	G	A	0.0145918	0.00214424	-0.1114	0.0659	0.695191
rs4616820	4	57745481	C	T	0.012479	0.00199079	-0.0935	0.0609	0.535048

rs4738684	8	59393273	A	G	-0.00994588	0.00208683	-0.0346	0.0647	0.334508
rs541041	2	21294975	G	A	0.0152241	0.00255168	0.1757	0.0762	0.180809
rs55829990	15	63790642	T	C	0.0191915	0.00207492	0.0058	0.0633	0.655979
rs590215	18	57904088	C	T	0.00462051	0.00222766	0.019	0.0701	0.734097
rs6003456	22	23356100	T	A	0.0122883	0.00233244	0.0004	0.0736	0.765364
rs613808	11	116710968	A	G	-0.024948	0.00220937	0.0335	0.0676	0.279985
rs61891388	11	66079818	T	G	-0.0115084	0.00198127	-0.014	0.0605	0.544054
rs62007299	15	77711719	G	A	0.0116231	0.00217065	-0.0568	0.0668	0.287451
rs6672758	1	230303512	C	T	-0.0146302	0.0024755	-0.0536	0.0762	0.199137
rs6782190	3	85639672	G	A	0.0189106	0.00205644	-0.0695	0.0638	0.352497
rs6966728	7	104618318	C	T	0.0113076	0.00201049	0.055	0.0612	0.537355
rs705117	4	72608115	C	T	0.0317739	0.00276853	-0.1853	0.0916	0.147721
rs7149014	14	29802911	T	C	0.0107334	0.0020584	0.0851	0.0628	0.370816
rs727857	2	58981967	G	A	0.0109766	0.00203429	-0.0385	0.0624	0.388495
rs72834856	6	22801858	T	G	0.0251376	0.00379985	-0.0071	0.1196	0.927943
rs72997623	11	75488054	C	A	-0.0257654	0.00353337	-0.0625	0.103	0.915323
rs7522116	1	41835685	C	T	0.012542	0.00199858	0.1126	0.0618	0.433716
rs7528419	1	109817192	A	G	-0.019866	0.00235556	0.0438	0.0754	0.775305
rs7569755	2	118648261	G	A	-0.0135962	0.00218248	0.0771	0.0678	0.709372
rs75741381	7	100809458	C	G	0.0137731	0.00278718	-0.0689	0.0861	0.852317
rs7604788	2	21190024	C	T	-0.0352194	0.0054801	-0.1243	0.1688	0.966596
rs76798800	1	154994978	G	T	0.00904347	0.00222959	-0.021	0.0779	0.733722
rs77532868	10	88081438	C	T	-0.0230071	0.0043429	0.2162	0.1636	0.945978
rs7784802	7	64015379	A	T	-0.0129774	0.00204446	0.0887	0.0665	0.639012
rs78151190	6	25619007	A	C	0.0179172	0.00293406	0.1043	0.0969	0.871246
rs78649910	4	3482213	T	A	0.019983	0.00320891	0.0171	0.0942	0.893826
rs8018720	14	39556185	G	C	0.0299593	0.0025742	0.0576	0.0806	0.176691
rs804281	8	11611865	A	G	-0.0161836	0.00199452	0.036	0.0618	0.416402

rs8091117	18	28919794	C	A	0.0241938	0.0039757	-0.0204	0.1165	0.934736
rs8113404	19	53065579	C	T	-0.0115758	0.00214261	0.0223	0.0664	0.695417
rs867772	1	220972343	A	G	0.0147054	0.00212274	-0.1698	0.0687	0.315533
rs9476310	6	57767576	C	T	-0.0108729	0.00197437	0.0103	0.0602	0.488661
rs9490317	6	121859499	T	C	-0.0106658	0.00198507	-0.0363	0.0617	0.554066
rs964184	11	116648917	G	C	-0.0414009	0.00290504	-0.0005	0.0873	0.131625
rs9861009	3	141654685	T	C	-0.0139778	0.00222312	0.0081	0.0671	0.272456

Table S3. List of single nucleotide polymorphisms used in the study (Lobar ICH).

