ORIGINAL RESEARCH

Genetically Determined Uric Acid and the Risk of Cardiovascular and Neurovascular Diseases: A Mendelian Randomization Study of Outcomes Investigated in Randomized Trials

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Background—Higher serum uric acid levels are associated with cardiovascular and neurovascular disease, but whether these relationships are causal is not known. We applied Mendelian randomization approaches to assess the association between genetically determined uric acid levels and outcomes under study in large clinical trials.

Methods and Results—We used 28 genetic variants related to serum uric acid as instruments to perform a range of 2-sample Mendelian randomization methods. Our analysis had statistical power to detect clinically relevant effects of genetically determined serum uric acid levels on the considered clinical outcomes; cognitive function, Alzheimer disease, coronary heart disease, myocardial infarction, systolic blood pressure, and stroke. There was some suggestive evidence for an association between higher genetically determined serum uric acid and cognitive function. There was also some suggestive evidence of a relationship between coronary heart disease, systolic blood pressure, and the serum uric acid genetic instruments, but likely related to genetic pleiotropy. Overall, there was no consistent evidence of a clinically relevant effect of genetically determined serum uric acid on any of the considered outcomes.

Conclusions—This Mendelian randomization study does not support a clinically relevant causal effect of genetically determined serum urate on a range of cardiovascular and neurovascular outcomes. The weak association of genetically determined serum urate with coronary heart disease and systolic blood pressure may be because of pleiotropic effects. If urate lowering drugs such as allopurinol are found to affect these outcomes in clinical trials, then the effects may be mediated through urate independent mechanisms. **(*J Am Heart Assoc*. 2019;8:e012738. DOI: 10.1161/JAHA.119.012738.)**

Key Words: Mendelian randomization • neurovascular disease • uric acid

Observational studies have shown a relationship between higher serum uric acid levels and increased risk of stroke, coronary heart disease (CHD), total cardiovascular events and incident hypertension.[1–4] There may also be a complicated relationship with dementia—hyperuricemia may accelerate cerebrovascular disease resulting in vascular dementia,[5] but may be neuroprotective in Alzheimer or Parkinson dementia, because of its antioxidant properties.[6] However, causality has not been confirmed and there is considerable potential for confounding. The Mendelian randomization (MR) approach can overcome some of the limitations of observational studies such as confounding or reverse causation to make causal inferences.[7] MR uses genetic variants randomly allocated at conception that are not associated with environmental confounders, such as single-nucleotide polymorphisms (SNPs), as instruments to study the effect of varying an exposure on risk of a particular outcome.[7] SNPs associated with uric acid can therefore be used as proxies for phenotypic serum uric acid levels to produce valid causal estimates when the underlying requisite assumptions of MR are met.[8]

Horizontal pleiotropy represents a violation of the requisite MR assumptions and occurs when the instruments are

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Clinical Perspective

What Is New?

- It is not known whether there is an association between serum uric acid and various cardiovascular and neurovascular outcomes.
- Mendelian randomization is a statistical approach that uses genetic variants such as single-nucleotide polymorphisms as genetic instruments to make causal inferences on the nature of an exposure-outcome relationship.
- This study used the Mendelian randomization technique to investigate the effect of genetically determined uric acid levels on cardiovascular and neurovascular outcomes under investigation in clinical trials.

What Are the Clinical Implications?

- We did not find evidence of any clinically relevant causal association between uric acid and coronary heart disease, myocardial infarction, systolic blood pressure, cognitive function, Alzheimer disease or any type of ischemic stroke.
- The protective role of urate lowering drugs on cardiovascular disease suggested by many observational studies and clinical trials might be attributable to urate independent mechanisms.

associated directly with the outcome independently of the exposure.[9] MR analyses studying the effects of uric acid on cardiovascular disease and hypertension have previously been performed, with some supporting a causal association.[10–12] In addition, a recent MR study did not find an association between serum uric acid levels and Alzheimer disease risk, but other dementia types or cognitive function were not investigated.[13] Similarly, to our knowledge there is no published MR investigation of the role of uric acid on ischemic stroke and its subtypes.

Clinical trials of allopurinol, the most widely used uric acid lowering drug, are underway in the setting of cardiovascular disease and are exploring effects on blood pressure, cardiovascular event rate in patients with CHD (ALL-HEART)[14] and on cognitive and cardiovascular outcomes in patients with stroke (XILO-FIST [Xanthine oxidase inhibition for improvement of long-term outcomes following ischaemic stroke and transient ischaemic attack]).[15] Numerous other small studies are in progress exploring surrogate outcomes. Allopurinol lowers serum uric acid in a dose dependent fashion, but also reduces the formation of reactive oxygen species and some of its vascular effects may be independent of uric acid reduction.[16] These clinical trials will help inform on whether allopurinol improves outcomes, although interpretation of the mechanism of any improvement will be limited.

In this study, we performed MR analyses investigating the relationship between genetically determined serum uric acid levels and the range of cardiovascular and associated outcomes under study in trials (cognitive performance, Alzheimer disease, CHD, myocardial infarction [MI], systolic blood pressure [SBP], ischemic stroke and its subtypes [large-artery atherosclerotic stroke {LAS}, cardioembolic stroke, and stroke caused by small-vessel disease {SVS}]). Methods for dealing with potential violations of the modelling assumptions were incorporated, including a range of statistical sensitivity analyses performed to investigate the robustness of the findings.

Methods

All data used in this study come from GWAS (genome-wide association study) meta-analyses for which ethical approval and patient consent were previously obtained. The data used are available upon reasonable request from the corresponding author.

Genetic Association Estimates

We used 28 SNPs associated with serum uric acid concentration at genome-wide significance ($P<5\times10^{-8}$) as genetic instruments. These were identified from a GWAS meta-analysis of 110 347 participants of European ancestry.[17] All 28 SNPs were replicated, and overall explained 5.8% of the variability in uric acid levels. In the largest study of the GWAS meta-analysis, the mean uric acid concentration was 6.0 mg/dL and the standard deviation (SD) was 1.5 mg/dL. The strength of each instrument was evaluated using F-statistic values, which were in turn calculated based on R^2, the proportion of phenotypic variance explained by each SNP.[18,19]

Genetic association estimates of SNP-outcome relationships were extracted from different data sets. For cognitive ability, SNPs were derived from a GWAS meta-analysis performed by the UK Biobank and Cognition Genomics Consortium (COGENT) on 257 841 participants of European origin.[20] Cognitive function was measured using a test of verbal-numerical reasoning in the UK Biobank, and neuropsychological assessments in COGENT study, further details for which are available in the original reporting studies.[21,22] Cognitive performance was standardized (mean=0 and SD=1). Genetic association estimates for Alzheimer disease were extracted from the discovery stage of the International Genomics of Alzheimer's Project (IGAP), a meta-analysis of 4 GWASs with a total of 17 008 cases and 37 154 controls, all of European ancestry.[23] The Coronary Artery Disease Genome Wide Replication and Meta-Analysis (CARDIoGRAM) plus The Coronary Artery Disease (C4D) (CARDIoGRAMplusC4D) 1000 Genomes-based GWAS meta-analysis was used to derive the association estimates for CHD and MI.[24] There were 60 801 CHD cases and 123 504 controls, with

Table 1. Characteristics of All Outcome Data Sets

Outcome	Consortium	Definition	Total Population	Ethnicity	Cases (%)	Controls	References
Cognitive performance	UK Biobank and COGENT	Cognitive performance was assessed using a test of verbal-numerical reasoning in UK Biobank and various neuropsychological tests in COGENT study	257 841	European	…	…	Lee et al (2018)[20]
Alzheimer disease	IGAP (Stage 1)	WHO definition; the most common form of dementia. Dementia is a syndrome in which there is deterioration in memory, thinking, behavior and the ability to perform everyday activities	54 162	European	17 008 (31.4%)	37 154	Lambert et al (2013)[23]
Coronary heart disease	CARDIoGRAMplusC4D	Coronary stenosis >30%, documented angina, documented myocardial infarction	184 305	77% European	60 801 (33.0%)	23 504	Nikpay et al (2015)[24]
Myocardial infarction	CARDIoGRAMplusC4D	Documented myocardial infarction; myocardial cell necrosis attributable to major and constant ischemia	54 162	77% European	42 560 (78.6%)	11 602	Nikpay et al (2015)[24]
Systolic blood pressure	UK Biobank	Electronically measured systolic blood pressure at baseline visit	473 891	White British	…	…	UK Biobank (Neale's lab) (2018)[25]
Ischemic stroke—any type	MEGASTROKE	WHO definition; rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting ≥24 h or leading to death, with no apparent cause other than of vascular origin of a neurological deficit persisting >24 h related to a vascular insult to the brain	514 791	Mixed	60 341 (11.7%)	454 450	Malik et al (2018)[26]
Ischemic stroke—cardioembolic stroke	MEGASTROKE	A type of ischemic stroke attributable to emboli coming from heart	514 791	Mixed	9006 (1.7%)	505 785	Malik et al (2018)[26]
Ischemic stroke—large-artery atherosclerotic stroke	MEGASTROKE	A type of ischemic stroke attributable to atherosclerosis of major intracranial arteries	514 791	Mixed	6688 (1.3%)	508 103	Malik et al (2018)[26]
Ischemic stroke—small-vessel disease stroke	MEGASTROKE	A type of ischemic stroke attributable to pathological processes of small arteries, arterioles, venules, and capillaries of the brain	514 791	Mixed	11 710 (2.3%)	503 081	Malik et al (2018)[26]

COGENT indicates Cognition Genomics Consortium; IGAP, International Genomics of Alzheimer Project; WHO, World Health Organization.

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the majority of participants (77%) being of European ancestry. The CHD definition included MI (≈70% of the total number of cases), acute coronary syndrome and angina pectoris. For SBP, data on 473 891 European-ancestry participants from the UK Biobank were used, with SBP estimates obtained from automated readings at baseline assessment, and having a mean value of 137.82 and an SD of 19.3 in the considered population.[25] Finally, for ischemic stroke and its subtypes LAS, cardioembolic stroke, and SVS, genetic association estimates were derived from a multi-ancestry GWAS performed by the MEGASTROKE Consortium, on 60 341 cases of any type of ischemic stroke (6688 of LAS; 9006 of cardioembolic stroke; 11 710 of SVS) and 454 450 controls.[26] Table 1 contains the information for all the data sets used in this study.

Mendelian Randomization Power Calculation

Information on the available sample size and the percentage of phenotypic variance explained by the instruments was used to perform power calculations for conventional MR analyses using the mRnd power calculator (available at http://cnsgenomics.com/shiny/mRnd/).[27] The smallest effect of uric acid (on all outcomes separately) required to achieve at least 80% statistical power given the sample size and percentage of phenotypic variance explained was calculated for the main analysis.

