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ORIGINAL RESEARCH

Modifiable Risk Factors for Intracranial Aneurysm and Aneurysmal Subarachnoid Hemorrhage: A Mendelian Randomization Study

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BACKGROUND: The aim of this study was to assess the associations of modifiable lifestyle factors (smoking, coffee consumption, sleep, and physical activity) and cardiometabolic factors (body mass index, glycemic traits, type 2 diabetes, systolic and diastolic blood pressure, lipids, and inflammation and kidney function markers) with risks of any (ruptured or unruptured) intracranial aneurysm and aneurysmal subarachnoid hemorrhage using Mendelian randomization.

METHODS AND RESULTS: Summary statistical data for the genetic associations with the modifiable risk factors and the outcomes were obtained from meta-analyses of genome-wide association studies. The inverse-variance weighted method was used as the main Mendelian randomization analysis, with additional sensitivity analyses conducted using methods more robust to horizontal pleiotropy. Genetic predisposition to smoking, insomnia, and higher blood pressure was associated with an increased risk of both intracranial aneurysm and aneurysmal subarachnoid hemorrhage. For intracranial aneurysm, the odds ratios were 3.20 (95% CI, 1.93–5.29) per SD increase in smoking index, 1.24 (95% CI, 1.10–1.40) per unit increase in log-odds of insomnia, and 2.92 (95% CI, 2.49–3.43) per 10 mm Hg increase in diastolic blood pressure. In addition, there was weak evidence for associations of genetically predicted decreased physical activity, higher triglyceride levels, higher body mass index, and lower low-density lipoprotein cholesterol levels with higher risk of intracranial aneurysm and aneurysmal subarachnoid hemorrhage, with 95% CI overlapping the null for at least 1 of the outcomes. All results were consistent in sensitivity analyses.

CONCLUSIONS: This Mendelian randomization study suggests that smoking, insomnia, and high blood pressure are major risk factors for intracranial aneurysm and aneurysmal subarachnoid hemorrhage.

Key Words: intracranial aneurysm ■ lifestyle ■ Mendelian randomization ■ risk factors ■ single-nucleotide polymorphisms ■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (aSAH) is a type of stroke that is often caused by the rupture of an intracranial aneurysm (IA) and is associated with high mortality and morbidity.[1,2] In light of poor outcomes of aSAH, identification of modifiable risk factors for IA formation and rupture is of great importance. Suggested risk factors for aSAH include smoking,[3–5] heavy alcohol consumption,[3,6,7] hypertension,[3,4] and sleep apnea,[8] whereas coffee consumption,[9] regular physical activity,[10–12] high body mass index,[4,13] diabetes,[3] and hypercholesterolemia[3,14] have been proposed as risk-reducing factors. In addition, impaired kidney function and chronic inflammation can damage the vascular endothelium, predisposing to IA and aSAH.[15] However, available data on risk factors for aSAH are mainly based on observational studies that

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CLINICAL PERSPECTIVE

What Is New?

- We performed Mendelian randomization to investigate the effect of modifiable lifestyle and cardiometabolic risk factors on risk of any (ruptured or unruptured) intracranial aneurysm (IA) and aneurysmal subarachnoid hemorrhage (aSAH).
- Genetic predisposition to smoking, insomnia, and higher blood pressure were associated with an increased risk of both IA and aSAH.
- In addition, there was weak evidence for associations of genetically predicted decreased physical activity, higher triglyceride levels, higher body mass index, and lower low-density lipoprotein cholesterol levels with higher risk of IA and aSAH.

What Are the Clinical Implications?

- Smoking, insomnia, and high blood pressure likely represent causal risk factors for IA and aSAH.
- These results add to the body of evidence on causal risk factors for IA and aSAH, and warrant further investigation towards identifying preventative and therapeutic opportunities.

Nonstandard Abbreviations and Acronyms

aSAH	aneurysmal subarachnoid hemorrhage
IA	intracranial aneurysm
IVW	inverse-variance weighted
MR	Mendelian randomization

are vulnerable to confounding and other biases, and the results are not conclusive. Hence, the causal associations of most modifiable risk factors other than smoking and high blood pressure with aSAH risk remain unestablished.

Mendelian randomization (MR) is an epidemiologic method that uses randomly allocated genetic variants related to the risk factor as instrumental variables to infer causality of the exposure–outcome relationship.[16] Here, we conducted a 2-sample MR study to assess the associations of genetically predicted modifiable lifestyle factors (smoking, alcohol and coffee consumption, sleep, and physical activity) and cardiometabolic factors (body mass index, glycemic traits and type 2 diabetes, systolic and diastolic blood pressure, lipids, inflammation, and kidney function biomarkers) with risk of any (both ruptured and unruptured) IA and aSAH.

METHODS

Data Availability

We used summary data from published studies that had obtained participant content and ethical approval. The analysis scripts are available on request to the authors.

Data Sources

Genetic associations for the lifestyle and cardiometabolic factors were obtained from summary statistics of large-scale genome-wide association studies (GWAS) comprising individuals of European ancestry.[17–31] Alcohol was omitted from the list of exposures because the principal single-nucleotide variation (SNV; formerly SNP) affecting alcohol consumption in individuals of European ancestry (ie, rs1229984 in *ADH1B*)[27] was not available in the outcome data sets and no suitable proxy SNV was available. The number of individuals included in each exposure GWAS are shown in Table 1.

For the outcomes (any [ruptured or unruptured] IA and aSAH), the genetic associations were taken from the International Stroke Genetics Consortium GWAS meta-analysis of individuals of European ancestry.[32] To avoid bias because of sample overlap in the summary statistics with the exposures, individuals from UK Biobank were excluded, resulting in 6252 cases and 59 544 controls for any (ruptured or unruptured) IA and 4196 cases and 59 544 controls for aSAH. For all exposures and outcomes, participant consent and ethical approval were obtained in the original studies.

Selection of Genetic Instrumental Variables

We selected SNVs that associated with the corresponding modifiable risk factor at $P<5\times10^{-8}$ as instrumental variables for the risk factor. For interleukin-6 receptor (IL6R), we considered genetic variants only within ±300 kb of the *IL6R* gene. The independence of the variants was ensured by clumping them so that variants with $r^2>0.01$ (based on European ancestry reference in 1000 Genomes Project) with the lead SNV within ±10 000 kb window were excluded.

