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

Ville Karhunen, PhD; Mark K. Bakker, MSc; Ynte M. Ruigrok, PhD; Dipender Gill, PhD; Susanna C. Larsson, PhD

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
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

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

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.\textsuperscript{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)\textsuperscript{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.\textsuperscript{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 $\pm$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 $\pm$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.
when all genetic variants used are valid instrumental variables. We used MR-Egger, weighted median, and weighted mode 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. The weighted median method provides robust causal estimates if more than half of the weights are provided by valid instrumental variables. The weighted mode provides robust causal estimates if the weights associated with valid instrumental variables are the largest among homogeneous subsets of instruments. 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 to explore the mutually adjusted direct effects of (1) insomnia liability and sleep apnea (proxied by snoring liability), (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.

| 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 (-9 h/d, compared with 7–8 h/d) | 0.10†                  |
| Long sleep duration$^{26}$           | 34,184 cases; 305,742 controls | 4              | Log-odds (-7 h/d, compared with 7–8 h/d) | 0.20†                  |
| 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) | 0.49                   |
| Sleep duration$^{26}$                | 446,118     | 54                 | Hours per day                            | 0.90                   |
| Smoking index$^{28}$                 | 462,690     | 85                 | SD (continuous lifetime smoking measure) |                        |
| 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$^{22}$                 | 188,577     | 60                 | SD                                       | 5.6                    |
| Type 2 diabetes$^{23}$               | 148,726 cases; 965,732 controls | 422            | Log-odds                                 | 0.90†                  |
| Fasting glucose$^{16}$               | 133,010     | 32                 | 1 mmol/L                                 | 2.8                    |
| Fasting insulin$^{18}$               | 133,010     | 9                  | 1 pmol/L (log-transformed)               | 0.27                   |
| HbA1c$^{20}$                         | 123,666     | 34                 | Percentage point                         | 1.9                    |
| Interleukin-6 receptor$^{21}$        | 343,524     | 2                  | SD C-reactive protein levels             | 0.46                   |
| Chronic kidney disease$^{20}$        | 41,395 cases; 439,303 controls | 21             | Log-odds                                 | 0.29†                  |
| Blood urea nitrogen$^{20}$           | 243,029     | 67                 | 1 mg/dL                                  | 2.0                    |
| eGFR$^{20}$                          | 567,460     | 235                | (mL×min$^{-1}$)/(1.73 m$^2$) (log-transformed) | 2.9                    |

$^{1}$Calculated assuming a logistic distribution for the liability.

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                   |
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| eGFR$^{20}$                          | 567,460     | 235                | (mL×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.
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](https://example.com/figure.png)

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            | 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) | 3.5×10⁻⁶ | 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.

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.