Mendelian Randomization Analyses and Investigation of Pleiotropy

For inverse-variance weighted (IVW) ratio method MR, we generated MR estimates for each SNP using the Wald estimator (ratio of SNP-outcome estimate over SNP-exposure estimate), with standard errors calculated using the Delta method to account for possible measurement error in both the exposure and outcome association estimates.[28,29] In the main analysis, the final effect estimate for each outcome was derived by pooling all MR estimates using the fixed-effects IVW method.[30] As this method assumes the absence of any horizontal pleiotropic effects of the genetic instruments on the considered outcome through pathways independent of the exposure (which in this case is serum uric acid) and is vulnerable to bias if this assumption does not hold, further MR methods that have less stringent assumptions on horizontal pleiotropy were therefore performed in sensitivity analyses. We estimated the intercept and slope of MR-Egger regression, which represent the average horizontal pleiotropy and a pleiotropy-adjusted MR estimate, respectively.[31] An intercept value for this regression that does not include the null ($P<0.05$) was considered indicative of horizontal pleiotropy.[31] MR-Egger makes the assumption that the strength of the instruments is not correlated to any pleiotropic effect that they have.[31] Additionally, the weighted median estimator was performed.[32] This is the weighted median effect of all the MR estimates produced by individual instruments, with weights equal to the inverse of the standard error.[32] It is valid when more than half the information from the analysis comes from valid instruments.[32] Finally, the Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) method was performed, which excludes outliers determined by the square of residual errors from the SNP-outcome against SNP-exposure regression to calculate an outlier-free effect estimate.[33]

Increased body mass index (BMI) has been causally associated with higher levels of serum uric acid in a recent MR study by Palmer et al.[11] To reduce any possible genetic confounding related to associations of the uric acid instruments with BMI, we adjusted for this using conventional regression-based multivariable MR.[34] Multivariable MR is a linear regression-based method with >1 explanatory variable.[34] The genetic association estimates for BMI were derived from a GWAS meta-analysis of the Genetic Investigation of Anthropometric Traits (GIANT) Consortium and UK Biobank, including ≈700 000 European-ancestry participants.[35]

An additional sensitivity analysis to deal with any potential horizontal pleiotropy was performed. We examined whether the 28 SNPs were associated with any traits other than uric acid levels, using the PhenoScanner online data set of publicly available GWAS results (http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner, accessed February 1, 2019), identifying associations that were genome-wide significant ($P<5\times10^{-8}$), and also considering proxy SNPs (linkage disequilibrium $r^2>0.8$).[36] The whole analysis was then repeated using only the SNPs that were exclusively associated with uric acid and/or gout. For the considered 9 outcomes, we accounted for multiple testing in the main analysis using a Bonferroni correction.

We used R software (version 3.5.1) and the MendelianRandomization[37] and MRPRESSO[33] software packages to perform analyses.

Results

All 28 SNPs had F-statistic values >10, suggesting that they were unlikely to introduce marked weak instrument bias into the MR analyses.[18] Table S1 contains the individual association estimates for uric acid and F-statistic values of each instrument SNP. Investigating potentially pleiotropic associations identified that only 7 out of the 28 instrument SNPs were exclusively associated with either uric acid levels and/or gout (Table S2). Power calculations for the conventional IVW

MR analyses using the 28 SNPs indicated >80% statistical power to detect an odds ratio (OR) <0.97 or >1.04 per 1 mg/dL increase in uric acid for the urate-CHD/MI relationships and a beta estimate smaller or >0.096 per 1 mg/dL increase in uric acid for the urate-SBP relationship. Similar power calculations were found for the MR analysis using the 7 SNPs specific to urate/gout. Tables S3 and S4 contain the power calculations for all outcomes for the 28 SNPs and 7 SNPs analyses, respectively. All results in this study are reported per 1 mg/dL increase in genetically determined uric acid.

Cognition and Alzheimer Disease

The results for uric acid and cognition are shown in Table 2. All analyses found an inverse relationship between serum uric acid level and cognitive performance. However, only the effect estimates from the weighted median method had a significant effect after adjusting for multiple testing using the Bonferroni correction ($P<0.005$) (weighted median estimate for the 7 only-urate associated SNPs: β −0.03; 95% CI −0.05–−0.01; $P=3.77\times10^{-04}$).[38] The intercept of the MR-Egger regression did not suggest the presence of directional pleiotropy ($P=0.72$). Results were consistent between all 28 and 7 SNPs.

Regarding Alzheimer disease, there was no demonstrable relationship with uric acid in any analysis (IVW method for the 7 SNPs analysis: OR 1.05; 95% CI 0.93–1.17; $P=0.48$). In addition, no horizontal pleiotropy was suggested by the MR-Egger test ($P=0.13$). Detailed results can be found in Table 2.

Coronary Heart Disease and Myocardial Infarction

There was an apparent effect of uric acid on CHD in outlier-corrected MR-PRESSO (OR 1.07; 95% CI 1.03–1.12; $P=2.99\times10^{-3}$), but not in any other method or in analyses restricted to the 7 SNPs specific for urate (Table 3). The MR-

Table 2. Results From All MR Analyses for the Association of Uric Acid With Cognitive Performance and Alzheimer Disease

Uric Acid on Cognition	β (95% CI)	*P* Value
Analysis with 28 SNPs		
Fixed-effects IVW	−0.02 (−0.04–0.01)	0.16
Weighted median	−0.03 (−0.05–−0.01)	1.00×10^{-03}
MR-Egger	−0.02 (−0.06–0.01)	0.22
MR-PRESSO (outliers corrected; 3 outliers)	−0.02 (−0.04–−0.01)	0.02
MR-PRESSO (raw)	−0.02 (−0.04–0.01)	0.17
MVMR adjusting for BMI	−0.02 (−0.04–0.01)	0.19
Analysis with 7 SNPs*		
Fixed-effects IVW	−0.03 (−0.06–0.00)	0.08
Weighted median	−0.03 (−0.05–−0.01)	3.77×10^{-04}
MR-Egger	−0.03 (−0.07–0.02)	0.27
MR-PRESSO (raw; 0 outliers)	−0.03 (−0.07–0.00)	0.09
Uric Acid on Alzheimer	**OR (95% CI)**	***P* Value**
Analysis with 28 SNPs		
Fixed-effects IVW	1.03 (0.96–1.10)	0.47
Weighted median	1.04 (0.95–1.14)	0.42
MR-Egger	1.08 (0.98–1.20)	0.12
MR-PRESSO (raw; 0 outliers)	1.03 (0.96–1.10)	0.49
MVMR adjusting for BMI	1.03 (0.96–1.11)	0.35
Analysis with 7 SNPs*		
Fixed-effects IVW	1.05 (0.93–1.17)	0.48
Weighted median	1.05 (0.95–1.15)	0.31
MR-Egger	1.06 (0.90–1.25)	0.48
MR-PRESSO (raw; 0 outliers)	1.04 (0.93–1.17)	0.49

BMI indicates body mass index; IVW, inverse variance weighted; MR-PRESSO, Mendelian Randomization Pleiotropy Residual Sum and Outlier; MR, Mendelian randomization; MVMR, multivariable Mendelian randomization analysis; SNP, single-nucleotide polymorphisms.
*The 7 non-pleiotropic SNPs that are associated with only uric acid or/and gout.

Table 3. Results From All MR Analyses for the Association of Uric Acid With Coronary Heart Disease, Myocardial Infarction, and Systolic Blood Pressure

Uric Acid on CHD	OR (95% CI)	*P* Value
Analysis with 28 SNPs		
Fixed-effects IVW	1.08 (1.02–1.14)	0.01
Weighted median	1.05 (0.99–1.11)	0.10
MR-Egger	1.02 (0.94–1.12)	0.63
MR-PRESSO (outlier corrected; 1 outlier)	1.07 (1.03–1.12)	2.99×10^{-03}
MR-PRESSO (raw)	1.08 (1.02–1.16)	0.02
MVMR adjusting for BMI	1.07 (1.01–1.14)	0.04
Analysis with 7 SNPs*		
Fixed-effects IVW	1.04 (0.97–1.11)	0.29
Weighted median	1.03 (0.97–1.09)	0.29
MR-Egger	1.03 (0.95–1.11)	0.58
MR-PRESSO (raw; 0 outliers)	1.04 (0.97–1.11)	0.29
Uric Acid on MI	**OR (95% CI)**	***P* Value**
Analysis with 28 SNPs		
Fixed-effects IVW	1.09 (1.02–1.16)	0.02
Weighted median	1.06 (0.99–1.12)	0.08
MR-Egger	1.01 (0.92–1.12)	0.80
MR-PRESSO (outlier corrected; 1 outlier)	1.08 (1.03–1.14)	4.41×10^{-03}
MR-PRESSO (raw)	1.10 (1.01–1.18)	0.03
MVMR adjusting for BMI	1.08 (1.00–1.17)	0.05
Analysis with 7 SNPs*		
Fixed-effects IVW	1.04 (0.97–1.12)	0.28
Weighted median	1.04 (0.98–1.11)	0.22
MR-Egger	1.03 (0.93–1.14)	0.54
MR-PRESSO (raw; 0 outliers)	1.04 (0.97–1.12)	0.28
Uric Acid on SBP	**β (95% CI)**	***P* Value**
Analysis with 28 SNPs		
Fixed-effects IVW	0.47 (−0.02 to 0.95)	0.07
Weighted median	0.23 (−0.07 to 0.53)	0.13
MR-Egger	−0.25 (−0.97 to 0.47)	0.49
MR-PRESSO (outlier corrected; 4 outliers)	0.58 (0.19–0.97)	0.01
MR-PRESSO (raw)	0.57 (−0.02 to 1.16)	0.07
MVMR adjusting for BMI	0.56 (−0.05 to 1.17)	0.08
Analysis with 7 SNPs*		
Fixed-effects IVW	0.34 (−0.18 to 0.86)	0.25
Weighted median	0.21 (−0.09 to 0.51)	0.15
MR-Egger	−0.12 (−0.53 to 0.30)	0.59
MR-PRESSO (outliers corrected; 1 outlier)	0.31 (−0.19 to 0.80)	0.28
MR-PRESSO (raw)	0.36 (−0.19 to 0.90)	0.25

BMI indicates body mass index; CHD, coronary heart disease; IVW, inverse variance weighted; MR-PRESSO, Mendelian Randomization Pleiotropy Residual Sum and Outlier; MI, myocardial infarction; MR, Mendelian randomization; MVMR, multivariable Mendelian randomization analysis; SBP, systolic blood pressure.
*The 7 non-pleiotropic SNPs that are associated with only uric acid or/and gout.

Egger test did not provide evidence of horizontal pleiotropy (*P*=0.06). Similar results were found for MI (Table 3).

Systolic Blood Pressure

In the main analysis using the 28 SNPs, 1 mg/dL increase in uric acid was associated with 0.47 mm Hg increase in SBP (IVW method: 95% CI −0.02–0.95; *P*=0.07). There was a suggestive association when performing the outlier corrected MR-PRESSO method with all 28 SNPs, but this was not statistically significant after Bonferroni correction (MR-PRESSO method; β 0.58; 95% CI 0.19–0.97; *P*=0.01) (Table 3). In addition, the MR-Egger test suggested the presence of horizontal pleiotropy when considering all 28 SNPs ($P=2\times10^{-3}$).

Stroke

The effect estimates for ischemic stroke and its subtypes were consistent throughout all analysis methods and were not suggestive of an association between uric acid and ischemic stroke or its subtypes (Table 4). The OR for the effect of genetically determined uric acid on any type of ischemic stroke when using the IVW method in the 28 SNPs analysis was 1.00 (95% CI 0.94–1.06; *P*=0.99) and was consistent after adjusting for BMI in multivariable Mendelian randomization (OR 0.99; 95% CI 0.92–1.07; *P*=0.89) or after using the 7 SNPs associated with only uric acid/gout (IVW: OR 0.96; 95% CI 0.91–1.02; *P*=0.20). The MR-Egger intercepts of all stroke analyses were found to be close to 0, indicating the absence of horizontal pleiotropy.