Statistical Analysis

To evaluate statistical power, we calculated the minimum detectable odds ratios (ORs) for the continuous exposures with 80% power and $\alpha=0.05$, based on the exposure GWAS sample size and the sum of the variance explained by the individual genetic instruments. For the main MR analysis, we used the multiplicative random-effects inverse-variance weighted method. This method provides consistent causal estimates

Table 1. Data Sources for the Genetically Predicted Modifiable Risk Factors

Trait	Sample size	Number of variants	Unit	Variance explained (%)
Lifestyle exposures				
Caffeine consumption[17]	47 341	2	SD	0.29
Coffee consumption[24]	375 833	10	50% increase	0.36
Insomnia*[25]	397 959 cases; 933 051 controls	143	Log-odds	0.53†
Long sleep duration[26]	34 184 cases; 305 742 controls	4	Log-odds (≥9 h/d, compared with 7–8 h/d)	0.10†
Physical activity[22]	377 234	6	SD (MET-minutes per week of moderate-to-vigorous physical activity)	0.08
Short sleep duration[26]	106 192 cases; 305 742 controls	19	Log-odds (<7 h/d, compared with 7–8 h/d)	0.20†
Sleep duration[26]	446 118	54	Hours per day	0.49
Smoking index[28]	462 690	85	SD (continuous lifetime smoking measure)	0.90
Smoking initiation[27]	1 232 091	235	SD (prevalence of smoking initiation, ie, ever smoker)	0.88†
Cardiometabolic exposures				
Body mass index[21]	806 834	967	SD	8.1
HDL-C[19]	188 577	113	SD	7.8
LDL-C[19]	188 577	88	SD	9.0
Systolic blood pressure[23]	318 417	214	10 mm Hg	3.4
Diastolic blood pressure[23]	318 417	721	10 mm Hg	6.2
Triglycerides[19]	188 577	60	SD	5.6
Type 2 diabetes[29]	148 726 cases; 965 732 controls	422	Log-odds	0.90†
Fasting glucose[18]	133 010	32	1 mmol/L	2.8
Fasting insulin[18]	133 010	9	1 pmol/L (log-transformed)	0.27
HbA1c[20]	123 665	34	Percentage point	1.9
Interleukin-6 receptor[31]	343 524	2	SD C-reactive protein levels	0.46
Chronic kidney disease[30]	41 395 cases; 439 303 controls	21	Log-odds	0.29†
Blood urea nitrogen[30]	243 029	67	1 mg/dL	2.0
eGFR[30]	567 460	235	$(mL \times min^{-1})/(1.73\ m^2)$ (log-transformed)	2.9

eGFR indicates estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and MET, metabolic equivalent of task.

*In UK Biobank, insomnia cases were defined as participants who answered "usually" on the question "Do you have trouble falling asleep at night or do you wake up in the middle of the night?" Participants who answered "never/rarely" or "sometimes" were defined as controls. In 23andMe, insomnia cases were defined as participants who affirmed at least 1 of the following questions: "Have you ever been diagnosed with, or treated for insomnia, insomnia but not narcolepsy, sleep apnea or restless leg syndrome?"; "Has a doctor ever told you that you have any of these conditions: insomnia?"; "Have you ever been diagnosed by a doctor with sleep disturbance?"; "Do you routinely have trouble getting to sleep at night?"; "What sleep disorders have you been diagnosed with? Please select all that apply: insomnia, trouble falling or staying asleep"; "In the last 2 years, have you taken prescription sleep aids?".

†Calculated assuming a logistic distribution for the liability.

when all genetic variants used are valid instrumental variables. We used MR-Egger,[33] weighted median,[34] and weighted mode[35] methods as sensitivity analyses, all of which are more robust to inclusions of invalid instrumental variables, with the trade-off of decreased statistical power. MR-Egger is robust to invalid instrumental variables, provided that the pleiotropic effects of the instruments are independent of the instrument strengths. The presence of horizontal pleiotropy was evaluated by the MR-Egger intercept test.[33] The weighted median method provides robust causal estimates if more than half of the weights are provided by valid instrumental variables.[34] The weighted mode provides robust causal estimates if the weights associated with valid instrumental variables are the largest among homogeneous subsets of instruments.[35] Finally, to further investigate the exposures with strong evidence for association on IA and aSAH risk in the main MR analysis, we conducted multivariable MR[36] to explore the mutually adjusted direct effects of (1) insomnia liability and sleep apnea (proxied by snoring liability[37]), (2) insomnia liability and systolic blood pressure, and (3) smoking index and systolic blood pressure. For multivariable MR, the considered instruments were SNVs that both associated at $P<5\times10^{-8}$ with either exposure under consideration, and were available in the outcome GWAS data set. The variants were clumped at $r^2>0.01$ as in the univariable MR described above,

based on the lower SNV-wise *P* value with the considered exposures.

The results are reported as ORs for the outcomes per unit increase in the exposure (Table 1). Insomnia, long and short sleep duration, type 2 diabetes, and chronic kidney disease were treated as binary exposures, and the ORs are per unit increase in the log-odds of the exposure. For smoking initiation as the exposure, the ORs are per SD increase in the prevalence of smoking initiation. For coffee consumption as the exposure, the ORs are per 50% increase in the exposure. For sleep duration, the ORs are per 1-hour increase of sleep per day. For systolic and diastolic blood pressure, the ORs are per 10 mm Hg increase. For hemoglobin A1c, the ORs are per percentage point increase in the exposure. For fasting glucose, the ORs are per mmol/L increase in glucose levels, and for fasting insulin, the ORs are per unit increase in log(insulin[pmol/L]). For blood urea nitrogen, the ORs are per mg/dL increase, and for estimated glomerular filtration rate (eGFR), the ORs are per unit increase in log(eGFR). For the rest of the exposures, the ORs are per 1-SD increase in the exposure (Table 1).

Strength of Evidence

As a reference value, the Bonferroni-corrected significance level for 23 exposures is 0.05/23=0.0022. However, we interpret the evidence based on the effect size, the consistency of the results (both in the sensitivity analyses and between the outcomes), and the statistical evidence as a continuous measure, and we refrain from dichotomous decisions based on any *P* value threshold.[38]

RESULTS

The minimum detectable ORs for the continuous exposures are given in Table S1. Of the 18 continuous exposures considered, we had adequate power to detect ORs at least ≥1.5 (or ≤0.67) per unit change in the exposure for 12 and 10 exposures for any IA and aSAH, respectively.

The MR estimates for the associations of the modifiable lifestyle and cardiometabolic factors with any IA and aSAH are presented in Figure. We found strong evidence for associations between genetically proxied