SNP	Chr	Position	Effect allele	Other allele	Beta exposure	SE exposure	Beta outcome	SE outcome	EAF
rs10070734	5	87940026	T	C	-0.0104228	0.00216827	-0.2048	0.0762	0.290475
rs10085881	7	21577960	T	C	0.0141794	0.00220864	0.0291	0.0817	0.717835
rs1038165	12	68665940	C	T	-0.0113988	0.00199136	0.0508	0.0686	0.416644
rs10426	19	51517798	G	A	-0.0245957	0.00239857	0.0675	0.0806	0.786581
rs10454087	17	40735641	C	T	0.0116466	0.00217735	-0.078	0.0734	0.715204
rs10859995	12	96375682	T	C	0.0402233	0.00199365	0.0168	0.0683	0.41738
rs10887718	10	82042624	C	T	0.0114771	0.00197171	-0.0903	0.0664	0.471793
rs10908419	1	154567699	G	A	0.0113875	0.0019657	-0.0932	0.0666	0.510028
rs10908465	1	155389688	C	T	-0.0157145	0.0022193	0.0556	0.0765	0.732654
rs11127186	2	28881407	T	C	-0.0110975	0.00200676	-0.0933	0.0677	0.504215
rs11182428	12	38526387	T	C	0.0118222	0.00196738	0.0658	0.067	0.479988
rs11264322	1	155087933	G	A	0.00983463	0.00199554	0.022	0.0691	0.570174
rs1149605	11	76485216	T	C	-0.0203649	0.00262634	0.1488	0.0932	0.829642
rs116970203	11	14876718	G	A	0.344103	0.00604043	0.2686	0.2844	0.972854
rs11732896	4	88287993	G	A	0.015001	0.00214451	-0.1945	0.0737	0.701193
rs12056768	8	116988527	T	G	0.0216054	0.0019971	-0.0245	0.0674	0.417109
rs12317268	12	21352541	A	G	0.0192946	0.00274768	-0.0304	0.0907	0.849004
rs12372115	12	97982701	G	T	0.0207748	0.00382803	-0.0678	0.1305	0.929278
rs1260326	2	27730940	T	C	-0.0205984	0.00200946	-0.0104	0.0687	0.393449
rs12794714	11	14913575	G	A	0.0692066	0.00198946	0.0238	0.0686	0.578149
rs12803256	11	71132868	A	G	-0.103558	0.0023682	0.0322	0.0738	0.223276
rs12881545	14	101176212	G	C	-0.00951387	0.00210312	0.1057	0.0723	0.326518
rs13060130	3	84440527	C	T	0.0135967	0.00283432	0.1168	0.1011	0.860343
rs13104260	4	70348090	G	A	-0.00648517	0.00225343	0.0225	0.078	0.743081
rs13284054	9	107669073	T	C	-0.0178056	0.00309215	0.1181	0.1035	0.882245
rs1352846	4	72617775	A	G	0.183861	0.00216171	-0.0563	0.0746	0.708555

rs1660839	11	71094232	G	A	-0.0289517	0.00227489	-0.0418	0.0784	0.751121
rs17216707	20	52732362	T	C	0.0362329	0.00260201	0.0702	0.0852	0.817326
rs17231506	16	56994528	C	T	0.0178297	0.00210314	-0.1814	0.072	0.676898
rs1800588	15	58723675	C	T	0.0308346	0.00238954	-0.0302	0.0813	0.784792
rs2012736	2	234622379	C	A	0.0455066	0.00361616	-0.2614	0.1188	0.919152
rs2037511	18	61366207	G	A	-0.0168582	0.00264423	0.059	0.0874	0.834022
rs2074735	22	31535872	G	C	-0.0275007	0.00401718	0.0094	0.1286	0.935944
rs212100	19	48376995	T	C	0.0602544	0.00265433	-0.0348	0.091	0.164003
rs2131925	1	63025942	G	T	0.0211261	0.00205682	0.071	0.0715	0.356411
rs2229742	21	16339172	G	C	0.0240457	0.00322702	-0.0551	0.1096	0.896533
rs2248551	6	131924689	G	A	0.0203669	0.00264676	-0.0284	0.0941	0.834819
rs2346264	7	133536351	A	C	0.0142533	0.00240377	-0.1081	0.0836	0.217301
rs261291	15	58680178	T	C	0.0256413	0.00205788	0.0126	0.0707	0.644799
rs2710651	2	63166379	G	A	0.0113064	0.00196984	-0.0152	0.0672	0.471888
rs2725371	8	30854033	A	G	-0.00861253	0.00215382	-0.0395	0.0749	0.302285
rs28692966	8	25892919	G	A	-0.0140087	0.00226945	0.0271	0.0772	0.747024
rs2952289	17	66464414	C	T	-0.0159269	0.00245912	0.0433	0.0834	0.201966
rs31612	5	108996643	T	C	0.0124544	0.00261401	0.1137	0.0864	0.825572
rs325384	15	100229761	C	T	0.0126665	0.00218846	-0.0262	0.0773	0.715856
rs34290760	8	9185179	C	G	0.0281839	0.00585264	-0.1629	0.2162	0.970879
rs35408430	1	17560195	C	T	0.0207679	0.00207182	0.0269	0.0714	0.657829
rs3849374	2	101443397	G	C	0.0159963	0.00258093	-0.0157	0.0875	0.82199
rs3925446	10	91495322	G	A	-0.0147869	0.002463	-0.0243	0.0864	0.800891
rs4121823	18	47144223	T	A	0.0165318	0.00274098	-0.1894	0.0963	0.154674
rs4327060	16	72807438	C	T	0.0226633	0.00433397	0.0107	0.1501	0.945604
rs4418728	10	94839724	G	T	-0.0111594	0.00197359	-0.0855	0.0674	0.54832
rs4575545	16	79755446	G	A	0.0145918	0.00214424	-0.047	0.0727	0.695191
rs4616820	4	57745481	C	T	0.012479	0.00199079	-0.0421	0.0667	0.535048