The association estimates of the SNPs with cognitive performance, Alzheimer disease, CHD, MI, SBP, and ischemic stroke and its subtypes are presented in Tables S5 through S13, respectively. Figures S1 through S9 are Forest plots representing the individual SNP MR estimates of the 28 SNPs for all outcomes, respectively. Funnel and Radial plots to visualize the presence of heterogeneity for every outcome are provided in Figures S10 through S18. Forest plots containing the association estimates found using each method for the uric acid-

Table 4. Results From All MR Analyses for the Association of Uric Acid With Ischemic Stroke and its Subtypes

Uric Acid on Ischemic Stroke	OR (95% CI)	*P* Value
Analysis with 28 SNPs		
Fixed-effects IVW	1.00 (0.94–1.06)	0.99
Weighted median	0.98 (0.93–1.03)	0.42
MR-Egger	0.95 (0.85–1.05)	0.31
MR-PRESSO (outlier corrected; 1 outlier)	1.00 (0.95–1.05)	0.87
MR-PRESSO (raw)	1.00 (0.94–1.08)	0.86
MVMR adjusting for BMI	0.99 (0.92–1.07)	0.89
Analysis with 7 SNPs*		
Fixed-effects IVW	0.96 (0.91–1.02)	0.20
Weighted median	0.97 (0.92–1.03)	0.33
MR-Egger	0.99 (0.93–1.06)	0.82
MR-PRESSO (raw; 0 outliers)	0.96 (0.91–1.02)	0.20
Uric Acid on CES	**OR (95% CI)**	***P* Value**
Analysis with 28 SNP		
Fixed-effects IVW	0.97 (0.89–1.05)	0.44
Weighted median	0.95 (0.86–1.05)	0.32
MR-Egger	0.92 (0.82–1.04)	0.20
MR-PRESSO (raw; 0 outliers)	0.97 (0.89–1.06)	0.49
MVMR adjusting for BMI	0.97 (0.89–1.06)	0.50
Analysis with 7 SNPs*		
Fixed-effects IVW	0.93 (0.87–1.00)	0.08
Weighted median	0.95 (0.85–1.06)	0.33
MR-Egger	0.97 (0.85–1.10)	0.60
MR-PRESSO (raw; 0 outliers)	0.93 (0.87–1.00)	0.08
LAS	**OR (95% CI)**	***P* Value**
Analysis with 28 SNPs		
Fixed-effects IVW	1.01 (0.88–1.15)	0.94
Weighted median	0.94 (0.83–1.07)	0.36
MR-Egger	0.89 (0.74–1.08)	0.24
MR-PRESSO (outliers corrected; 1 outlier)	1.00 (0.88–1.13)	0.98
MR-PRESSO (raw)	1.01 (0.88–1.16)	0.87
MVMR adjusting for BMI	1.00 (0.86–1.15)	0.98
Analysis with 7 SNPs*		
Fixed-effects IVW	0.92 (0.84–1.01)	0.13
Weighted median	0.93 (0.81–1.06)	0.27
MR-Egger	0.93 (0.79–1.10)	0.41
MR-PRESSO (raw; 0 outliers)	0.92 (0.84–1.01)	0.13
SVS	**OR (95% CI)**	***P* Value**
Analysis with 28 SNPs		
Fixed-effects IVW	1.04 (0.92–1.16)	0.55
Weighted median	1.05 (0.94–1.17)	0.41
MR-Egger	1.08 (0.90–1.28)	0.42
MR-PRESSO (outliers corrected; 1 outlier)	1.03 (0.93–1.13)	0.62
MR-PRESSO (raw)	1.04 (0.92–1.17)	0.54
MVMR adjusting for BMI	1.02 (0.90–1.15)	0.79
Analysis with 7 SNPs*		
Fixed-effects IVW	1.02 (0.93–1.12)	0.71
Weighted median	1.04 (0.92–1.17)	0.56
MR-Egger	1.09 (0.94–1.26)	0.27
MR-PRESSO (raw; 0 outliers)	1.02 (0.93–1.12)	0.72

BMI indicates body mass index; CES, cardioembolic stroke; IVW, inverse variance weighted; LAS, large-artery atherosclerotic stroke; MR, Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy Residual Sum and Outlier; MVMR, multivariable Mendelian randomization analysis; SVS, small-vessel stroke.
*The 7 non-pleiotropic SNPs that are associated with only uric acid or/and gout.

cognition and uric acid-Alzheimer disease analyses are provided in Figures S19 and S20, respectively. Similarly, Figure S21 is a Forest plot of the uric acid-CHD and uric acid-MI relationships, with Figures S22 and S23 the same for uric acid-SBP and uric acid-ischemic stroke and its subtypes, respectively.

Discussion

Our study did not provide consistent MR evidence to support a causal effect of genetically determined serum uric acid levels on cognitive function, Alzheimer disease, CHD, MI, or ischemic stroke, including its subtypes (cardioembolic stroke, SVS, and LAS), despite the associations observed in many observational studies.[1–5] Although there was some evidence for an association with cognitive function, coronary outcomes and SBP, the findings did not survive correction for multiple testing and sensitivity analyses investigating bias related to pleiotropy. Although the analysis with 7 instrument SNPs had lower statistical power than that with 28 SNPs, it is important to appreciate that all the IVW MR analyses had sufficient power to detect clinically meaningful associations. These results will therefore help interpret results from ongoing clinical trials and inform the direction of future study.

Our results were suggestive of an inverse association between uric acid and cognitive performance, as the effect estimates of this relationship were consistent throughout all analysis methods and approached statistical significance, even after accounting for multiple testing. Whether this effect is of clinical importance, however, needs to be clarified and more

research is needed. We also need to acknowledge that this study does not exclude the presence of smaller effects, or effects of allopurinol lowering drugs distinct from the effect of general urate lowering. Any relationship between uric acid levels and cognitive function or dementia is likely to be complex given the heterogeneous nature of dementias, the antioxidant effects of uric acid and the detrimental effects of chronic hyperuricemia on the vasculature. Observational studies suggest the relationship may differ by dementia subtype. In a recent systematic review and meta-analysis, serum uric acid levels were lower in people with Alzheimer disease and dementia associated with Parkinson disease but there was no association with vascular dementia.[39] Experimental studies suggest a neuroprotective effect of uric acid which may be beneficial in some neurodegenerative disorders,[6] but also that chronic hyperuricemia could induce cognitive impairment via vascular damage.[5] Our data support this. Studies assessing the relationship between instrumental variables for uric acid and vascular dementia would be helpful.

Considering the other outcomes, while for CHD and SBP there was some evidence of an association, the importance and clinical relevance of this is debatable. Our analysis for SBP suggested that 1 mg/dL increase in genetically determined uric acid would increase blood pressure by 0.34 mm Hg (IVW for the 7 SNPs analysis: 95% CI −0.18–0.86; P=0.25). However, other MR studies do support a causal role for hyperuricemia in hypertension[10,12] (although there are discordant reports[11,40]) and clinical trials suggest a larger effect. A clinical trial of uric acid lowering therapies in adolescents showed an ≈10 mm Hg fall in SBP with both allopurinol and probenecid.[41,42] If a fall of this magnitude was present in older adults, it would be associated with a 41% reduction in stroke events and a 22% reduction in CHD events.[41,42] Whether these changes exist in older adults at risk of cardiovascular disease now needs to be established in clinical trials. The presence of a small effect in an MR study in the predominantly "healthy" UK Biobank population does not exclude a similar larger and important effect of uric acid reduction in hyperuricemia adults at increased risk. Further clinical trials are needed to assess this. The fact that both a xanthine oxidase inhibitor and a uricosuric drug lowered blood pressure in adolescents raises the possibility that this effect is mediated by uric acid itself and not by xanthine oxidase inhibition or a reduction in oxidative stress. However, there are alternative explanations. The effects of xanthine oxidase inhibitors may be uric acid independent; high doses of allopurinol, but not probenecid, improved measures of endothelial function in adults with heart failure and it is of interest that trials of uric acid reduction have been neutral in this setting.[43,44] Further, probenecid may exert its effects via changes in renal function and MR studies have suggested that activity of uric acid transporters rather than the level of uric acid itself is related to renal function.[45] Whether the observed effects of probenecid on renal function are because of this mechanism or a uric acid effect is unclear. Further clinical study should aim to establish this.

MR studies have also shown an association between uric acid and CHD[10,12] but again there are conflicting reports.[40] Hypertension is the biggest risk factor for stroke and if hyperuricemia causes this, a downstream effect on the risk of stroke would be expected. Stroke is a heterogeneous condition and the presence of an association with CHD makes it attractive to hypothesize there would be an association with LAS, which overlap in its etiology.[26] However, we saw no MR evidence of this.

The findings of this study will help plan and interpret results of clinical trials of uric acid reduction. Both allopurinol and probenecid have been shown to reduce blood pressure in adolescents by between 6 and 10 mm Hg systolic.[41,42] Allopurinol has also been shown to reduce left ventricular hypertrophy and carotid intima media thickness.[43,46,47] Left ventricular hypertrophy is a key risk factor for stroke and the lack of association with stroke (and LAS in particular in our study) raises the possibility that these effects are mediated by xanthine oxidase and not uric acid. Our data do not exclude potentially beneficial effects of allopurinol that are mediated via uric acid independent mechanism. Indeed, if clinical trials of allopurinol yield benefit on outcomes such as stroke, we could infer these effects are uric acid independent. Furthermore, patients with stroke have a higher risk of cognitive impairment and cardiac disease so a potentially beneficial effect of uric acid reduction in this population cannot be excluded. Overall however, we feel our data suggest trials of uric acid reduction in the setting of cardiovascular disease should focus on cardiac end points or blood pressure reduction. It is likely that if clinically important effects are seen that they will at least in part be because of urate independent mechanisms. Further, the potential for genetic information to identify people with particularly harmful forms of hyperuricemia, or who are most likely to respond to uric acid reduction, should be considered. This could be done by analysis of genetic data in ongoing trials.

Strengths of our study include the large sample size for each MR analysis with good statistical power. Both the 28 and 7 SNPs analyses had sufficient power to detect clinically relevant effect estimates (Tables S3 and S4). The availability of large-scale GWASs for a range of relevant neurological and vascular outcomes further allowed investigation across the relevant outcome phenotypes in a manner more efficient that afforded by clinical trial,[48] and also overcoming the issues of confounding and reverse causation bias that can limit traditional observational research.[49] Furthermore, robust methods were applied to deal with possible violations of the requisite assumptions of MR, including horizontal pleiotropy.[50]

Limitations of this work include the fact that the sample size for subtypes of stroke was smaller than for other analyses, having potential implications for fine-mapping the effects of uric acid on stroke subtypes that vary in their underlying etiology and pathophysiology.[26] Furthermore, it is important to appreciate that MR measures the cumulative effect of lifelong exposure to genetic variants related to serum uric acid levels, and that this is not the same as studying the effect of a discrete clinical intervention in adult life.[51] These MR results should therefore not be extrapolated to assume the effect of clinical intervention on uric acid levels, particularly as the MR approach may be subject to some residual bias related to pleiotropy despite the pleiotropy robust approaches. Furthermore, therapies for uric acid reduction may be having effects on neurological and vascular disease partly unrelated to their effects on uric acid.[43–47] Finally, because of the fact that there is no available power calculation technique for MR-Egger, we were not able to provide statistical power calculations for this analysis. Therefore, our analysis could contain false negative results on the MR-Egger test for directional pleiotropy.

Conclusions

In conclusion, our study did not provide consistent evidence to support that genetically determined serum uric acid has a clinically relevant causal effect on risk of the considered cardiovascular and neurovascular outcomes. If there is an effect of urate lowering drugs on these mechanisms, it may be mediated by urate independent mechanisms.