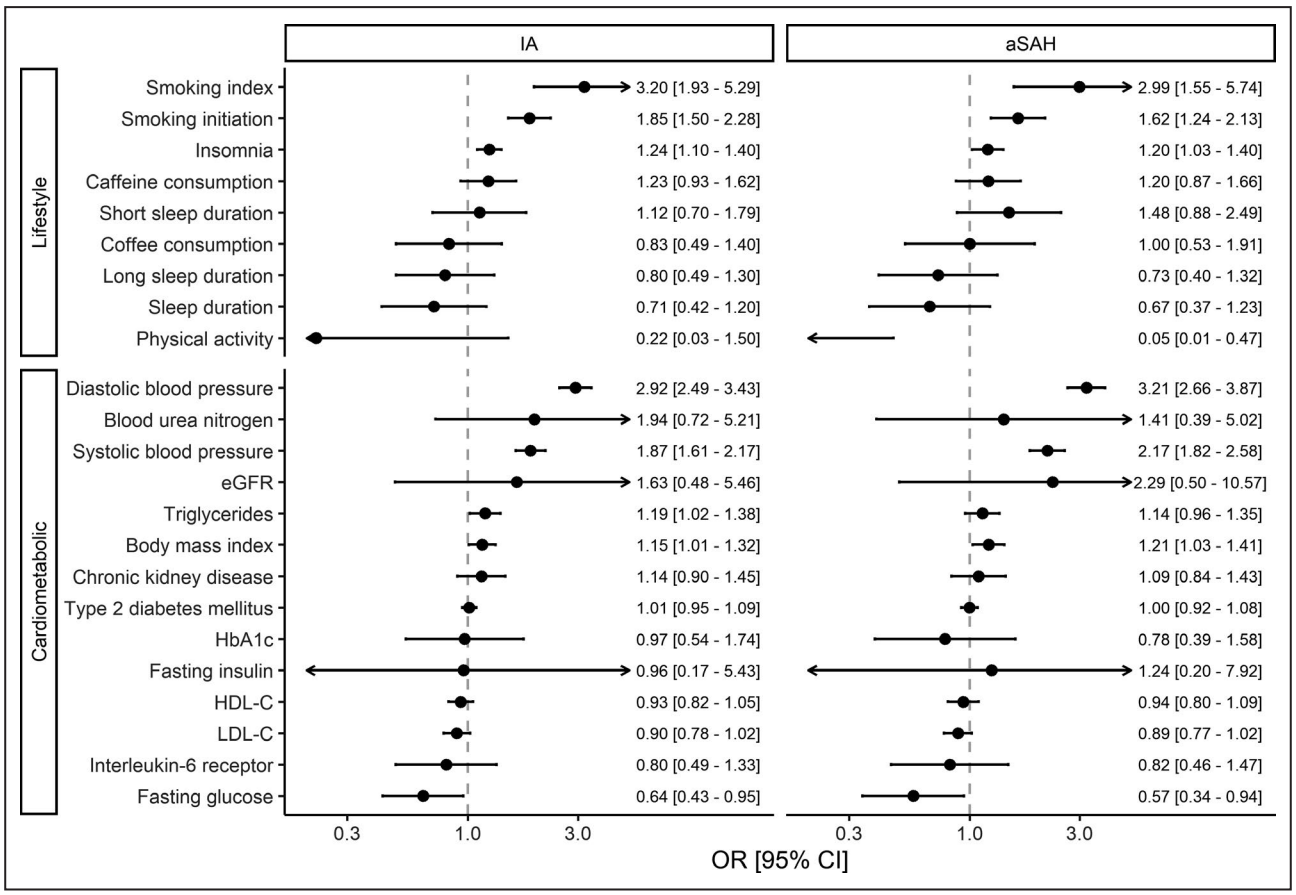

Figure. Associations of genetically predicted lifestyle and cardiometabolic factors with risk of any (ruptured or unruptured) IA and aSAH, using multiplicative random-effects inverse-variance weighted method.
aSAH indicates aneurysmal subarachnoid hemorrhage; eGFR estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IA, intracranial aneurysm; LDL-C, low-density lipoprotein cholesterol; and OR, odds ratio.

Table 2. Multivariable Mendelian Randomization Results of Mutually Adjusted Direct Effects on Risk of Any (Ruptured or Unruptured) IA and aSAH for Exposures That Showed Evidence for Association in the Main Mendelian Randomization

Trait	IA			aSAH		
	Number of variants	OR (95% CI)	*P* value	Number of variants	OR (95% CI)	*P* value
Insomnia	269	1.29 (1.06–1.58)	0.012	230	1.30 (1.03–1.65)	0.030
SBP		1.87 (1.62–2.17)	2.8×10^{-15}		2.13 (1.80–2.53)	6.9×10^{-16}
Insomnia	104	1.27 (1.07–1.50)	0.006	88	1.28 (1.05–1.55)	0.017
Sleep apnea		3.43 (0.89–13.24)	0.077		3.01 (0.64–14.24)	0.17
Smoking	330	5.78 (3.14–10.62)	3.5×10^{-8}	295	4.91 (2.42–9.94)	1.4×10^{-5}
SBP		1.82 (1.59–2.09)	5.6×10^{-16}		2.15 (1.83–2.52)	4.3×10^{-18}

aSAH indicates aneurysmal subarachnoid hemorrhage; IA, intracranial aneurysm; OR, odds ratio; and SBP, systolic blood pressure.

smoking, insomnia liability, and blood pressure with increased risk of both any IA (OR [95% CI] per 1-SD increase in smoking index 3.20 [1.93–5.29], $P=5.8\times10^{-6}$; OR per 1-SD increase in the prevalence of smoking initiation 1.85 [1.50–2.28], $P=1.4\times10^{-8}$; OR per unit increase in log-odds of insomnia liability 1.24 [1.10–1.40], $P=5.0\times10^{-4}$; OR per 10 mm Hg increase in diastolic blood pressure 2.92 [2.49–3.43], $P=8.4\times10^{-40}$; OR per 10 mm Hg increase in systolic blood pressure 1.87 [1.61–2.17], $P=1.4\times10^{-16}$) and aSAH (OR per 1-SD increase in smoking index 3.00 [1.55–5.74], $P=0.0010$; OR per 1-SD increase in the prevalence of smoking initiation 1.62 [1.24–2.12], $P=4.6\times10^{-4}$; OR per unit increase in log-odds of insomnia liability 1.20 [1.03–1.40], $P=0.023$; OR per 10 mm Hg increase in diastolic and systolic blood pressure 3.21 [2.66–3.87], $P=2.1\times10^{-34}$ and 2.17 [1.82–2.58], $P=2.4\times10^{-18}$, respectively). There was also weak evidence of association for genetically predicted decreased physical activity, higher triglyceride levels, higher body mass index, and lower low-density lipoprotein cholesterol levels with increased risk of both outcomes, with 95% CI overlapping the null for at least 1 of the outcomes. Increased fasting glucose levels were associated with lower risk of any IA (OR per unit increase in fasting glucose levels 0.64 [0.43–0.95], $P=0.029$) and aSAH (OR, 0.57 [0.34–0.94], $P=0.029$); however, these results were not supported by the point estimates from sensitivity analysis more robust to horizontal pleiotropy (Figure S1).

For the exposures that showed evidence for association in inverse-variance weighted results, the MR-Egger intercept test indicated evidence for horizontal pleiotropy with genetically predicted systolic and diastolic blood pressure and risk of both IA ($P=0.004$ for systolic, $P=0.001$ for diastolic) and aSAH ($P=0.008$ for systolic, $P=2\times10^{-4}$ for diastolic), and weaker evidence for horizontal pleiotropy of genetically predicted smoking initiation liability ($P=0.03$) with aSAH risk (Table S2). However, all point estimates in sensitivity analyses by weighted median and weighted mode methods for these exposures were consistent with the main inverse-variance weighted analysis (Table S2; Figure S1). In the multivariable MR investigation of direct effects adjusted for genetically predicted effects of other relevant exposures, there was evidence for direct effects of smoking (independent of blood pressure), blood pressure (independent of insomnia liability or smoking), and insomnia liability (independent of sleep apnea or blood pressure), with point estimates concordant with those in univariable MR (Table 2).