rs4738684	8	59393273	A	G	-0.00994588	0.00208683	0.0141	0.0725	0.334508
rs541041	2	21294975	G	A	0.0152241	0.00255168	0.0821	0.085	0.180809
rs55829990	15	63790642	T	C	0.0191915	0.00207492	0.0089	0.0695	0.655979
rs590215	18	57904088	C	T	0.00462051	0.00222766	0.0838	0.0782	0.734097
rs6003456	22	23356100	T	A	0.0122883	0.00233244	-0.0071	0.0824	0.765364
rs613808	11	116710968	A	G	-0.024948	0.00220937	0.1353	0.0747	0.279985
rs61891388	11	66079818	T	G	-0.0115084	0.00198127	-0.0365	0.0673	0.544054
rs62007299	15	77711719	G	A	0.0116231	0.00217065	0.0333	0.0739	0.287451
rs6672758	1	230303512	C	T	-0.0146302	0.0024755	-0.1721	0.0851	0.199137
rs6782190	3	85639672	G	A	0.0189106	0.00205644	-0.0788	0.0689	0.352497
rs6966728	7	104618318	C	T	0.0113076	0.00201049	-0.0063	0.0667	0.537355
rs705117	4	72608115	C	T	0.0317739	0.00276853	-0.05	0.0984	0.147721
rs7149014	14	29802911	T	C	0.0107334	0.0020584	0.1049	0.0691	0.370816
rs727857	2	58981967	G	A	0.0109766	0.00203429	-0.044	0.0681	0.388495
rs72834856	6	22801858	T	G	0.0251376	0.00379985	-0.0928	0.1298	0.927943
rs72997623	11	75488054	C	A	-0.0257654	0.00353337	-0.1364	0.1145	0.915323
rs7522116	1	41835685	C	T	0.012542	0.00199858	0.1021	0.0676	0.433716
rs7528419	1	109817192	A	G	-0.019866	0.00235556	0.03	0.0817	0.775305
rs7569755	2	118648261	G	A	-0.0135962	0.00218248	-0.0163	0.0728	0.709372
rs75741381	7	100809458	C	G	0.0137731	0.00278718	-0.1322	0.0932	0.852317
rs7604788	2	21190024	C	T	-0.0352194	0.0054801	0.1844	0.1992	0.966596
rs77532868	10	88081438	C	T	-0.0230071	0.0043429	0.1326	0.1812	0.945978
rs7784802	7	64015379	A	T	-0.0129774	0.00204446	0.0769	0.073	0.639012
rs78151190	6	25619007	A	C	0.0179172	0.00293406	-0.0572	0.103	0.871246
rs78649910	4	3482213	T	A	0.019983	0.00320891	0.0008	0.1054	0.893826
rs8018720	14	39556185	G	C	0.0299593	0.0025742	0.0342	0.0901	0.176691
rs804281	8	11611865	A	G	-0.0161836	0.00199452	-0.0266	0.0684	0.416402
rs8091117	18	28919794	C	A	0.0241938	0.0039757	0.0411	0.1275	0.934736