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SUPPLEMENTAL MATERIAL

Table S1. All 28 SNPs for serum urate from Köttgen et al study (1)

	SNP	chr	EA	OA	EAF	GX	SE_GX	pval	N	MAF	R2	F-statistic
1	rs10480300	7	T	C	0.280	0.035	0.006	4.10E-09	110,347	0.28	0.00030828	34.016363
2	rs10821905	10	A	G	0.180	0.057	0.007	7.40E-17	110,347	0.18	0.00060053	66.2645023
3	rs11264341	1	T	C	0.430	-0.050	0.006	6.20E-19	110,347	0.43	0.00062893	69.3988818
4	rs1165151	6	T	G	0.470	-0.091	0.005	7.00E-70	110,347	0.47	0.00299282	330.23968
5	rs1171614	10	T	C	0.220	-0.079	0.007	2.30E-28	110,347	0.22	0.00115291	127.217045
6	rs1178977	7	A	G	0.810	0.047	0.007	1.20E-12	110,347	0.19	0.00040838	45.0619972
7	rs12498742	4	A	G	0.770	0.373	0.006	1.00E-10	110,347	0.23	0.03383799	3733.81943
8	rs1260326	2	T	C	0.410	0.074	0.005	1.20E-44	110,347	0.41	0.00198108	218.600121
9	rs1394125	15	A	G	0.340	0.043	0.006	2.50E-13	110,347	0.34	0.00046523	51.3358205
10	rs1471633	1	A	C	0.460	0.059	0.005	1.20E-29	110,347	0.46	0.00126025	139.060742
11	rs17050272	2	A	G	0.430	0.035	0.006	1.60E-10	110,347	0.43	0.00030828	34.016363
12	rs17632159	5	C	G	0.310	-0.039	0.006	3.50E-11	110,347	0.31	0.00038274	42.2326812
13	rs17786744	8	A	G	0.580	-0.029	0.005	1.4E-08	110,347	0.42	0.00030476	33.6288335
14	rs2078267	11	T	C	0.510	-0.073	0.006	9.40E-38	110,347	0.49	0.00133968	147.825449
15	rs2231142	4	T	G	0.110	0.217	0.009	1.00E-134	110,347	0.11	0.00524073	578.28328
16	rs2941484	8	T	C	0.440	0.044	0.005	4.40E-17	110,347	0.44	0.00070129	77.3835879
17	rs3741414	12	T	C	0.240	-0.072	0.007	2.20E-25	110,347	0.24	0.00095784	105.69171
18	rs478607	11	A	G	0.840	-0.047	0.007	4.40E-11	110,347	0.16	0.00040838	45.0619972
19	rs653178	12	T	C	0.510	-0.035	0.005	7.20E-12	110,347	0.49	0.00044386	48.9769195
20	rs6598541	15	A	G	0.360	0.043	0.006	4.80E-15	110,347	0.36	0.00046523	51.3358205
21	rs675209	6	T	C	0.270	0.061	0.006	1.30E-23	110,347	0.27	0.00093582	103.261577
22	rs6770152	3	T	G	0.580	-0.044	0.005	2.60E-16	110,347	0.42	0.00070129	77.3835879
23	rs7188445	16	A	G	0.330	-0.032	0.005	1.60E-09	110,347	0.33	0.00037106	40.9436884

24	rs7193778	16	T	C	0.860	-0.046	0.008	8.20E-10	110,347	0.14	0.00029953	33.0516981
25	rs7224610	17	A	C	0.580	-0.042	0.005	5.40E-17	110,347	0.42	0.00063903	70.512993
26	rs729761	6	T	G	0.300	-0.047	0.006	8.00E-16	110,347	0.3	0.00055577	61.3253415
27	rs7953704	12	A	G	0.470	-0.029	0.005	2.6E-08	110,347	0.47	0.00030476	33.6288335
28	rs7976059	12	T	G	0.350	0.032	0.005	1.90E-09	110,347	0.35	0.00037106	40.9436884

SNP: each SNP's id; chr: chromosome; EA: effect allele; OA: other allele; EAF: effect allele frequency for GX; GX: beta for the SNP-urate relationship; SE_GX: standard error of GX; pval: p-value of GX; N: sample size of the study from which each SNP was found; MAF: minor allele frequency; R2: % of variance in cognition explained by each SNP, calculated by: R2=2*GX^2*MAF*(1-MAF)/[2*GX^2*MAF*(1-MAF)+ SE_GX^2*2*N*MAF*(1-MAF)](2); F-statistic: a measurement of instrument's strength, calculated by: F-statistic=R2*(N-2)/1-R2 (3)

Table S2. The 7 SNPs that are only associated with serum urate or/and gout (1) after excluding the pleiotropic SNPs using Phenoscanner (4)

	SNP	chr	EA	OA	EAF	GX	SE_GX	pval	R2	F-statistic
1	rs12498742	4	A	G	0.77	0.373	0.006	1.00E-10	0.03383799	3733.81943
2	rs1471633	1	A	C	0.46	0.059	0.005	1.20E-29	0.00126025	139.060742
3	rs2078267	11	T	C	0.51	-0.073	0.006	9.40E-38	0.00133968	147.825449
4	rs2941484	8	T	C	0.44	0.044	0.005	4.40E-17	0.00070129	77.3835879
5	rs6770152	3	T	G	0.58	-0.044	0.005	2.60E-16	0.00070129	77.3835879
6	rs7224610	17	A	C	0.58	-0.042	0.005	5.40E-17	0.00063903	70.512993
7	rs7976059	12	T	G	0.35	0.032	0.005	1.90E-09	0.00037106	40.9436884

SNP: each SNP's id; chr: chromosome; EA: effect allele; OA: other allele; EAF: effect allele frequency for GX; GX: beta for the SNP-urate relationship; SE_GX: standard error of GX; pval: p-value of GX

Table S3. Power calculations for all analyses using the 28 SNPs. The calculations were made using the mRnd power calculator (available at http://cnsgenomics.com/shiny/mRnd/) (5)

CHD						
% of variance in urate explained by the 28 SNPs	Type-I error rate	Sample size of the outcome dataset; CARDIoGRAMplusC4D 1000 Genomes-based GWAS (6)	Proportion of CAD cases		minimum OR to have >80% power	maximum OR to have >80% power
0.058	0.05	184,305	0.33		0.97	1.04
MI						
% of variance in urate explained by the 28 SNPs	Type-I error rate	Sample size of the outcome dataset; CARDIoGRAMplusC4D 1000 Genomes-based GWAS (6)	Proportion of MI cases		minimum OR to have >80% power	maximum OR to have >80% power
0.058	0.05	184,305	0.23		0.96	1.04
COGNITION						
% of variance in urate explained by the 28 SNPs	Type-I error rate	Sample size of the outcome dataset; (Lee et al) (7)	β OLS*	σ2 (x)**	σ2 (y) ***	minimum beta to have >80% power
0.058	0.05	257,841	0	2.25	1	0.135
SBP						
% of variance in urate explained by the 28 SNPs	Type-I error rate	Sample size of the outcome dataset; SBP automated (UK biobank) (8)	β OLS*	σ2 (x)**	σ2 (y) ***	minimum beta to have >80% power
0.058	0.05	473,891	0	2.25	1	0.096
ALZHEIMER						
% of variance in urate explained by the 28 SNPs	Type-I error rate	Sample size of the outcome dataset; IGAP 1st stage (9)	Proportion of Alzheimer cases		minimum OR to have >80% power	maximum OR to have >80% power
0.058	0.05	54,162	0.31		0.93	1.08
STROKE						
% of variance in urate explained by the 28 SNPs	Type-I error rate	Sample size of the outcome dataset; MEGASTROKE (10)	Proportion of **any ischemic stroke** cases		minimum OR to have >80% power	maximum OR to have >80% power

0.058	0.05	514,791	0.12	0.97	1.03
% of variance in urate explained by the 28 SNPs	Type-I error rate	Sample size of the outcome dataset; METASTROKE (10)	Proportion of **CES stroke** cases	minimum OR to have >80% power	maximum OR to have >80% power
0.058	0.05	514,791	0.02	0.92	1.08
% of variance in urate explained by the 28 SNPs	Type-I error rate	Sample size of the outcome dataset; METASTROKE (10)	Proportion of **LAS stroke** cases	minimum OR to have >80% power	maximum OR to have >80% power
0.058	0.05	514,791	0.013	0.91	1.10
% of variance in urate explained by the 28 SNPs	Type-I error rate	Sample size of the outcome dataset; METASTROKE (10)	Proportion of **SVS stroke** cases	minimum OR to have >80% power	maximum OR to have >80% power
0.058	0.05	514,791	0.023	0.92	1.07

* the observational association estimate of the exposure-outcome relationship
** variance of the exposure variable (x),
*** variance of the outcome variable (y)
CHD; coronary heart disease, MI; myocardial infraction, SBP; systolic blood pressure, CES; cardioembolic stroke, LAS; large vessels stroke, SVS; small vessels stroke

Table S4. Power calculations for all analyses using the 7 SNPs. The calculations were made using the mRnd power calculator (available at http://cnsgenomics.com/shiny/mRnd/) (5) **.**

CHD						
% of variance in urate explained by the 7 SNPs	Type-I error rate	Sample size of the outcome dataset; CARDIoGRAMplusC4D 1000 Genomes-based GWAS (6)	Proportion of CAD cases		minimum OR to have >80% power	maximum OR to have >80% power
0.039	0.05	184,305	0.33		0.95	1.05
MI						
% of variance in urate explained by the 7 SNPs	Type-I error rate	Sample size of the outcome dataset; CARDIoGRAMplusC4D 1000 Genomes-based GWAS (6)	Proportion of MI cases		minimum OR to have >80% power	maximum OR to have >80% power
0.039	0.05	184,305	0.23		0.95	1.05
COGNITION						
% of variance in urate explained by the 7 SNPs	Type-I error rate	Sample size of the outcome dataset; (Lee et al) (7)	β OLS*	σ2 (x)**	σ2 (y) ***	minimum beta to have >80% power
0.039	0.05	257,841	0	2.25	1	0.250
SBP						
% of variance in urate explained by the 7 SNPs	Type-I error rate	Sample size of the outcome dataset; SBP automated (UK biobank) (8)	β OLS*	σ2 (x)**	σ2 (y) ***	minimum beta to have >80% power
0.039	0.05	473,891	0	2.25	1	0.193
ALZHEIMER						
% of variance in urate explained by the 7 SNPs	Type-I error rate	Sample size of the outcome dataset; IGAP 1st stage (9)	Proportion of Alzheimer cases		minimum OR to have >80% power	maximum OR to have >80% power
0.039	0.05	54,162	0.31		0.91	1.10
STROKE						
% of variance in urate explained by the 7 SNPs	Type-I error rate	Sample size of the outcome dataset; MEGASTROKE (10)	Proportion of **any ischemic stroke** cases		minimum OR to have >80% power	maximum OR to have >80% power

0.039	0.05	514,791	0.12	0.96	1.04
% of variance in urate explained by the 7 SNPs	Type-I error rate	Sample size of the outcome dataset; METASTROKE (10)	Proportion of **CES stroke** cases	minimum OR to have >80% power	maximum OR to have >80% power
0.039	0.05	514,791	0.02	0.90	1.13
% of variance in urate explained by the 7 SNPs	Type-I error rate	Sample size of the outcome dataset; METASTROKE (10)	Proportion of **LAS stroke** cases	minimum OR to have >80% power	maximum OR to have >80% power
0.039	0.05	514,791	0.013	0.88	1.12
% of variance in urate explained by the 7 SNPs	Type-I error rate	Sample size of the outcome dataset; METASTROKE (10)	Proportion of **SVS stroke** cases	minimum OR to have >80% power	maximum OR to have >80% power
0.039	0.05	514,791	0.023	0.90	1.10