**DISCUSSION**

The present MR study further investigated 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=5.8×10⁻⁶; OR per 1-SD increase in the prevalence of smoking initiation 1.85 [1.50–2.28], P=1.4×10⁻⁵; OR per unit increase in log-odds of insomnia liability 1.24 [1.10–1.40], P=5.0×10⁻⁴; OR per 10 mm Hg increase in diastolic blood pressure 2.92 [2.49–3.43], P=8.4×10⁻⁴⁰; OR per 10 mm Hg increase in systolic blood pressure 1.87 [1.61–2.17], P=1.4×10⁻¹⁸) 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=4.6×10⁻⁴⁰; 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=2.1×10⁻³⁴ and 2.17 [1.82–2.58], P=2.4×10⁻¹⁸, 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=2×10⁻⁴ 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).
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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**Affiliations**
Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom (V.K., D.G.); Research Unit of Mathematical Sciences (V.K.); and Center for Life Course Health Research (V.K.), University of Oulu, Finland; Department of Neurology and Neurosurgery, University Medical Center, Utrecht Brain Center, Utrecht University, Utrecht, the Netherlands (M.K.B., Y.M.R.); Clinical Pharmacology and Therapeutics Section, Institute of Medical and Biomedical Education and Institute for Infection and Immunity, St George's, University of London, London, United Kingdom (D.G.); Clinical Pharmacology Group, Pharmacy and Medicines Directorate, St George's University Hospitals NHS Foundation Trust, London, United Kingdom (D.G.); Novo Nordisk Research Centre Oxford, Oxford, United Kingdom (D.G.); Unit of Medical Epidemiology, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden (S.C.L.); and Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (S.C.L.).
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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
Table S2
Figure S1
**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      | Smoking initiation     | IA      | Weighted Median | 143  | 1,2382  | 1,0978     | 1,3965      | 0,0005  |                   |
| Lifestyle      | Smoking initiation     | IA      | MR-Egger        | 143  | 1,1186  | 0,6081     | 2,0574      | 0,7186  | 0,7389            |
| Lifestyle      | Smoking initiation     | IA      | Weighted Median | 143  | 1,2743  | 1,0767     | 1,5081      | 0,0048  |                   |
| Lifestyle      | Smoking initiation     | 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  |                   |
| Category                  | Variable                     | Method     | Estimator | Lower CI | Upper CI |
|--------------------------|------------------------------|------------|-----------|----------|----------|
| Lifestyle                | Long sleep duration          | IA         | MR-Egger  | 1.1545   | 0.1654   | 8.0601   | 0.8848   | 0.6991   |
| Lifestyle                | Long sleep duration          | IA         | Weighted Median | 0.7161   | 0.3968   | 1.2924   | 0.2677   |
| Lifestyle                | Long sleep duration          | IA         | Weighted Mode | 0.6545   | 0.3130   | 1.3687   | 0.2601   |
| Lifestyle                | Sleep duration               | IA         | Weighted Median | 0.7134   | 0.4228   | 1.2040   | 0.2060   |
| Lifestyle                | Sleep duration               | IA         | MR-Egger  | 1.0103   | 0.1473   | 6.9304   | 0.9917   | 0.7127   |
| Lifestyle                | Sleep duration               | IA         | Weighted Median | 0.6403   | 0.3084   | 1.3291   | 0.2315   |
| Lifestyle                | Sleep duration               | IA         | Weighted Mode | 0.5593   | 0.1722   | 1.8167   | 0.3337   |
| Lifestyle                | Physical activity            | IA         | Weighted Median | 0.6493   | 0.0322   | 1.4982   | 0.1218   |