rs8113404	19	53065579	C	T	-0.0115758	0.00214261	-0.0452	0.0729	0.695417
rs867772	1	220972343	A	G	0.0147054	0.00212274	-0.1675	0.0741	0.315533
rs9476310	6	57767576	C	T	-0.0108729	0.00197437	-0.0008	0.0667	0.488661
rs9490317	6	121859499	T	C	-0.0106658	0.00198507	-0.0659	0.0665	0.554066
rs964184	11	116648917	G	C	-0.0414009	0.00290504	0.1177	0.0943	0.131625
rs9861009	3	141654685	T	C	-0.0139778	0.00222312	0.0095	0.0739	0.272456

Table S4. Sensetivity analysis using Multivariable MR.

	MV MR VitD - SBP	MV MR VitD - LDL-C	MV MR VitD - Longevity
	OR (95%CI; p)	OR (95%CI; p)	OR (95%CI; p)
All ICH	1.61 (1.05-2.4; p=0.03)	1.65 (1.07-2.53; p=0.02)	1.58 (1.04-2.41; p=0.03)
Lobar ICH	1.43 (0.85-1.43; p=0.17)	1.44 (0.86-1.44; p=0.16)	1.42 (0.85-2.37; p=0.18)
Non-Lobar ICH	1.88 (1.18-2.99; p=0.008)	1.97 (1.24-3.13; p=0.004)	1.85 (1.17-2.94; p=0.009)

SBP= systolic blood pressure. LDL-C = Low density lipoprotein cholesterol. ICH = Intracerebral hemorrhage. VitD = Vitamin D. OR = odds ratio. 95%CI = 95% confidence interval.

Figure S1. The leave-one-out plot for all ICH.