* the observational association estimate of the exposure-outcome relationship
** variance of the exposure variable (x),
*** variance of the outcome variable (y)
CHD; coronary heart disease, MI; myocardial infraction, SBP; systolic blood pressure, CES; cardioembolic stroke, LAS; large vessels stroke, SVS; small vessels stroke

Table S5. The association estimates of the 28 SNPs for urate (1) with cognitive performance (7)

	SNP	chr	EA	OA	EAF	GY	SE_GY	pval
1	rs10480300	7	C	T	0.704	-0.001	0.003	0.780
2	rs10821905	10	A	G	0.165	-0.001	0.004	0.856
3	rs11264341	1	T	C	0.412	0.000	0.003	0.878
4	rs1165151	6	G	T	0.551	-0.010	0.003	0.000
5	rs1171614	10	T	C	0.257	0.007	0.003	0.038
6	rs1178977	7	G	A	0.197	-0.007	0.004	0.047
7	rs12498742	4	A	G	0.779	-0.011	0.003	0.001
8	rs1260326	2	C	T	0.587	-0.003	0.003	0.237
9	rs1394125	15	G	A	0.645	-0.001	0.003	0.639
10	rs1471633	1	C	A	0.510	0.002	0.003	0.572
11	rs17050272	2	G	A	0.563	0.002	0.003	0.437
12	rs17632159	5	G	C	0.685	-0.003	0.003	0.389
13	rs17786744	8	G	A	0.439	0.003	0.003	0.348
14	rs2078267	11	C	T	0.442	0.003	0.003	0.249
15	rs2231142	4	G	T	0.893	0.001	0.005	0.886
16	rs2941484	8	T	C	0.422	-0.004	0.003	0.141
17	rs3741414	12	T	C	0.221	-0.010	0.003	0.002
18	rs478607	11	G	A	0.136	0.008	0.004	0.045
19	rs653178	12	C	T	0.473	-0.006	0.003	0.044
20	rs6598541	15	G	A	0.677	-0.004	0.003	0.197
21	rs675209	6	C	T	0.708	0.002	0.003	0.546
22	rs6770152	3	G	T	0.444	0.013	0.003	0.000
23	rs7188445	16	A	G	0.354	0.004	0.003	0.140
24	rs7193778	16	T	C	0.855	-0.009	0.004	0.032
25	rs7224610	17	A	C	0.585	0.004	0.003	0.136
26	rs729761	6	T	G	0.282	-0.006	0.003	0.054
27	rs7953704	12	A	G	0.481	0.003	0.003	0.272
28	rs7976059	12	G	T	0.645	0.006	0.003	0.050

SNP: each SNP's id; chr: chromosome; EA: effect allele, OA: other allele; EAF: effect allele frequency for GY; GY: beta for the SNP-cognition relationship; SE_GY: standard error of GY; pval: p-value of GY

Table S6. The association estimates of the 28 SNPs for urate (1) with Alzheimer's disease (9)

	SNP	chr	EA	OA	GY	SE_GY	pval
1	rs10480300	7	T	C	0.014	0.017	0.4349
2	rs10821905	10	A	G	-0.025	0.021	0.2371
3	rs11264341	1	T	C	0.005	0.017	0.7549
4	rs1165151	6	T	G	-0.004	0.016	0.8201
5	rs1171614	10	T	C	-0.004	0.019	0.8503
6	rs1178977	7	G	A	-0.011	0.021	0.6132
7	rs12498742	4	G	A	0.014	0.018	0.4517
8	rs1260326	2	T	C	-0.001	0.016	0.9608
9	rs1394125	15	A	G	0.028	0.017	0.09825
10	rs1471633	1	A	C	0.029	0.016	0.07095
11	rs17050272	2	A	G	0.005	0.017	0.7625
12	rs17632159	5	C	G	-0.012	0.017	0.4888
13	rs17786744	8	G	A	0.015	0.016	0.3461
14	rs2078267	11	C	T	-0.022	0.016	0.1722
15	rs2231142	4	T	G	0.025	0.026	0.3347
16	rs2941484	8	T	C	0.011	0.016	0.4893
17	rs3741414	12	T	C	0.009	0.019	0.6299
18	rs478607	11	G	A	0.018	0.022	0.4173
19	rs653178	12	C	T	0.027	0.016	0.09708
20	rs6598541	15	A	G	0.005	0.016	0.7584
21	rs675209	6	T	C	-0.011	0.018	0.5271
22	rs6770152	3	G	T	0.015	0.016	0.3378
23	rs7188445	16	A	G	0.016	0.017	0.3453
24	rs7193778	16	C	T	-0.005	0.023	0.8233
25	rs7224610	17	C	A	0.018	0.016	0.2631
26	rs729761	6	T	G	0.020	0.019	0.2834
27	rs7953704	12	A	G	0.012	0.016	0.4454
28	rs7976059	12	T	G	-0.031	0.017	0.07669

SNP: each SNP's id; chr: chromosome; EA: effect allele, OA: other allele; GY: beta for the SNP-Alzheimer's disease relationship; SE_GY: standard error of GY; pval: p-value of GY

Table S7. The association estimates of the 28 SNPs for urate (1) with coronary heart disease (CHD) (6)

	SNP	chr	EA	OA	EAF	GY	SE_GY	pval
1	rs10480300	7	C	T	0.758	0.017	0.011	0.1365408
2	rs10821905	10	G	A	0.820	0.023	0.012	0.055396
3	rs11264341	1	C	T	0.568	-0.017	0.010	0.081745
4	rs1165151	6	G	T	0.539	-0.016	0.009	0.0815358
5	rs1171614	10	C	T	0.762	-0.012	0.012	0.3340968
6	rs1178977	7	A	G	0.823	0.006	0.013	0.6071614
7	rs12498742	4	A	G	0.767	0.012	0.011	0.2830966
8	rs1260326	2	C	T	0.610	-0.003	0.010	0.7349392
9	rs1394125	15	G	A	0.691	-0.006	0.011	0.5658209
10	rs1471633	1	A	C	0.537	0.017	0.010	0.0749271
11	rs17050272	2	G	A	0.597	-0.006	0.010	0.5597656
12	rs17632159	5	G	C	0.691	-0.003	0.010	0.7899725
13	rs17786744	8	A	G	0.630	-0.005	0.010	0.6015566
14	rs2078267	11	C	T	0.540	0.001	0.010	0.9107651
15	rs2231142	4	G	T	0.887	0.024	0.015	0.1143624
16	rs2941484	8	C	T	0.563	-0.010	0.009	0.2861924
17	rs3741414	12	C	T	0.799	-0.012	0.012	0.3185743
18	rs478607	11	A	G	0.810	0.005	0.013	0.668657
19	rs653178	12	T	C	0.579	-0.064	0.010	5.15E-10
20	rs6598541	15	G	A	0.598	0.006	0.009	0.5183619
21	rs675209	6	C	T	0.645	0.016	0.010	0.1229597
22	rs6770152	3	T	G	0.573	-0.019	0.009	0.0409614
23	rs7188445	16	G	A	0.705	0.007	0.011	0.515785
24	rs7193778	16	T	C	0.836	-0.009	0.014	0.4928628
25	rs7224610	17	A	C	0.607	0.006	0.010	0.5373028
26	rs729761	6	G	T	0.718	-0.013	0.011	0.2615705
27	rs7953704	12	G	A	0.527	-0.009	0.009	0.3281571
28	rs7976059	12	G	T	0.632	0.004	0.010	0.6806164

SNP: each SNP's id; chr: chromosome; EA: effect allele, OA: other allele; EAF: effect allele frequency for GY; GY: beta for the SNP-CHD relationship; SE_GY: standard error of GY; pval: p-value of GY

Table S8. The association estimates of the 28 SNPs for urate (1) with myocardial infarction (MI) (6)

	SNP	chr	EA	OA	EAF	GY	SE_GY	pval
1	rs10480300	7	T	C	0.245	0.010	0.013	0.41820349
2	rs10821905	10	A	G	0.176	0.035	0.013	0.00932379
3	rs11264341	1	T	C	0.421	-0.016	0.011	0.13180104
4	rs1165151	6	G	T	0.533	-0.023	0.010	0.02632004
5	rs1171614	10	C	T	0.742	-0.002	0.014	0.87910941
6	rs1178977	7	G	A	0.172	0.007	0.014	0.63826783
7	rs12498742	4	G	A	0.228	0.013	0.012	0.29664083
8	rs1260326	2	T	C	0.422	-0.001	0.011	0.9166279
9	rs1394125	15	A	G	0.299	-0.002	0.012	0.88583215
10	rs1471633	1	C	A	0.452	0.016	0.011	0.13190286
11	rs17050272	2	A	G	0.378	0.005	0.011	0.64781176
12	rs17632159	5	C	G	0.298	-0.007	0.011	0.51468404
13	rs17786744	8	G	A	0.369	-0.005	0.011	0.65350967
14	rs2078267	11	T	C	0.438	-0.008	0.011	0.47673314
15	rs2231142	4	T	G	0.110	0.022	0.017	0.19174707
16	rs2941484	8	T	C	0.430	-0.018	0.010	0.07495691
17	rs3741414	12	T	C	0.193	0.003	0.014	0.82049052
18	rs478607	11	A	G	0.776	0.004	0.014	0.78504645
19	rs653178	12	T	C	0.558	-0.077	0.012	2.84E-11
20	rs6598541	15	G	A	0.580	0.010	0.011	0.35000693
21	rs675209	6	C	T	0.627	0.018	0.011	0.10676248
22	rs6770152	3	T	G	0.559	-0.017	0.010	0.11390205
23	rs7188445	16	A	G	0.291	0.005	0.012	0.65739895
24	rs7193778	16	T	C	0.811	0.003	0.015	0.83535075
25	rs7224610	17	A	C	0.587	0.003	0.011	0.78176886
26	rs729761	6	G	T	0.696	-0.018	0.012	0.14330225
27	rs7953704	12	G	A	0.513	-0.019	0.010	0.0648285
28	rs7976059	12	T	G	0.357	0.006	0.011	0.55745239

SNP: each SNP's id; chr: chromosome; EA: effect allele, OA: other allele; EAF: effect allele frequency for GY; GY: beta for the SNP-MI relationship; SE_GY: standard error of GY; pval: p-value of GY

Table S9. The association estimates of the 28 SNPs for urate (1) with systolic blood pressure (SBP) (8)

	SNP	chr	EA	OA	GY	SE_GY	pval
1	rs10480300	7	T	C	0.015	0.003	1.45E-07
2	rs10821905	10	A	G	0.009	0.003	0.00435053
3	rs11264341	1	T	C	-0.008	0.002	0.00082043
4	rs1165151	6	G	T	-0.006	0.002	0.00999244
5	rs1171614	10	C	T	-0.008	0.003	0.00897198
6	rs1178977	7	G	A	0.001	0.003	0.676104
7	rs12498742	4	G	A	0.004	0.003	0.21947
8	rs1260326	2	C	T	0.005	0.003	0.0439014
9	rs1394125	15	A	G	0.002	0.003	0.47681
10	rs1471633	1	C	A	0.002	0.002	0.313305
11	rs17050272	2	A	G	0.002	0.002	0.353964
12	rs17632159	5	C	G	0.003	0.003	0.348555
13	rs17786744	8	G	A	0.004	0.003	0.158785
14	rs2078267	11	T	C	0.000	0.002	0.998987
15	rs2231142	4	T	G	-0.011	0.004	0.00493599
16	rs2941484	8	T	C	0.008	0.002	0.00218681
17	rs3741414	12	T	C	-0.009	0.003	0.00195694
18	rs478607	11	A	G	-0.005	0.003	0.136448
19	rs653178	12	T	C	-0.021	0.002	1.16E-17
20	rs6598541	15	G	A	-0.001	0.003	0.618474
21	rs675209	6	C	T	-0.001	0.003	0.592666
22	rs6770152	3	T	G	-0.006	0.002	0.0220286
23	rs7188445	16	A	G	0.001	0.003	0.654585
24	rs7193778	16	T	C	-0.016	0.003	2.19E-06
25	rs7224610	17	A	C	-0.008	0.003	0.0024854
26	rs729761	6	G	T	0.002	0.003	0.506385
27	rs7953704	12	G	A	-0.004	0.002	0.124599
28	rs7976059	12	T	G	0.005	0.003	0.048739