DISCUSSION

The present MR study found further evidence for smoking and high blood pressure as the strongest risk factors for IA and aSAH. This study additionally found evidence that insomnia may be a novel risk factor for IA and aSAH. These results were consistent in multivariable MR, indicating direct effects of these exposures on IA and aSAH risk. Weak evidence of possible associations was found for higher triglyceride levels and body mass index with increased risk of both IA and aSAH and for higher levels of moderate-to-vigorous physical activity and low-density lipoprotein cholesterol with decreased risk of the outcomes. Other lifestyle and cardiometabolic factors showed no strong and consistent associations with either IA or aSAH.

Results of this MR study support the findings of previous studies,[3–5] which have shown that smoking is a strong risk factor for aSAH. Tobacco smoke contains nicotine and numerous other substances that could promote vascular endothelial dysfunction and IA rupture.[39,40] Accumulated evidence indicates that endothelial dysfunction, hemodynamic stress, and inflammatory responses play a central role in IA formation, growth, and rupture.[41] Mechanistic evidence indicates that nicotine exposure increases IA rupture risk through actions on the vascular cell nicotinic acetylcholine receptors containing α7 subunits, leading to increased levels of vascular endothelial growth factor, platelet-derived growth factor-B, and inflammatory cytokines.[39]

Studies of coffee consumption and risk of aSAH are limited and results are inconsistent, with an inverse[9] and a neutral[42] association observed in cohorts of Swedish women and Finnish male smokers, respectively. We observed no association of genetically predicted coffee or caffeine intake with IA or aSAH. However, the CIs were broad, and weak associations in either direction cannot be ruled out.

Data on the role of sleep in the development of IA formation and rupture are scarce, but a previous observational study found an increased risk for aSAH in patients with sleep apnea.[8] No association between short or long sleep duration and subarachnoid hemorrhage was found in a cohort of Swedish adults.[43] Here, we found evidence to support associations of insomnia with increased risk of IA and aSAH. The results were similar in multivariable MR, where we found evidence for a direct effect of insomnia liability, after adjusting for either blood pressure or sleep apnea. The point estimates for other sleep-related traits (total sleep duration, short sleep, and long sleep) were consistent with our finding for insomnia liability, albeit with large uncertainty in the estimates. Given the limited data, whether lack of sleep is an etiological risk factor for both IA and aSAH risk merits further study.

Regular physical activity was associated with a reduced risk of aSAH in a cohort of 8006 men of Japanese ancestry,[11] a cohort of 65 521 Finnish adults,[10] and a cohort of >1 million UK women.[12] Our MR results provide tentative support for a causal association between physical activity and decreased risk of aSAH; however, caution should be warranted because of the large uncertainty in our estimates. Physical activity may reduce the risk of aSAH by improving endothelial function,[44] lowering blood pressure,[45] and decreasing systemic inflammation.[46]

Among cardiometabolic risk factors, previous studies have conclusively revealed that hypertension is associated with an increased risk of aSAH,[3,4,32] supported by our MR results for systolic and diastolic blood pressure, but have yielded conflicting results for body mass index[4,13,47] and diabetes.[3,4] Body mass index was inversely associated with risk of aSAH in women but was not associated with aSAH in men in a pooled analysis of 21 Swedish cohort studies.[4] An inverse association between body mass index and risk of aSAH was also observed in a cohort of 1.3 million UK women.[13] In contrast, a borderline significant positive association between body mass index and aSAH was observed in a previous MR study in UK women and men[47] and the present MR study in another population. High body mass index is a strong risk factor for type 2 diabetes, which was found to be inversely associated with aSAH in a meta-analysis of case–control studies[3] and nonsignificantly inversely associated with aSAH in a pooled analysis of cohort studies.[4] In our analysis, there was no evidence for association of type 2 diabetes with IA or aSAH, and further research on the causal associations of adiposity and type 2 diabetes with risk of aSAH is necessary. With regard to lipids, limited observational data, mainly case–control studies, suggest that hypercholesterolemia[3] and high levels of high-density lipoprotein[14] are associated with a lower risk of aSAH.[3] Our MR findings provided weak evidence for positive and negative associations for triglyceride levels and low-density lipoprotein cholesterol levels, respectively, with only modest effect sizes.

Major strengths of this study include the MR design, which reduced confounding and reverse causality. We were able to utilize the summary statistics from the largest GWAS on IA and aSAH to date, which ensured maximal statistical power. Population stratification bias was minimized by restricting the analyses to individuals of European descent. With regard to limitations, the statistical power was low in some analyses as demonstrated in Table S1, because of instrumental variables only explaining a small proportion of variance in the exposure, particularly for physical activity, and coffee and caffeine consumption. Another limitation is that because we used summarized data, we could not assess nonlinear associations. Finally, our analyses were restricted to individuals of European ancestry and may therefore not be generalizable to other populations.

In conclusion, this MR study found that genetic predisposition to smoking, insomnia, and high blood pressure was robustly associated with increased risk of IA and aSAH. Physical activity, body mass index, triglyceride levels, and low-density lipoprotein cholesterol levels may also affect the risk of both IA and aSAH. These results add to the triangulation of evidence on risk factors of IA and aSAH, and warrant further investigation in future large MR and other epidemiological studies.

ARTICLE INFORMATION

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Disclosures

Gill is employed part-time by Novo Nordisk. The other authors have no conflicts of interest to disclose.

Supplementary Material

Tables S1–S2
Figure S1

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SUPPLEMENTAL MATERIAL

Supplemental material for:

Modifiable Risk Factors for Intracranial Aneurysm and Aneurysmal Subarachnoid Hemorrhage: A Mendelian Randomization Study

Table S1. Minimum detectable odds ratios*

Exposure	Intracranial aneurysm	Subarachnoid hemorrhage
Alcohol consumption	> 1.98, < 0.50	> 2.44, < 0.41
Body mass index	> 1.14, < 0.88	> 1.18, < 0.85
Blood urea nitrogen	> 1.30, < 0.77	> 1.39, < 0.72
Caffeine consumption	> 1.99, < 0.50	> 2.29, < 0.44
Chronic kidney disease	NA	NA
Coffee consumption	> 1.86, < 0.54	> 2.15, < 0.47
Diastolic blood pressure	> 1.16, < 0.86	> 1.21, < 0.83
eGFR	> 1.25, < 0.80	> 1.32, < 0.76
Fasting glucose	> 1.25, < 0.80	> 1.31, < 0.76
Fasting insulin	> 2.05, < 0.49	> 2.45, < 0.41
HbA1c	> 1.31, < 0.77	> 1.39, < 0.72
High-density lipoprotein cholesterol	> 1.14, < 0.88	> 1.18, < 0.85
Interleukin-6 receptor	> 1.73, < 0.58	> 1.93, < 0.52
Insomnia	NA	NA
Low-density lipoprotein cholesterol	> 1.13, < 0.88	> 1.14, < 0.87
Physical activity	> 3.75, < 0.27	> 5.55, < 0.18
Systolic blood pressure	> 1.22, < 0.82	> 1.30, < 0.77
Sleep duration	> 1.70, < 0.59	> 1.97, < 0.51
Long sleep duration	NA	NA
Short sleep duration	NA	NA
Smoking index	> 1.48, < 0.68	> 1.69, < 0.59
Smoking initiation	NA	NA
Type 2 diabetes mellitus	NA	NA
Triglycerides	> 1.17, < 0.85	> 1.21, < 0.82