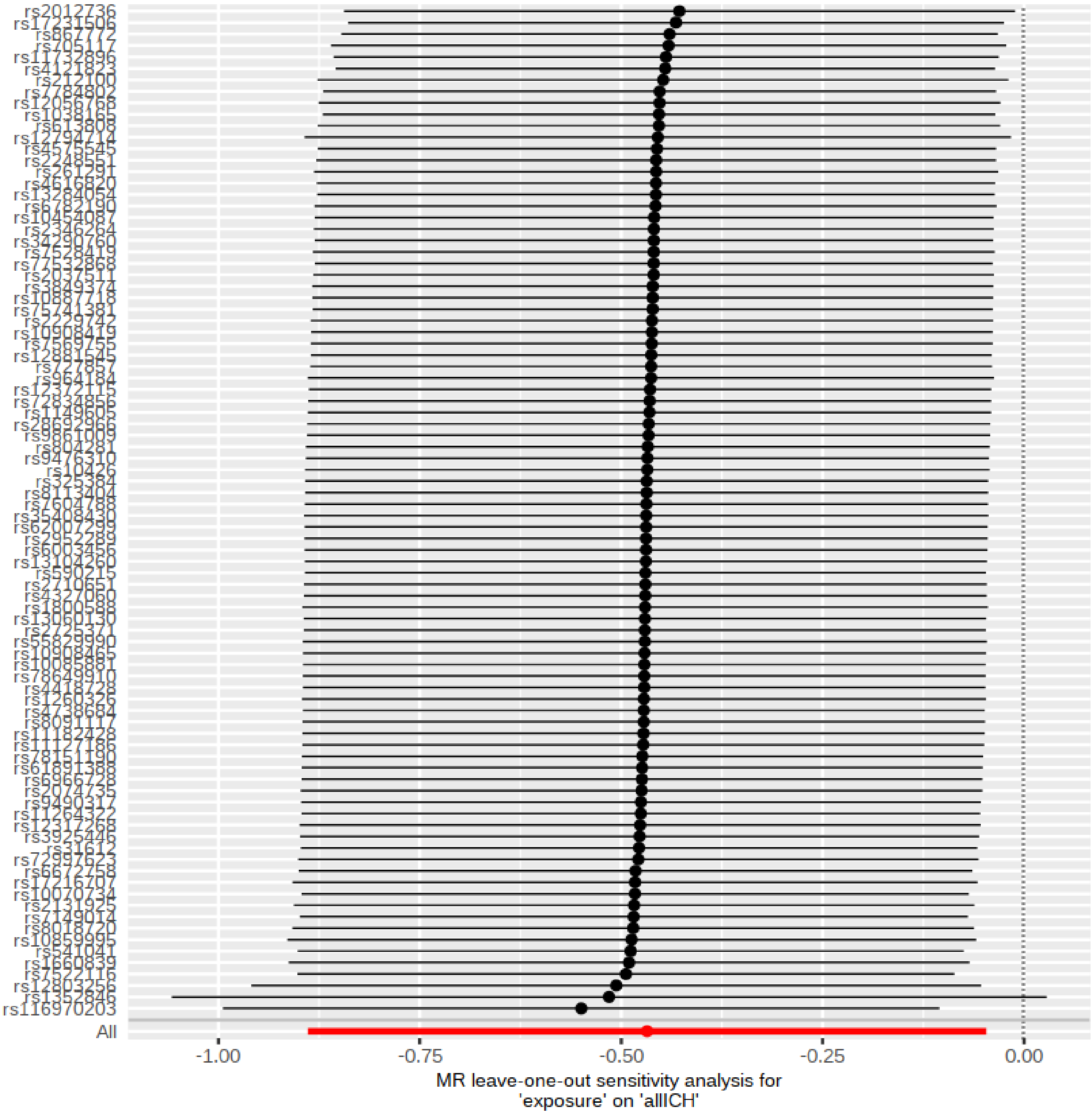

Figure S2. The leave-one-out plots for lobar ICH.