SNP: each SNP's id; chr: chromosome; EA: effect allele, OA: other allele; GY: beta for the SNP-SBP relationship; SE_GY: standard error of GY; pval: p-value of GY

Table S10.The association estimates of the 28 SNPs for urate (1) with any ischemic stroke (IS) (10)

	SNP	chr	EA	OA	EAF	GY	SE_GY	pval
1	rs10480300	7	T	C	0.268	0.015	0.010	0.1382
2	rs10821905	10	A	G	0.193	-0.007	0.011	0.5244
3	rs11264341	1	T	C	0.468	-0.007	0.009	0.4156
4	rs1165151	6	T	G	0.432	-0.012	0.009	0.1708
5	rs1171614	10	T	C	0.226	-0.003	0.012	0.7939
6	rs1178977	7	A	G	0.811	0.008	0.012	0.5083
7	rs12498742	4	A	G	0.728	-0.010	0.011	0.366
8	rs1260326	2	T	C	0.414	0.006	0.009	0.5155
9	rs1394125	15	A	G	0.333	0.010	0.010	0.2888
10	rs1471633	1	A	C	0.537	0.007	0.010	0.4749
11	rs17050272	2	A	G	0.424	-0.010	0.009	0.2692
12	rs17632159	5	C	G	0.302	0.008	0.009	0.3547
13	rs17786744	8	A	G	0.624	-0.008	0.009	0.3781
14	rs2078267	11	T	C	0.491	0.021	0.010	0.03
15	rs2231142	4	T	G	0.175	-0.003	0.013	0.8286
16	rs2941484	8	T	C	0.454	-0.007	0.009	0.4401
17	rs3741414	12	T	C	0.227	-0.002	0.011	0.8872
18	rs478607	11	A	G	0.787	-0.017	0.011	0.1007
19	rs653178	12	T	C	0.543	-0.077	0.010	4.31E-14
20	rs6598541	15	A	G	0.409	0.011	0.009	0.1887
21	rs675209	6	T	C	0.346	-0.014	0.010	0.153
22	rs6770152	3	T	G	0.566	0.012	0.009	0.1693
23	rs7188445	16	A	G	0.312	-0.002	0.009	0.8374
24	rs7193778	16	T	C	0.861	-0.009	0.012	0.4761
25	rs7224610	17	A	C	0.631	0.002	0.009	0.8432
26	rs729761	6	T	G	0.247	-0.014	0.011	0.1802
27	rs7953704	12	A	G	0.487	-0.023	0.008	0.005882
28	rs7976059	12	T	G	0.414	-0.010	0.009	0.2491

SNP: each SNP's id; chr: chromosome; EA: effect allele, OA: other allele; EAF: effect allele frequency for GY; GY: beta for the SNP-IS relationship; SE_GY: standard error of GY; pval: p-value of GY

Table S11. The association estimates of the 28 SNPs for urate (1) with cardio-embolic stroke (CES) (10)

	SNP	chr	EA	OA	EAF	GY	SE_GY	pval
1	rs10480300	7	T	C	0.268	0.006	0.020	0.7797
2	rs10821905	10	A	G	0.194	0.022	0.023	0.3331
3	rs11264341	1	T	C	0.447	-0.034	0.017	0.05135
4	rs1165151	6	T	G	0.456	0.006	0.018	0.74
5	rs1171614	10	T	C	0.227	0.011	0.023	0.6229
6	rs1178977	7	A	G	0.814	0.014	0.024	0.5559
7	rs12498742	4	A	G	0.744	-0.019	0.021	0.3559
8	rs1260326	2	T	C	0.407	-0.013	0.019	0.4791
9	rs1394125	15	A	G	0.343	-0.006	0.020	0.7566
10	rs1471633	1	A	C	0.513	-0.005	0.018	0.7993
11	rs17050272	2	A	G	0.421	-0.007	0.018	0.6876
12	rs17632159	5	C	G	0.307	0.021	0.019	0.2671
13	rs17786744	8	A	G	0.612	0.007	0.018	0.7048
14	rs2078267	11	T	C	0.500	0.029	0.018	0.1192
15	rs2231142	4	T	G	0.147	0.002	0.028	0.9473
16	rs2941484	8	T	C	0.446	-0.002	0.017	0.9104
17	rs3741414	12	T	C	0.235	0.005	0.022	0.8014
18	rs478607	11	A	G	0.809	0.025	0.024	0.2943
19	rs653178	12	T	C	0.541	-0.058	0.020	0.003023
20	rs6598541	15	A	G	0.393	0.038	0.017	0.02562
21	rs675209	6	T	C	0.321	-0.013	0.021	0.513
22	rs6770152	3	T	G	0.572	-0.003	0.017	0.8761
23	rs7188445	16	A	G	0.315	-0.016	0.018	0.3768
24	rs7193778	16	T	C	0.858	-0.003	0.025	0.9134
25	rs7224610	17	A	C	0.610	0.011	0.018	0.5317
26	rs729761	6	T	G	0.258	0.008	0.022	0.7082
27	rs7953704	12	A	G	0.487	-0.024	0.017	0.1624
28	rs7976059	12	T	G	0.387	-0.015	0.018	0.4187

SNP: each SNP's id; chr: chromosome; EA: effect allele, OA: other allele; EAF: effect allele frequency for GY; GY: beta for the SNP-CE relationship; SE_GY: standard error of GY; pval: p-value of GY

Table S12. The association estimates of the 28 SNPs for urate (1) with large-artery atherosclerotic stroke (LAS) (10)

	SNP	chr	EA	OA	EAF	GY	SE_GY	pval
1	rs10480300	7	T	C	0.269	0.030	0.026	0.2486
2	rs10821905	10	A	G	0.183	0.015	0.028	0.6083
3	rs11264341	1	T	C	0.484	-0.032	0.021	0.1239
4	rs1165151	6	T	G	0.426	-0.032	0.022	0.1419
5	rs1171614	10	T	C	0.227	0.038	0.029	0.1838
6	rs1178977	7	A	G	0.823	0.023	0.028	0.4106
7	rs12498742	4	A	G	0.740	-0.027	0.026	0.3058
8	rs1260326	2	T	C	0.436	0.012	0.022	0.5781
9	rs1394125	15	A	G	0.324	0.045	0.024	0.06338
10	rs1471633	1	A	C	0.546	0.008	0.023	0.7251
11	rs17050272	2	A	G	0.431	-0.024	0.021	0.2399
12	rs17632159	5	C	G	0.304	0.011	0.022	0.6205
13	rs17786744	8	A	G	0.635	0.001	0.021	0.9619
14	rs2078267	11	T	C	0.496	0.028	0.024	0.2299
15	rs2231142	4	T	G	0.192	-0.008	0.029	0.7724
16	rs2941484	8	T	C	0.447	-0.001	0.020	0.9471
17	rs3741414	12	T	C	0.216	-0.009	0.027	0.7512
18	rs478607	11	A	G	0.799	-0.046	0.027	0.08713
19	rs653178	12	T	C	0.534	-0.094	0.026	0.000238
20	rs6598541	15	A	G	0.414	0.017	0.020	0.3917
21	rs675209	6	T	C	0.364	-0.025	0.025	0.3254
22	rs6770152	3	T	G	0.553	0.014	0.020	0.501
23	rs7188445	16	A	G	0.313	0.044	0.022	0.04303
24	rs7193778	16	T	C	0.862	-0.081	0.029	0.005975
25	rs7224610	17	A	C	0.639	0.025	0.022	0.2496
26	rs729761	6	T	G	0.244	-0.024	0.026	0.3675
27	rs7953704	12	A	G	0.490	-0.041	0.020	0.03757
28	rs7976059	12	T	G	0.437	0.016	0.021	0.4463

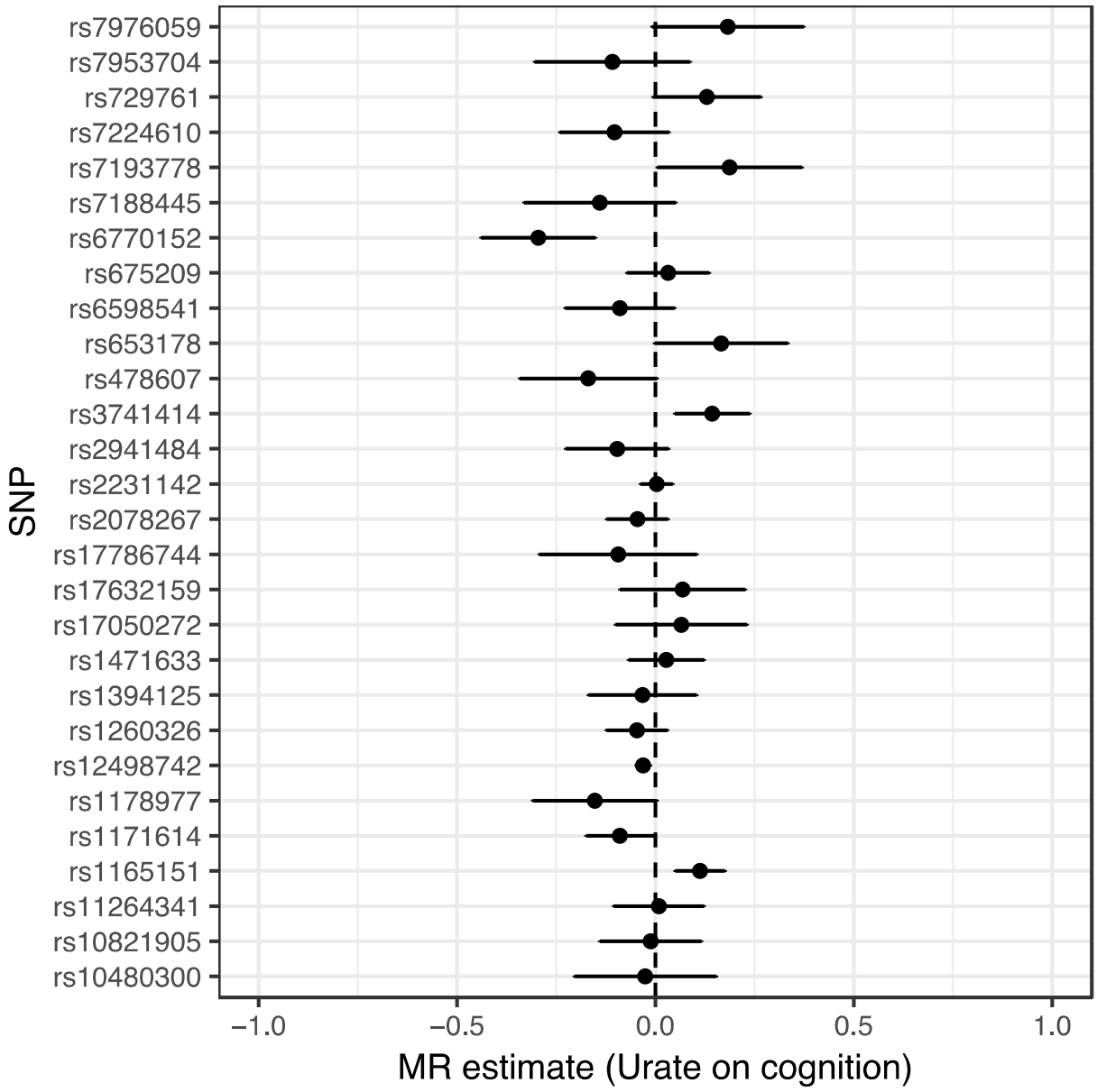
SNP: each SNP's id; chr: chromosome; EA: effect allele, OA: other allele; EAF: effect allele frequency for GY; GY: beta for the SNP-LAS relationship; SE_GY: standard error of GY; pval: p-value of GY