*Minimum detectable odds ratio for the continuous exposures with 80% power (alpha = 0.05) and based on the exposure genome-wide association study sample size and the sum of the variance explained by the individual genetic instruments.

Table S2. Associations of genetically predicted exposures and intracranial aneurysm and aneurysmal subarachnoid hemorrhage in main and sensitivity analyses

Group	Exposure	Outcome	Method	SNPs	OR	95%_CI_low	95%_CI_high	p-value	p-value pleiotropy
Lifestyle	Smoking index	IA	IVW-RE	85	3,1985	1,9347	5,2878	5,82E-06	
Lifestyle	Smoking index	IA	MR-Egger	85	8,0469	0,9194	70,4329	0,0596	0,3915
Lifestyle	Smoking index	IA	Weighted Median	85	3,3335	1,7879	6,2155	0,0002	
Lifestyle	Smoking index	IA	Weighted Mode	85	2,0699	0,3743	11,4477	0,4045	
Lifestyle	Smoking initiation	IA	IVW-RE	235	1,8484	1,4952	2,2850	0,0000	
Lifestyle	Smoking initiation	IA	MR-Egger	235	2,7557	1,1367	6,6805	0,0249	0,3626
Lifestyle	Smoking initiation	IA	Weighted Median	235	2,0337	1,5197	2,7216	1,37E-08	
Lifestyle	Smoking initiation	IA	Weighted Mode	235	1,6888	0,7564	3,7705	0,2010	
Lifestyle	Insomnia	IA	IVW-RE	143	1,2382	1,0978	1,3965	0,0005	
Lifestyle	Insomnia	IA	MR-Egger	143	1,1186	0,6081	2,0574	0,7186	0,7389
Lifestyle	Insomnia	IA	Weighted Median	143	1,2743	1,0767	1,5081	0,0048	
Lifestyle	Insomnia	IA	Weighted Mode	143	1,2266	0,7388	2,0366	0,4298	
Lifestyle	Caffeine consumption	IA	IVW-RE	2	1,2257	0,9297	1,6160	0,1490	
Lifestyle	Short sleep duration	IA	IVW-RE	19	1,1220	0,7032	1,7903	0,6292	
Lifestyle	Short sleep duration	IA	MR-Egger	19	1,0288	0,1147	9,2258	0,9798	0,9367
Lifestyle	Short sleep duration	IA	Weighted Median	19	1,0992	0,6332	1,9083	0,7367	
Lifestyle	Short sleep duration	IA	Weighted Mode	19	1,1241	0,4724	2,6748	0,7915	
Lifestyle	Alcohol consumption	IA	IVW-RE	56	0,8622	0,3885	1,9137	0,7155	
Lifestyle	Alcohol consumption	IA	MR-Egger	56	0,5845	0,0700	4,8821	0,6200	0,6982
Lifestyle	Alcohol consumption	IA	Weighted Median	56	0,7160	0,2599	1,9731	0,5184	
Lifestyle	Alcohol consumption	IA	Weighted Mode	56	0,4892	0,1184	2,0214	0,3233	
Lifestyle	Coffee consumption	IA	IVW-RE	10	0,8269	0,4875	1,4028	0,4810	
Lifestyle	Coffee consumption	IA	MR-Egger	10	1,1072	0,3563	3,4409	0,8602	0,5641
Lifestyle	Coffee consumption	IA	Weighted Median	10	1,0034	0,5472	1,8398	0,9913	
Lifestyle	Coffee consumption	IA	Weighted Mode	10	1,1311	0,6027	2,1228	0,7013	
Lifestyle	Long sleep duration	IA	IVW-RE	4	0,7968	0,4875	1,3023	0,3648	

Lifestyle	Long sleep duration	IA	MR-Egger	4	1,1545	0,1654	8,0601	0,8848	0,6991
Lifestyle	Long sleep duration	IA	Weighted Median	4	0,7161	0,3968	1,2924	0,2677	
Lifestyle	Long sleep duration	IA	Weighted Mode	4	0,6545	0,3130	1,3687	0,2601	
Lifestyle	Sleep duration	IA	IVW-RE	54	0,7134	0,4228	1,2040	0,2060	
Lifestyle	Sleep duration	IA	MR-Egger	54	1,0103	0,1473	6,9304	0,9917	0,7127
Lifestyle	Sleep duration	IA	Weighted Median	54	0,6403	0,3084	1,3291	0,2315	
Lifestyle	Sleep duration	IA	Weighted Mode	54	0,5593	0,1722	1,8167	0,3337	
Lifestyle	Physical activity	IA	IVW-RE	6	0,2196	0,0322	1,4982	0,1218	
Lifestyle	Physical activity	IA	MR-Egger	6	0,0011	0,0000	78,5456	0,2314	0,3442
Lifestyle	Physical activity	IA	Weighted Median	6	0,0999	0,0130	0,7686	0,0269	
Lifestyle	Physical activity	IA	Weighted Mode	6	0,0553	0,0031	0,9971	0,0498	
Cardiometabolic	Diastolic blood pressure	IA	IVW-RE	721	2,9227	2,4925	3,4271	8,38E-40	
Cardiometabolic	Diastolic blood pressure	IA	MR-Egger	721	5,4346	3,5999	8,2041	8,88E-16	0,0014
Cardiometabolic	Diastolic blood pressure	IA	Weighted Median	721	2,8770	2,2997	3,5993	2,29E-20	
Cardiometabolic	Diastolic blood pressure	IA	Weighted Mode	721	2,6370	1,1465	6,0651	0,0225	
Cardiometabolic	Blood urea nitrogen	IA	IVW-RE	67	1,9416	0,7231	5,2134	0,1880	
Cardiometabolic	Blood urea nitrogen	IA	MR-Egger	67	2,7888	0,1878	41,4029	0,4562	0,7772
Cardiometabolic	Blood urea nitrogen	IA	Weighted Median	67	1,1348	0,2854	4,5131	0,8575	
Cardiometabolic	Blood urea nitrogen	IA	Weighted Mode	67	0,4220	0,0613	2,9073	0,3809	
Cardiometabolic	Systolic blood pressure	IA	IVW-RE	214	1,8696	1,6117	2,1687	1,42E-16	
Cardiometabolic	Systolic blood pressure	IA	MR-Egger	214	3,6572	2,2723	5,8861	9,29E-08	0,0037
Cardiometabolic	Systolic blood pressure	IA	Weighted Median	214	1,7832	1,4970	2,1242	9,18E-11	
Cardiometabolic	Systolic blood pressure	IA	Weighted Mode	214	1,4929	0,9253	2,4089	0,1007	
Cardiometabolic	eGFR	IA	IVW-RE	235	1,6261	0,4839	5,4645	0,4317	
Cardiometabolic	eGFR	IA	MR-Egger	235	0,0588	0,0030	1,1632	0,0628	0,0173
Cardiometabolic	eGFR	IA	Weighted Median	235	1,5335	0,2371	9,9198	0,6536	
Cardiometabolic	eGFR	IA	Weighted Mode	235	3,2552	0,0544	194,9203	0,5719	
Cardiometabolic	Triglycerides	IA	IVW-RE	60	1,1870	1,0196	1,3819	0,0271	
Cardiometabolic	Triglycerides	IA	MR-Egger	60	1,0621	0,8386	1,3452	0,6170	0,2295
Cardiometabolic	Triglycerides	IA	Weighted Median	60	1,1392	0,9120	1,4231	0,2508	