| Lifestyle                | Physical activity            | IA         | MR-Egger  | 0.6545   | 0.3130   | 1.3687   | 0.2601   |
| Lifestyle                | Physical activity            | IA         | Weighted Mode | 0.6545   | 0.3130   | 1.3687   | 0.2601   |
| Cardiometabolic          | Diastolic blood pressure     | IA         | IVW-RE    | 2.9227   | 2.4925   | 3.4271   | 8.38E-40 |
| Cardiometabolic          | Diastolic blood pressure     | IA         | MR-Egger  | 5.4346   | 3.5999   | 8.2041   | 8.88E-16 |
| Cardiometabolic          | Diastolic blood pressure     | IA         | Weighted Median | 2.8770   | 2.2997   | 3.5993   | 2.29E-20 |
| Cardiometabolic          | Diastolic blood pressure     | IA         | Weighted Mode | 2.6370   | 1.1465   | 6.0651   | 0.0225   |
| Cardiometabolic          | Blood urea nitrogen          | IA         | IVW-RE    | 1.9416   | 0.7231   | 5.2134   | 0.1880   |
| Cardiometabolic          | Blood urea nitrogen          | IA         | MR-Egger  | 2.7888   | 0.1878   | 4.1029   | 0.4562   | 0.7772   |
| Cardiometabolic          | Blood urea nitrogen          | IA         | Weighted Median | 1.1348   | 0.2854   | 4.5131   | 0.8575   |
| Cardiometabolic          | Blood urea nitrogen          | IA         | Weighted Mode | 0.4220   | 0.0613   | 2.9073   | 0.3809   |
| Cardiometabolic          | Systolic blood pressure      | IA         | IVW-RE    | 1.8696   | 1.6117   | 2.1687   | 1.42E-16 |
| Cardiometabolic          | Systolic blood pressure      | IA         | MR-Egger  | 3.6572   | 2.2723   | 5.8861   | 9.29E-08 | 0.0037   |
| Cardiometabolic          | Systolic blood pressure      | IA         | Weighted Median | 1.7832   | 1.4970   | 2.1242   | 9.18E-11 |
| Cardiometabolic          | Systolic blood pressure      | IA         | Weighted Mode | 1.4929   | 0.9253   | 2.4089   | 0.1007   |
| Cardiometabolic          | eGFR                         | IA         | IVW-RE    | 1.6261   | 0.4839   | 5.4645   | 0.4317   |
| Cardiometabolic          | eGFR                         | IA         | MR-Egger  | 0.0588   | 0.0030   | 1.1632   | 0.0628   | 0.0173   |
| Cardiometabolic          | eGFR                         | IA         | Weighted Median | 1.5335   | 0.2371   | 9.9198   | 0.6536   |
| Cardiometabolic          | eGFR                         | IA         | Weighted Mode | 3.2552   | 0.0544   | 194.9203 | 0.5719   |
| Cardiometabolic          | Triglycerides                | IA         | IVW-RE    | 1.1870   | 1.0196   | 1.3819   | 0.0271   |
| Cardiometabolic          | Triglycerides                | IA         | MR-Egger  | 1.0621   | 0.8386   | 1.3452   | 0.6170   | 0.2295   |
| Cardiometabolic          | Triglycerides                | IA         | Weighted Median | 1.1392   | 0.9120   | 1.4231   | 0.2508   |
| Disease                                | Variable            | Method      | N  | Mean (95% CI)     | p-value |
|----------------------------------------|---------------------|-------------|----|------------------|---------|
| Cardiometabolic                        | Triglycerides       | Weighted Mode | 60 | 1.1751 (0.9535, 1.4482) | 0.1302  |
| Cardiometabolic                        | Body mass index     | IVW-RE      | 967| 1.1537 (1.0095, 1.3186) | 0.0359  |
| Cardiometabolic                        | Body mass index     | MR-Egger    | 967| 0.9867 (0.6767, 1.4386) | 0.9445  |
| Cardiometabolic                        | Body mass index     | Weighted Mode | 967| 1.1991 (0.9742, 1.4760) | 0.0866  |
| Cardiometabolic                        | Chronic kidney disease | IVW-RE    | 21 | 1.1440 (0.9001, 1.4539) | 0.2714  |
| Cardiometabolic                        | Chronic kidney disease | MR-Egger | 21 | 1.9347 (1.0206, 3.6677) | 0.0431  |
| Cardiometabolic                        | Chronic kidney disease | Weighted Mode | 21 | 1.3581 (1.0875, 1.7675) | 0.0436  |