Table S13. The association estimates of the 28 SNPs for urate (1) with small-vessel stroke (SVS) (10)

	SNP	chr	EA	OA	EAF	GY	SE_GY	pval
1	rs10480300	7	T	C	0.265	-0.021	0.024	0.3765
2	rs10821905	10	A	G	0.178	-0.017	0.025	0.489
3	rs11264341	1	T	C	0.521	0.014	0.017	0.4048
4	rs1165151	6	T	G	0.388	-0.041	0.019	0.03197
5	rs1171614	10	T	C	0.228	-0.004	0.026	0.8896
6	rs1178977	7	A	G	0.822	0.011	0.023	0.6485
7	rs12498742	4	A	G	0.721	0.018	0.024	0.4411
8	rs1260326	2	T	C	0.453	0.021	0.018	0.2346
9	rs1394125	15	A	G	0.304	-0.032	0.021	0.126
10	rs1471633	1	A	C	0.578	0.007	0.020	0.7272
11	rs17050272	2	A	G	0.436	-0.031	0.017	0.07663
12	rs17632159	5	C	G	0.297	0.042	0.018	0.02171
13	rs17786744	8	A	G	0.653	0.010	0.018	0.5885
14	rs2078267	11	T	C	0.486	0.020	0.022	0.3554
15	rs2231142	4	T	G	0.219	0.005	0.023	0.8172
16	rs2941484	8	T	C	0.452	-0.008	0.017	0.6376
17	rs3741414	12	T	C	0.204	0.021	0.023	0.3575
18	rs478607	11	A	G	0.771	-0.035	0.021	0.09941
19	rs653178	12	T	C	0.544	-0.104	0.023	8.42E-06
20	rs6598541	15	A	G	0.434	0.004	0.017	0.7922
21	rs675209	6	T	C	0.408	-0.014	0.022	0.5217
22	rs6770152	3	T	G	0.539	0.013	0.017	0.4429
23	rs7188445	16	A	G	0.309	0.004	0.018	0.8338
24	rs7193778	16	T	C	0.865	-0.016	0.025	0.5174
25	rs7224610	17	A	C	0.669	-0.007	0.019	0.7091
26	rs729761	6	T	G	0.226	-0.055	0.022	0.01285
27	rs7953704	12	A	G	0.491	-0.008	0.016	0.6139
28	rs7976059	12	T	G	0.483	-0.023	0.018	0.1978

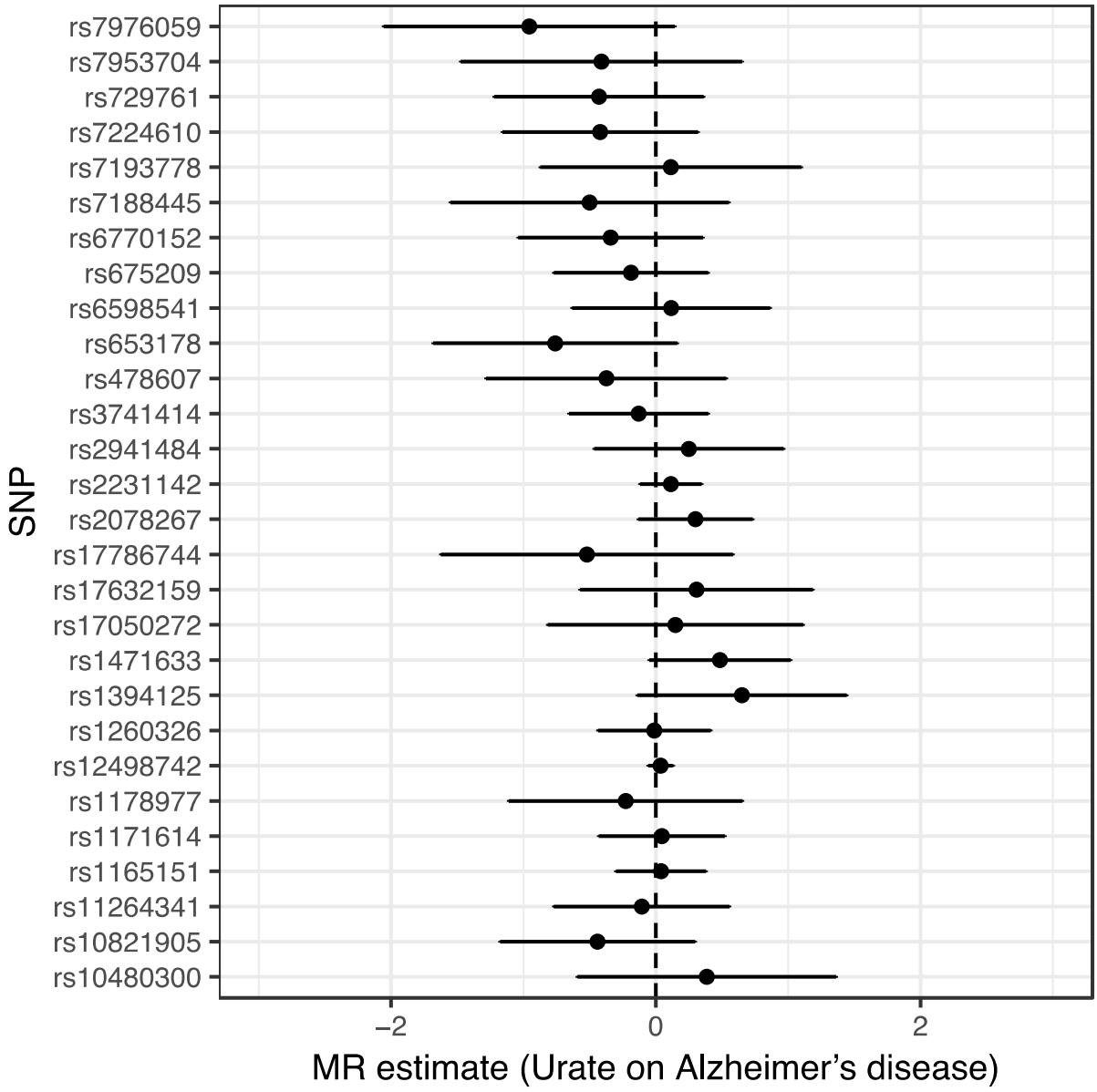
SNP: each SNP's id; chr: chromosome; EA: effect allele, OA: other allele; EAF: effect allele frequency for GY; GY: beta for the SNP-SVS relationship; SE_GY: standard error of GY; pval: p-value of GY

Figure S1. Forest plot of the 28 MR estimates of the urate-cognitive performance relationship.



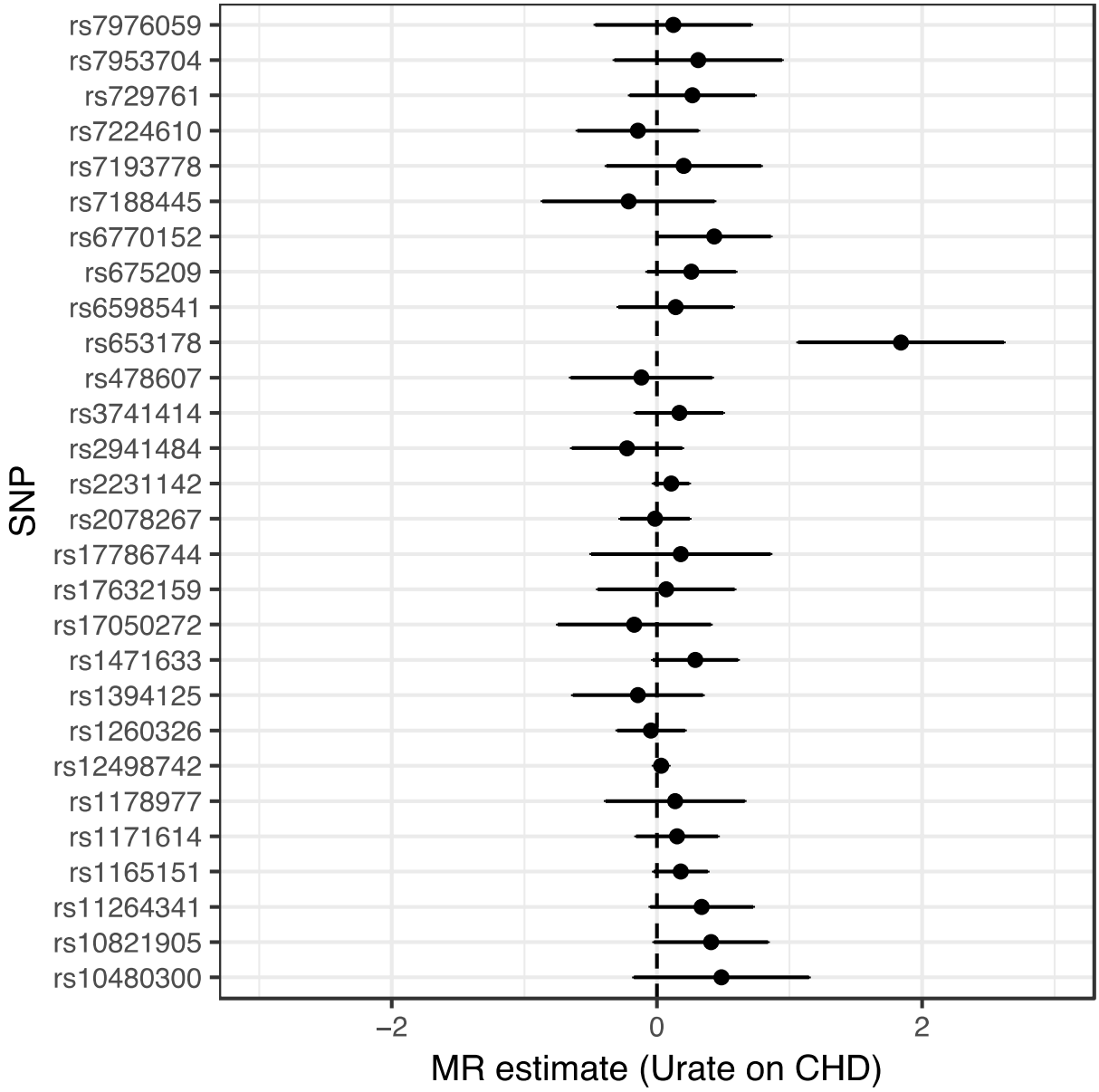
Each dot indicates the effect estimate of each SNP with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S2. Forest plot of the 28 MR estimates of the urate-Alzheimer's disease relationship.