Cardiometabolic	Triglycerides	IA	Weighted Mode	60	1,1751	0,9535	1,4482	0,1302	
Cardiometabolic	Body mass index	IA	IVW-RE	967	1,1537	1,0095	1,3186	0,0359	
Cardiometabolic	Body mass index	IA	MR-Egger	967	0,9867	0,6767	1,4386	0,9445	0,3848
Cardiometabolic	Body mass index	IA	Weighted Median	967	1,1991	0,9742	1,4760	0,0866	
Cardiometabolic	Body mass index	IA	Weighted Mode	967	1,4877	0,9178	2,4114	0,1070	
Cardiometabolic	Chronic kidney disease	IA	IVW-RE	21	1,1440	0,9001	1,4539	0,2714	
Cardiometabolic	Chronic kidney disease	IA	MR-Egger	21	1,9347	1,0206	3,6677	0,0431	0,0847
Cardiometabolic	Chronic kidney disease	IA	Weighted Median	21	1,3581	1,0875	1,6959	0,0069	
Cardiometabolic	Chronic kidney disease	IA	Weighted Mode	21	1,3350	1,0083	1,7675	0,0436	
Cardiometabolic	Type 2 diabetes mellitus	IA	IVW-RE	422	1,0136	0,9458	1,0863	0,7024	
Cardiometabolic	Type 2 diabetes mellitus	IA	MR-Egger	422	0,8829	0,7568	1,0300	0,1132	0,0496
Cardiometabolic	Type 2 diabetes mellitus	IA	Weighted Median	422	0,9718	0,8753	1,0790	0,5925	
Cardiometabolic	Type 2 diabetes mellitus	IA	Weighted Mode	422	0,8695	0,7288	1,0373	0,1204	
Cardiometabolic	HbA1c	IA	IVW-RE	34	0,9683	0,5378	1,7434	0,9144	
Cardiometabolic	HbA1c	IA	MR-Egger	34	0,9770	0,1810	5,2742	0,9784	0,9911
Cardiometabolic	HbA1c	IA	Weighted Median	34	0,9230	0,3941	2,1614	0,8535	
Cardiometabolic	HbA1c	IA	Weighted Mode	34	0,9447	0,2964	3,0109	0,9234	
Cardiometabolic	Fasting insulin	IA	IVW-RE	9	0,9585	0,1691	5,4332	0,9618	
Cardiometabolic	Fasting insulin	IA	MR-Egger	9	0,2732	0,0000	4248511	0,8779	0,8812
Cardiometabolic	Fasting insulin	IA	Weighted Median	9	0,4446	0,0762	2,5954	0,3679	
Cardiometabolic	Fasting insulin	IA	Weighted Mode	9	0,1236	0,0026	5,9757	0,2907	
Cardiometabolic	HDL cholesterol	IA	IVW-RE	113	0,9317	0,8244	1,0531	0,2576	
Cardiometabolic	HDL cholesterol	IA	MR-Egger	113	1,0550	0,8452	1,3168	0,6359	0,1882
Cardiometabolic	HDL cholesterol	IA	Weighted Median	113	0,9145	0,7597	1,1010	0,3453	
Cardiometabolic	HDL cholesterol	IA	Weighted Mode	113	0,9361	0,7769	1,1279	0,4874	
Cardiometabolic	LDL cholesterol	IA	IVW-RE	88	0,8959	0,7842	1,0234	0,1054	
Cardiometabolic	LDL cholesterol	IA	MR-Egger	88	0,9669	0,7810	1,1970	0,7570	0,3705
Cardiometabolic	LDL cholesterol	IA	Weighted Median	88	0,9705	0,8179	1,1515	0,7314	
Cardiometabolic	LDL cholesterol	IA	Weighted Mode	88	0,9845	0,8373	1,1576	0,8504	
Cardiometabolic	Interleukin-6 receptor	IA	IVW-RE	2	0,8049	0,4865	1,3318	0,3983	