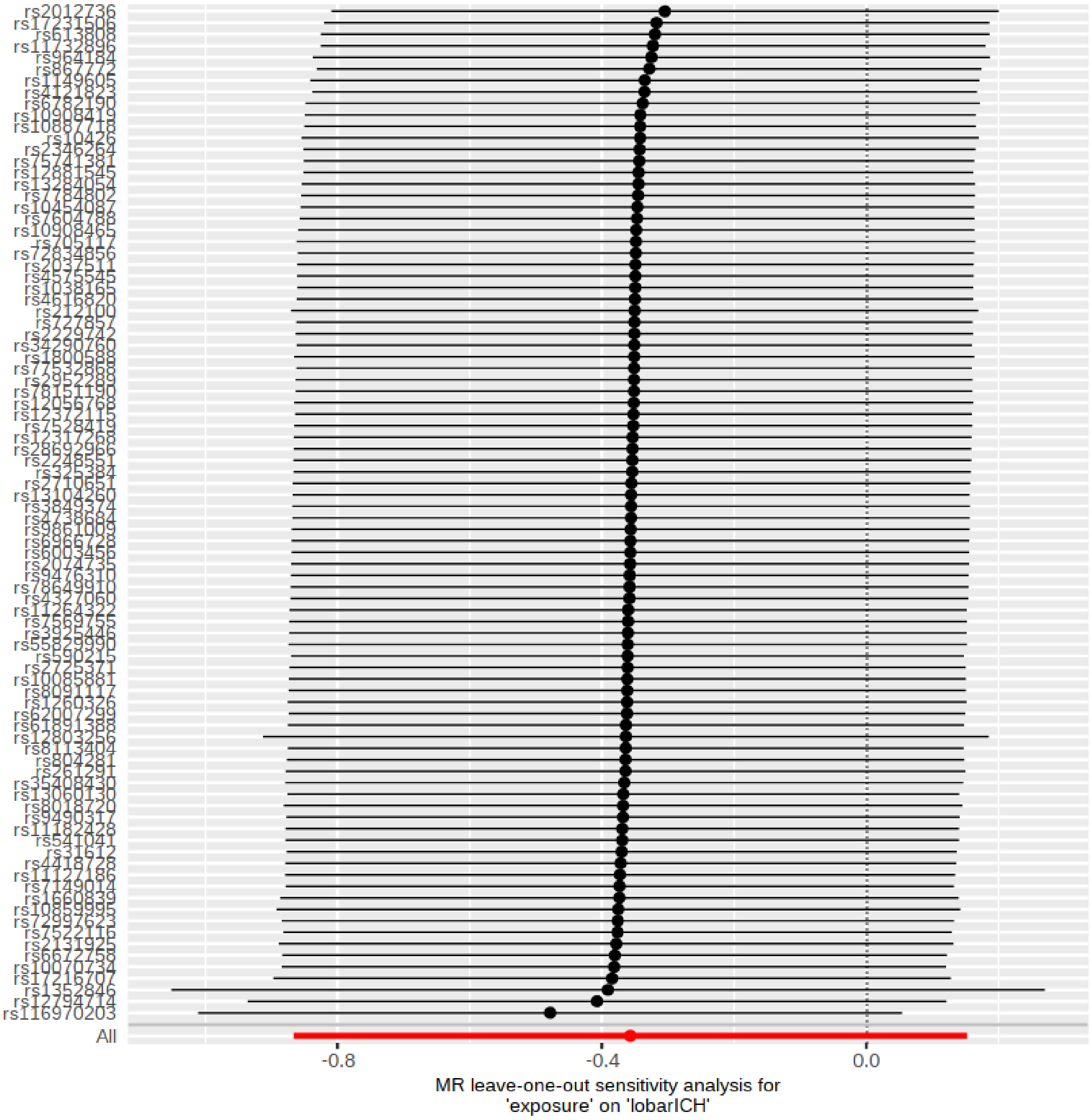

Figure S3. The leave-one-out plots for non-lobar ICH.