| Cardiometabolic                        | Type 2 diabetes mellitus | IVW-RE | 422| 1.0136 (0.9458, 1.0863) | 0.7024  |
| Cardiometabolic                        | Type 2 diabetes mellitus | MR-Egger | 422| 0.9718 (0.8753, 1.0790) | 0.5925  |
| Cardiometabolic                        | Type 2 diabetes mellitus | Weighted Mode | 422| 0.8695 (0.7288, 1.0373) | 0.1204  |
| Cardiometabolic                        | HbA1c               | IVW-RE      | 34 | 0.9683 (0.5378, 1.7434) | 0.9144  |
| Cardiometabolic                        | HbA1c               | MR-Egger    | 34 | 0.9770 (0.1810, 5.2742) | 0.9784  |
| Cardiometabolic                        | HbA1c               | Weighted Mode | 34 | 0.9230 (0.3941, 2.1614) | 0.8535  |
| Cardiometabolic                        | HbA1c               | Weighted Mode | 34 | 0.9447 (0.2964, 3.0109) | 0.9234  |
| Cardiometabolic                        | Fasting insulin     | IVW-RE      | 9  | 0.9585 (0.1691, 5.4332) | 0.9618  |
| Cardiometabolic                        | Fasting insulin     | MR-Egger    | 9  | 0.2732 (0.0000, 4248511) | 0.8779  |
| Cardiometabolic                        | Fasting insulin     | Weighted Mode | 9  | 0.4446 (0.0762, 2.5954) | 0.3679  |
| Cardiometabolic                        | HDL cholesterol     | IVW-RE      | 113| 0.9317 (0.8244, 1.0531) | 0.2576  |
| Cardiometabolic                        | HDL cholesterol     | MR-Egger    | 113| 1.0550 (0.8452, 1.3168) | 0.6359  |
| Cardiometabolic                        | HDL cholesterol     | Weighted Mode | 113| 0.9145 (0.7597, 1.1010) | 0.3453  |
| Cardiometabolic                        | HDL cholesterol     | Weighted Mode | 113| 0.9361 (0.7769, 1.1279) | 0.4874  |
| Cardiometabolic                        | LDL cholesterol     | IVW-RE      | 88 | 0.8959 (0.7842, 1.0234) | 0.1054  |
| Cardiometabolic                        | LDL cholesterol     | MR-Egger    | 88 | 0.9669 (0.7810, 1.1970) | 0.7570  |
| Cardiometabolic                        | LDL cholesterol     | Weighted Mode | 88 | 0.9705 (0.8179, 1.1515) | 0.7314  |
| Cardiometabolic                        | LDL cholesterol     | Weighted Mode | 88 | 0.9845 (0.8373, 1.1576) | 0.8504  |
| Cardiometabolic                        | Interleukin-6 receptor | IVW-RE | 2  | 0.8049 (0.4865, 1.3318) | 0.3983  |
| Category         | Metric                | Method  | Estimate | Standard Error | Lower 95% CI | Upper 95% CI |
|------------------|-----------------------|---------|----------|----------------|--------------|--------------|
| Cardiometabolic  | Fasting glucose IA    | IVW-RE  | 0.6391   | 0.4278         | 0.9548       | 0.0288       |
| Cardiometabolic  | Fasting glucose IA    | MR-Egger| 1.0586   | 0.5040         | 2.2238       | 0.8804       |
| Cardiometabolic  | Fasting glucose IA    | Weighted Median | 0.8572   | 0.5222         | 1.4072       | 0.5424       |
| Lifestyle        | Smoking index aSAH    | IVW-RE  | 2.9861   | 1.5538         | 5.7388       | 0.0010       |
| Lifestyle        | Smoking index aSAH    | MR-Egger| 25.6901  | 1.6637         | 396.6874     | 0.0201       |
| Lifestyle        | Smoking index aSAH    | Weighted Median | 2.0573   | 0.9239         | 4.5814       | 0.0774       |
| Lifestyle        | Smoking initiation aSAH | IVW-RE | 1.6217   | 1.2372         | 2.1257       | 0.0005       |
| Lifestyle        | Smoking initiation aSAH | MR-Egger| 5.1285   | 1.7086         | 15.3938      | 0.0036       |
| Lifestyle        | Smoking initiation aSAH | Weighted Median | 2.1689   | 1.5006         | 3.1348       | 0.0343       |
| Lifestyle        | Smoking initiation aSAH | Weighted Mode | 3.0090   | 1.2050         | 7.5142       | 0.0183       |
| Lifestyle        | Insomnia aSAH         | IVW-RE  | 1.1986   | 1.0252         | 1.4014       | 0.0231       |