Cardiometabolic	Fasting glucose	IA	IVW-RE	32	0,6391	0,4278	0,9548	0,0288	
Cardiometabolic	Fasting glucose	IA	MR-Egger	32	1,0586	0,5040	2,2238	0,8804	0,1165
Cardiometabolic	Fasting glucose	IA	Weighted Median	32	0,8572	0,5222	1,4072	0,5424	
Cardiometabolic	Fasting glucose	IA	Weighted Mode	32	0,8269	0,5193	1,3167	0,4233	
Lifestyle	Smoking index	aSAH	IVW-RE	66	2,9861	1,5538	5,7388	0,0010	
Lifestyle	Smoking index	aSAH	MR-Egger	66	25,6901	1,6637	396,6874	0,0201	0,1128
Lifestyle	Smoking index	aSAH	Weighted Median	66	2,0573	0,9239	4,5814	0,0774	
Lifestyle	Smoking index	aSAH	Weighted Mode	66	1,6760	0,2102	13,3657	0,6259	
Lifestyle	Smoking initiation	aSAH	IVW-RE	190	1,6217	1,2372	2,1257	0,0005	
Lifestyle	Smoking initiation	aSAH	MR-Egger	190	5,1285	1,7086	15,3938	0,0036	0,0343
Lifestyle	Smoking initiation	aSAH	Weighted Median	190	2,1689	1,5006	3,1348	3,79E-05	
Lifestyle	Smoking initiation	aSAH	Weighted Mode	190	3,0090	1,2050	7,5142	0,0183	
Lifestyle	Insomnia	aSAH	IVW-RE	109	1,1986	1,0252	1,4014	0,0231	
Lifestyle	Insomnia	aSAH	MR-Egger	109	1,1289	0,5396	2,3618	0,7475	0,8706
Lifestyle	Insomnia	aSAH	Weighted Median	109	1,1832	0,9527	1,4694	0,1280	
Lifestyle	Insomnia	aSAH	Weighted Mode	109	1,1230	0,6164	2,0460	0,7047	
Lifestyle	Caffeine consumption	aSAH	IVW-RE	2	1,2035	0,8719	1,6611	0,2601	
Lifestyle	Short sleep duration	aSAH	IVW-RE	14	1,4819	0,8809	2,4929	0,1383	
Lifestyle	Short sleep duration	aSAH	MR-Egger	14	2,9471	0,1939	44,7913	0,4363	0,6139
Lifestyle	Short sleep duration	aSAH	Weighted Median	14	1,4557	0,7107	2,9815	0,3047	
Lifestyle	Short sleep duration	aSAH	Weighted Mode	14	1,3632	0,4629	4,0150	0,5740	
Lifestyle	Alcohol consumption	aSAH	IVW-RE	46	0,7232	0,3164	1,6530	0,4423	
Lifestyle	Alcohol consumption	aSAH	MR-Egger	46	0,9197	0,1040	8,1298	0,9400	0,8150
Lifestyle	Alcohol consumption	aSAH	Weighted Median	46	0,5593	0,1594	1,9622	0,3642	
Lifestyle	Alcohol consumption	aSAH	Weighted Mode	46	0,5455	0,0941	3,1627	0,4991	
Lifestyle	Coffee consumption	aSAH	IVW-RE	9	1,0027	0,5251	1,9147	0,9935	
Lifestyle	Coffee consumption	aSAH	MR-Egger	9	0,9359	0,2310	3,7912	0,9260	0,9115
Lifestyle	Coffee consumption	aSAH	Weighted Median	9	1,1272	0,5448	2,3320	0,7469	
Lifestyle	Coffee consumption	aSAH	Weighted Mode	9	1,1713	0,5101	2,6893	0,7093	
Lifestyle	Long sleep duration	aSAH	IVW-RE	4	0,7291	0,4032	1,3186	0,2960	

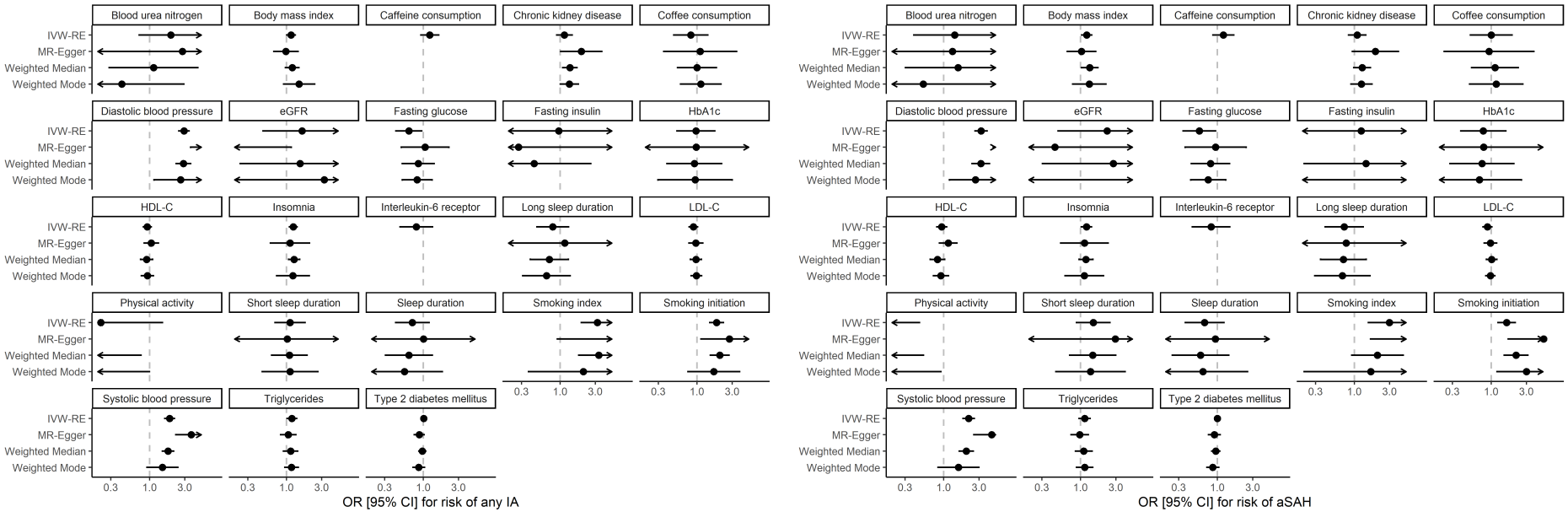
Lifestyle	Long sleep duration	aSAH	MR-Egger	4	0,7792	0,0761	7,9758	0,8335	0,9538
Lifestyle	Long sleep duration	aSAH	Weighted Median	4	0,7131	0,3504	1,4515	0,3511	
Lifestyle	Long sleep duration	aSAH	Weighted Mode	4	0,6907	0,2918	1,6347	0,3998	
Lifestyle	Sleep duration	aSAH	IVW-RE	47	0,6708	0,3669	1,2266	0,1947	
Lifestyle	Sleep duration	aSAH	MR-Egger	47	0,9375	0,1059	8,2972	0,9538	0,7540
Lifestyle	Sleep duration	aSAH	Weighted Median	47	0,5888	0,2445	1,4181	0,2376	
Lifestyle	Sleep duration	aSAH	Weighted Mode	47	0,6383	0,1593	2,5576	0,5261	
Lifestyle	Physical activity	aSAH	IVW-RE	5	0,0543	0,0063	0,4678	0,0080	
Lifestyle	Physical activity	aSAH	MR-Egger	5	0,0003	0,0000	133,9815	0,2250	0,4345
Lifestyle	Physical activity	aSAH	Weighted Median	5	0,0425	0,0034	0,5328	0,0144	
Lifestyle	Physical activity	aSAH	Weighted Mode	5	0,0181	0,0004	0,9122	0,0449	
Cardiometabolic	Diastolic blood pressure	aSAH	IVW-RE	651	3,2096	2,6627	3,8690	2,05E-34	
Cardiometabolic	Diastolic blood pressure	aSAH	MR-Egger	651	7,6051	4,6743	12,3735	2,22E-16	0,0002
Cardiometabolic	Diastolic blood pressure	aSAH	Weighted Median	651	3,1726	2,4245	4,1515	3,93E-17	
Cardiometabolic	Diastolic blood pressure	aSAH	Weighted Mode	651	2,6823	1,1950	6,0204	0,0168	
Cardiometabolic	Blood urea nitrogen	aSAH	IVW-RE	64	1,4062	0,3942	5,0162	0,5993	
Cardiometabolic	Blood urea nitrogen	aSAH	MR-Egger	64	1,3093	0,0387	44,2434	0,8807	0,9660
Cardiometabolic	Blood urea nitrogen	aSAH	Weighted Median	64	1,5625	0,3023	8,0763	0,5943	
Cardiometabolic	Blood urea nitrogen	aSAH	Weighted Mode	64	0,5288	0,0409	6,8434	0,6258	
Cardiometabolic	Systolic blood pressure	aSAH	IVW-RE	188	2,1696	1,8236	2,5814	2,40E-18	
Cardiometabolic	Systolic blood pressure	aSAH	MR-Egger	188	4,4641	2,5548	7,8001	1,49E-07	0,0078
Cardiometabolic	Systolic blood pressure	aSAH	Weighted Median	188	2,0175	1,6240	2,5063	2,30E-10	
Cardiometabolic	Systolic blood pressure	aSAH	Weighted Mode	188	1,5856	0,8395	2,9948	0,1554	
Cardiometabolic	eGFR	aSAH	IVW-RE	216	2,2873	0,4951	10,5671	0,2893	
Cardiometabolic	eGFR	aSAH	MR-Egger	216	0,4500	0,0095	21,2913	0,6849	0,3680
Cardiometabolic	eGFR	aSAH	Weighted Median	216	2,7807	0,3043	25,4133	0,3650	
Cardiometabolic	eGFR	aSAH	Weighted Mode	216	7,5182	0,0283	1999,2246	0,4788	
Cardiometabolic	Triglycerides	aSAH	IVW-RE	54	1,1356	0,9571	1,3474	0,1450	
Cardiometabolic	Triglycerides	aSAH	MR-Egger	54	0,9701	0,7424	1,2678	0,8242	0,1352
Cardiometabolic	Triglycerides	aSAH	Weighted Median	54	1,1027	0,8510	1,4290	0,4595	