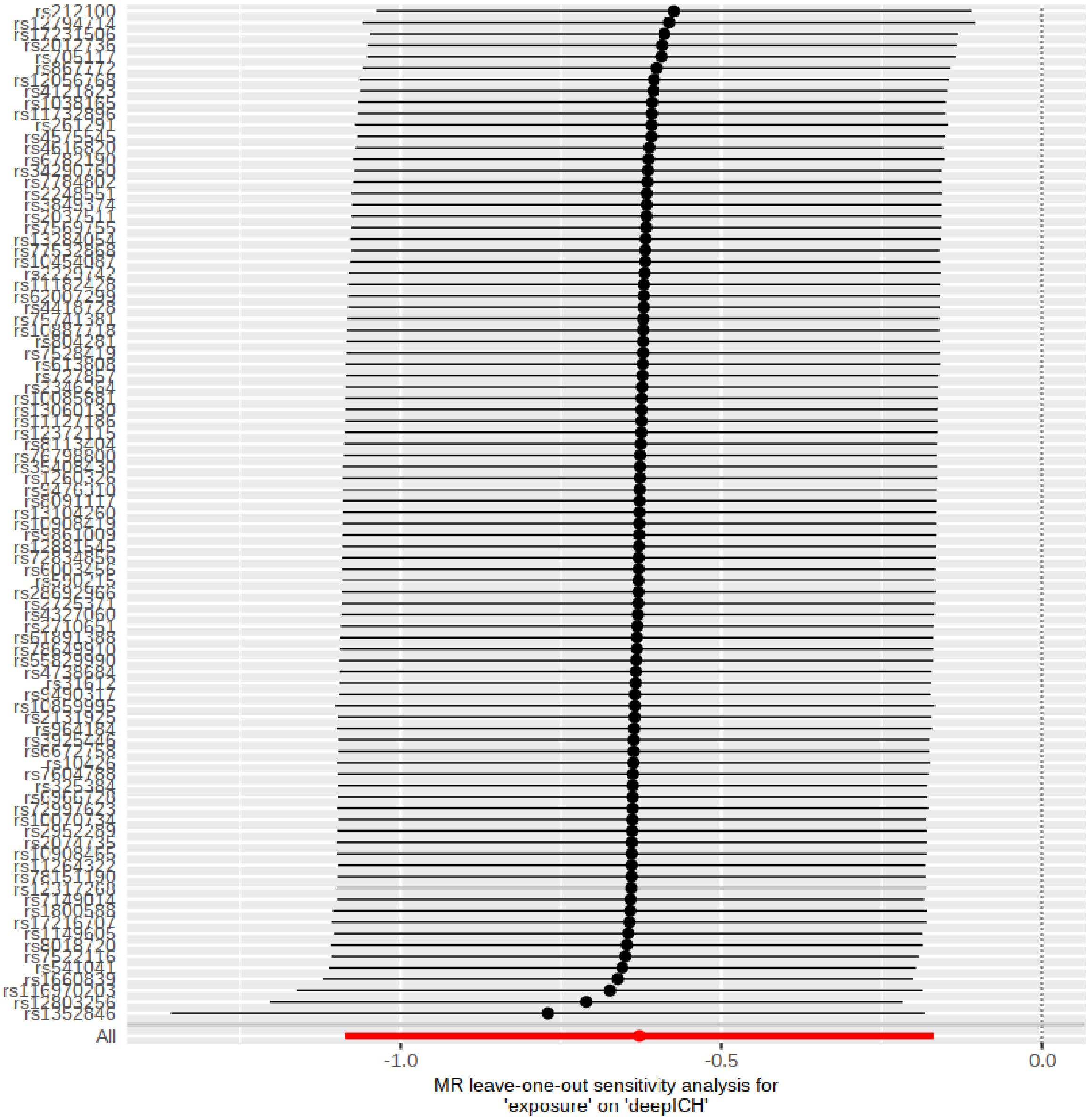

Figure S4. The Cook's distance plot for all ICH.

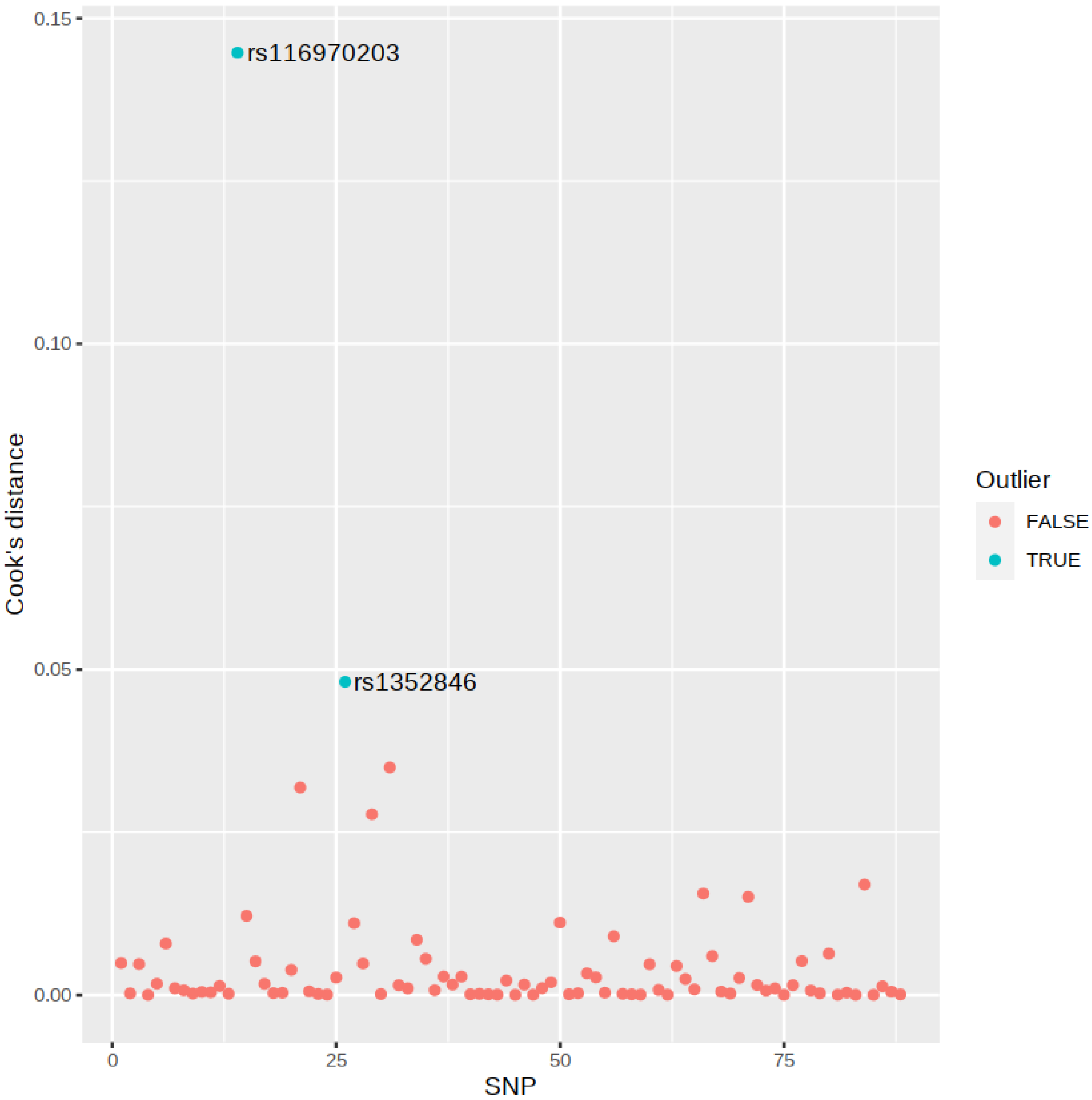

Figure S5. The Cook's distance plot for lobar ICH.