| Lifestyle        | Insomnia aSAH         | MR-Egger| 1.1289   | 0.5396         | 2.3618       | 0.7475       |
| Lifestyle        | Insomnia aSAH         | Weighted Median | 1.1832   | 0.9527         | 1.4694       | 0.1280       |
| Lifestyle        | Insomnia aSAH         | Weighted Mode | 1.1230   | 0.6164         | 2.0460       | 0.7047       |
| Lifestyle        | Caffeine consumption aSAH | IVW-RE | 1.2035   | 0.8719         | 1.6611       | 0.2601       |
| Lifestyle        | Short sleep duration aSAH | IVW-RE | 1.4819   | 0.8809         | 2.4929       | 0.1383       |
| Lifestyle        | Short sleep duration aSAH | MR-Egger| 2.9471   | 0.1939         | 44.7913      | 0.4363       |
| Lifestyle        | Short sleep duration aSAH | Weighted Median | 1.4557   | 0.7107         | 2.9815       | 0.3047       |
| Lifestyle        | Short sleep duration aSAH | Weighted Mode | 1.3632   | 0.4629         | 4.0150       | 0.5740       |
| Lifestyle        | Alcohol consumption aSAH | IVW-RE | 0.7232   | 0.3164         | 1.6530       | 0.4423       |
| Lifestyle        | Alcohol consumption aSAH | MR-Egger| 0.9197   | 0.1040         | 8.1298       | 0.9400       |
| Lifestyle        | Alcohol consumption aSAH | Weighted Median | 0.5593   | 0.1594         | 1.9622       | 0.3642       |
| Lifestyle        | Alcohol consumption aSAH | Weighted Mode | 0.5455   | 0.0941         | 3.1627       | 0.4991       |
| Lifestyle        | Coffee consumption aSAH | IVW-RE  | 1.0027   | 0.5251         | 1.9147       | 0.9935       |
| Lifestyle        | Coffee consumption aSAH | MR-Egger| 0.9359   | 0.2310         | 3.7912       | 0.9260       |
| Lifestyle        | Coffee consumption aSAH | Weighted Median | 1.1272   | 0.5448         | 2.3320       | 0.7469       |
| Lifestyle        | Coffee consumption aSAH | Weighted Mode | 1.1713   | 0.5101         | 2.6893       | 0.7093       |
| Lifestyle        | Long sleep duration aSAH | IVW-RE | 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 | 0.6383 | 0.1593 | 2.5576 | 0.5261 |
| Lifestyle | Sleep duration | aSAH | Weighted Mode | 47 | 0.6907 | 0.2918 | 1.6347 | 0.3998 |
| 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 | 1.5093 | 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 |
| Condition                        | Method          | aSAH | Weighted Mode | 54  | 1,1340 | 0,8821 | 1,4577 | 0,3266 |
|---------------------------------|-----------------|------|---------------|-----|--------|--------|--------|--------|
| Cardiometabolic                 | Triglycerides   | 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 |
| Cardiometabolic                 | Body mass index | aSAH | Weighted Mode | 911 | 1,3125 | 0,7831 | 2,1999 | 0,3021 |
| Cardiometabolic                 | Chronic kidney  | aSAH | IVW-RE        | 21  | 1,0935 | 0,8356 | 1,4309 | 0,5149 |
| Cardiometabolic                 | Type 2 diabetes | aSAH | MR-Egger      | 383 | 0,9493 | 0,8387 | 1,0745 | 0,4102 |
| Cardiometabolic                 | HbA1c           | aSAH | IVW-RE        | 31  | 0,7825 | 0,3876 | 1,5797 | 0,4939 |
| Cardiometabolic                 | Fasting insulin | aSAH | MR-Egger      | 8   | 0,0561 | 0,0000 | 0,7612 | 0,7423 |
| Cardiometabolic                 | HDL cholesterol | aSAH | IVW-RE        | 102 | 0,9378 | 0,8047 | 1,0930 | 0,4112 |
| Cardiometabolic                 | LDL cholesterol | aSAH | MR-Egger      | 102 | 1,1488 | 0,8753 | 1,5078 | 0,3174 |
| Cardiometabolic                 | LDL cholesterol | aSAH | Weighted Mode | 102 | 0,8227 | 0,6587 | 1,0274 | 0,0852 |
| Cardiometabolic                 | LDL 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 |
| Cardiometabolic                 | LDL cholesterol | aSAH | Weighted Mode | 84  | 1,0165 | 0,8650 | 1,1946 | 0,8421 |
| 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.