Cardiometabolic	Triglycerides	aSAH	Weighted Mode	54	1,1340	0,8821	1,4577	0,3266	
Cardiometabolic	Body mass index	aSAH	IVW-RE	911	1,2077	1,0324	1,4129	0,0184	
Cardiometabolic	Body mass index	aSAH	MR-Egger	911	1,0281	0,6605	1,6002	0,9024	0,4455
Cardiometabolic	Body mass index	aSAH	Weighted Median	911	1,3317	1,0308	1,7204	0,0284	
Cardiometabolic	Body mass index	aSAH	Weighted Mode	911	1,3125	0,7831	2,1999	0,3021	
Cardiometabolic	Chronic kidney disease	aSAH	IVW-RE	21	1,0935	0,8356	1,4309	0,5149	
Cardiometabolic	Chronic kidney disease	aSAH	MR-Egger	21	1,9333	0,9454	3,9536	0,0709	0,0942
Cardiometabolic	Chronic kidney disease	aSAH	Weighted Median	21	1,2754	0,9836	1,6539	0,0664	
Cardiometabolic	Chronic kidney disease	aSAH	Weighted Mode	21	1,2497	0,8998	1,7355	0,1835	
Cardiometabolic	Type 2 diabetes mellitus	aSAH	IVW-RE	383	0,9985	0,9208	1,0827	0,9708	
Cardiometabolic	Type 2 diabetes mellitus	aSAH	MR-Egger	383	0,9080	0,7568	1,0894	0,2990	0,2538
Cardiometabolic	Type 2 diabetes mellitus	aSAH	Weighted Median	383	0,9493	0,8387	1,0745	0,4102	
Cardiometabolic	Type 2 diabetes mellitus	aSAH	Weighted Mode	383	0,8650	0,7194	1,0401	0,1232	
Cardiometabolic	HbA1c	aSAH	IVW-RE	31	0,7825	0,3876	1,5797	0,4939	
Cardiometabolic	HbA1c	aSAH	MR-Egger	31	0,7914	0,1049	5,9727	0,8205	0,9907
Cardiometabolic	HbA1c	aSAH	Weighted Median	31	0,7521	0,2782	2,0337	0,5746	
Cardiometabolic	HbA1c	aSAH	Weighted Mode	31	0,6961	0,1882	2,5754	0,5874	
Cardiometabolic	Fasting insulin	aSAH	IVW-RE	8	1,2434	0,1952	7,9211	0,8176	
Cardiometabolic	Fasting insulin	aSAH	MR-Egger	8	0,0561	0,0000	6533732	0,7612	0,7423
Cardiometabolic	Fasting insulin	aSAH	Weighted Median	8	1,4436	0,2098	9,9319	0,7091	
Cardiometabolic	Fasting insulin	aSAH	Weighted Mode	8	6,4921	0,1167	361,0099	0,3616	
Cardiometabolic	HDL cholesterol	aSAH	IVW-RE	102	0,9378	0,8047	1,0930	0,4112	
Cardiometabolic	HDL cholesterol	aSAH	MR-Egger	102	1,1488	0,8753	1,5078	0,3174	0,0782
Cardiometabolic	HDL cholesterol	aSAH	Weighted Median	102	0,8227	0,6587	1,0274	0,0852	
Cardiometabolic	HDL cholesterol	aSAH	Weighted Mode	102	0,9166	0,7257	1,1577	0,4648	
Cardiometabolic	LDL cholesterol	aSAH	IVW-RE	84	0,8890	0,7744	1,0205	0,0946	
Cardiometabolic	LDL cholesterol	aSAH	MR-Egger	84	0,9771	0,8064	1,1838	0,8126	0,1677
Cardiometabolic	LDL cholesterol	aSAH	Weighted Median	84	1,0165	0,8650	1,1946	0,8421	
Cardiometabolic	LDL cholesterol	aSAH	Weighted Mode	84	0,9756	0,8481	1,1223	0,7294	
Cardiometabolic	Interleukin-6 receptor	aSAH	IVW-RE	2	0,8197	0,4573	1,4695	0,5045	

Cardiometabolic	Fasting glucose	aSAH	IVW-RE	27	0,5694	0,3435	0,9439	0,0290	
Cardiometabolic	Fasting glucose	aSAH	MR-Egger	27	0,9449	0,3643	2,4506	0,9072	0,2208
Cardiometabolic	Fasting glucose	aSAH	Weighted Median	27	0,8041	0,4430	1,4598	0,4737	
Cardiometabolic	Fasting glucose	aSAH	Weighted Mode	27	0,7492	0,4346	1,2916	0,2987	

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; IA, intracranial aneurysm; IVW-RE, inverse-variance weighted random effects; LDL, low-density lipoprotein; MR, Mendelian randomization; OR, odds ratio; SE, standard error; SNPs, single-nucleotide polymorphisms.

Figure S1. Associations of genetically predicted exposures and intracranial aneurysm and aneurysmal subarachnoid hemorrhage in main and sensitivity analyses



Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; IA, intracranial aneurysm; IVW-RE, inverse-variance weighted random effects; LDL, low-density lipoprotein; MR, Mendelian randomization; OR, odds ratio.