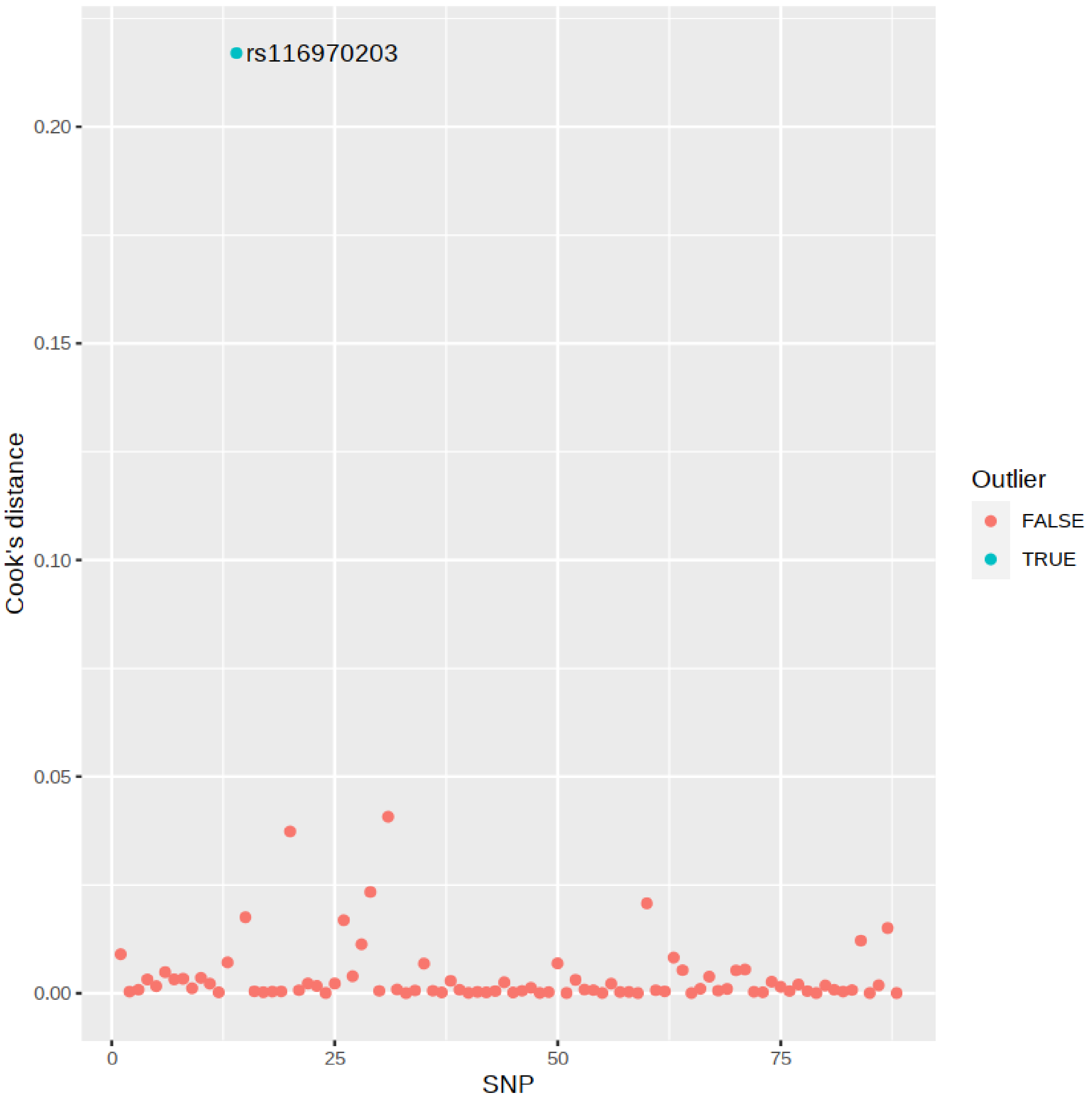

Figure S6. The Cook's distance plot for non-lobar ICH.