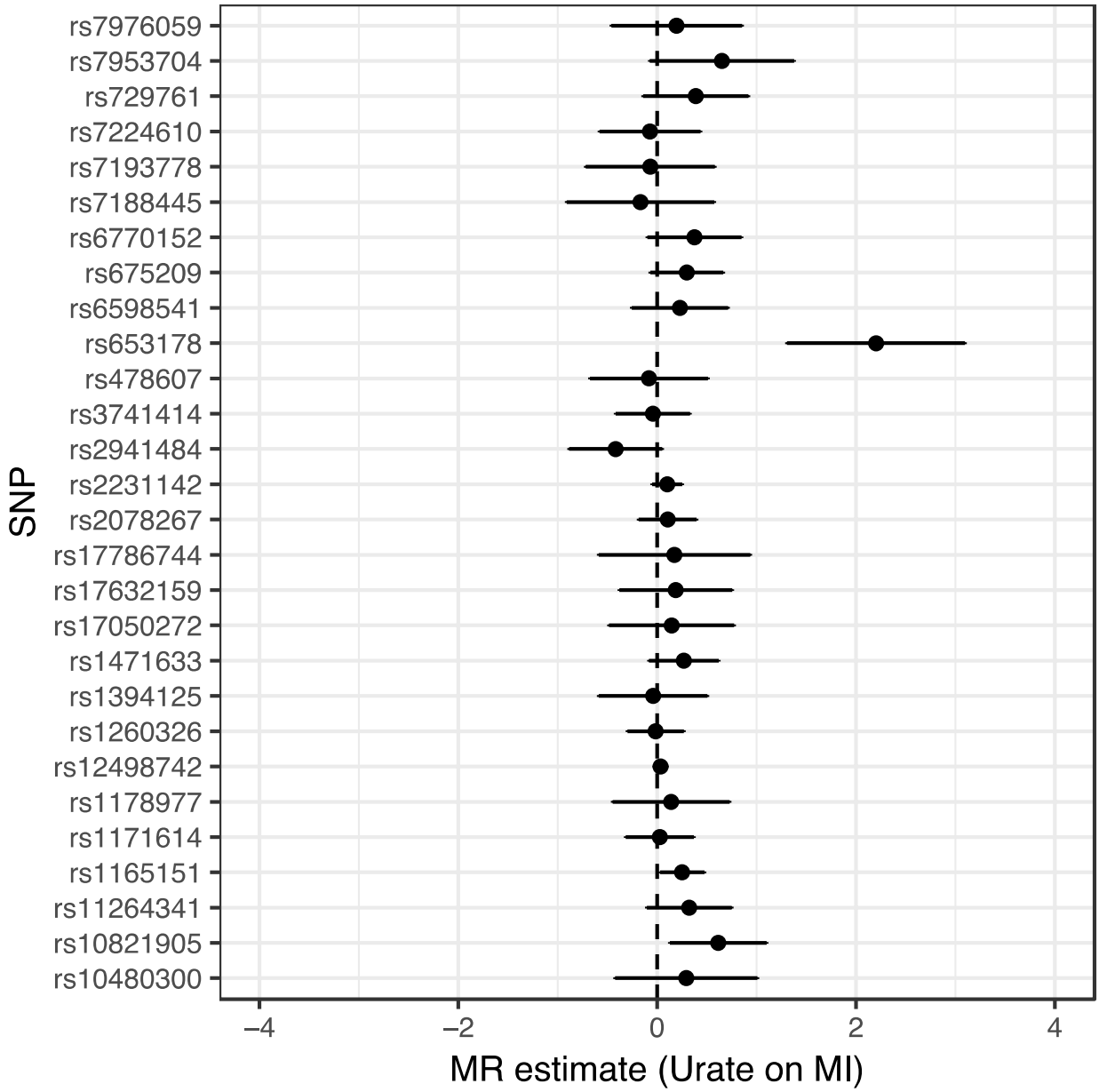
Each dot indicates the effect estimate (logOR) of each SNP with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S3. Forest plot of the 28 MR estimates of the urate-coronary heart disease (CHD) relationship.



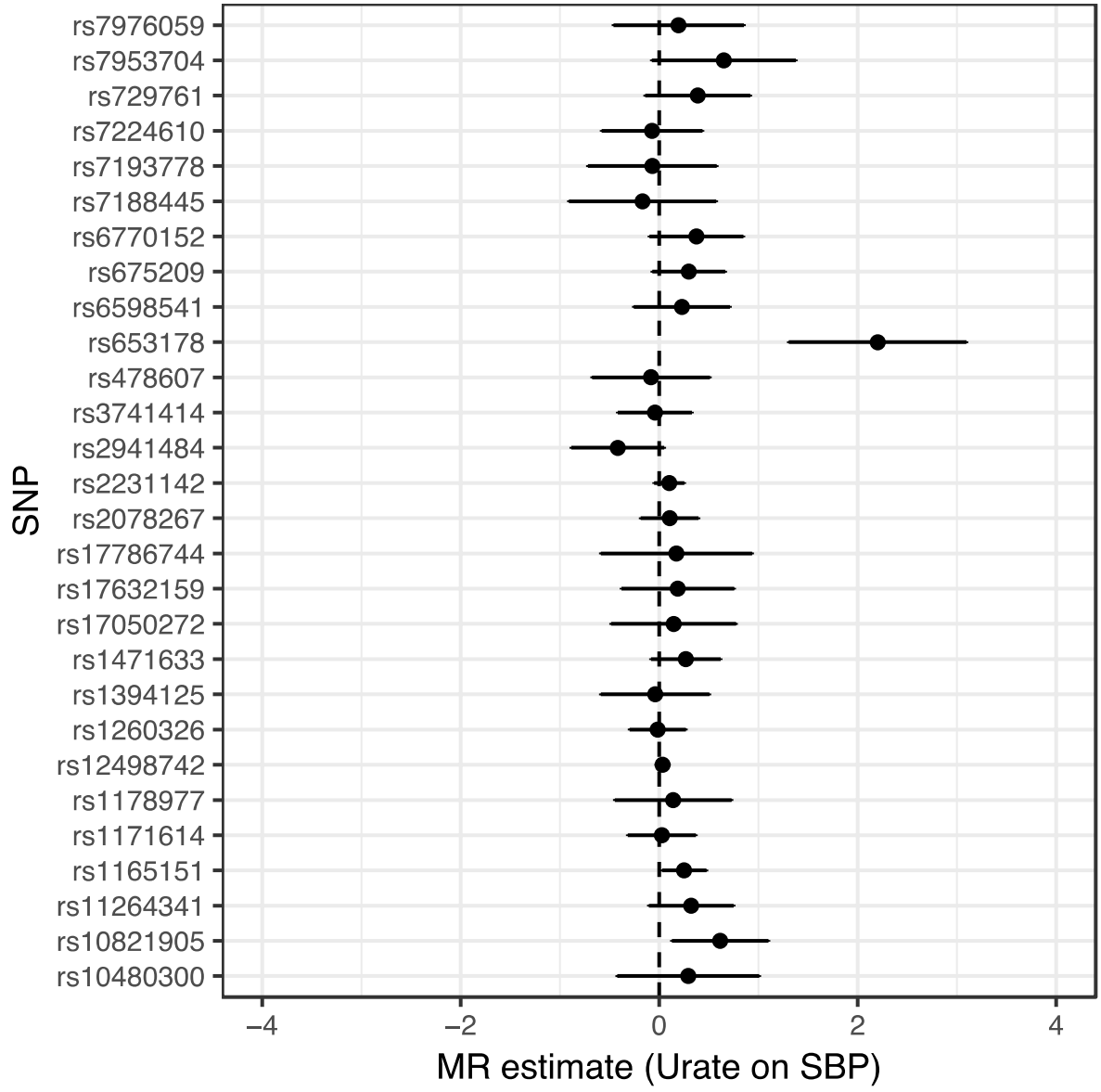
Each dot indicates the effect estimate (logOR) of each SNP with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S4. Forest plot of the 28 MR estimates of the urate-myocardial infarction (MI) relationship.



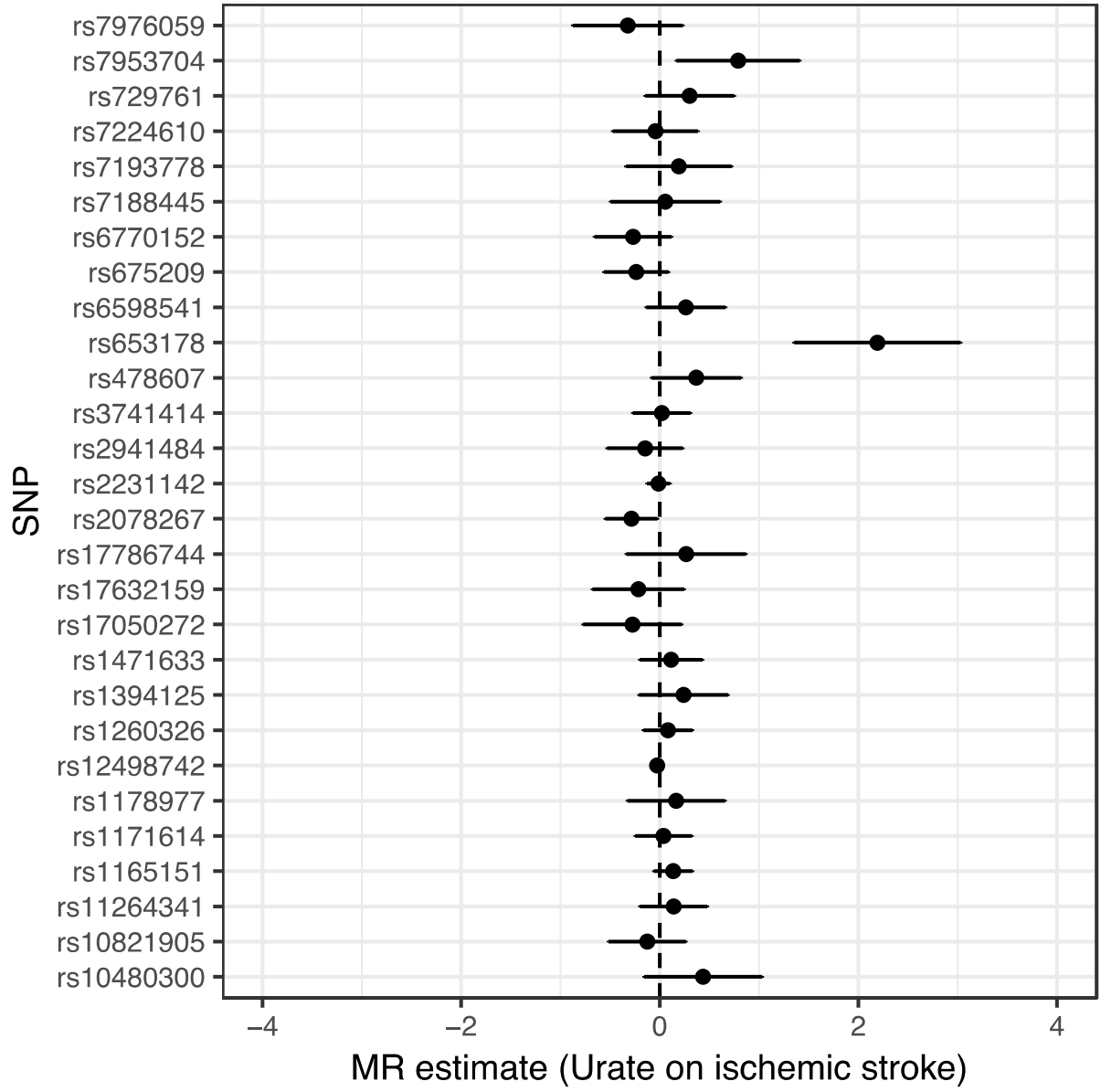
Each dot indicates the effect estimate (logOR) of each SNP with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S5. Forest plot of the 28 MR estimates of the urate-systolic blood pressure (SBP) relationship.



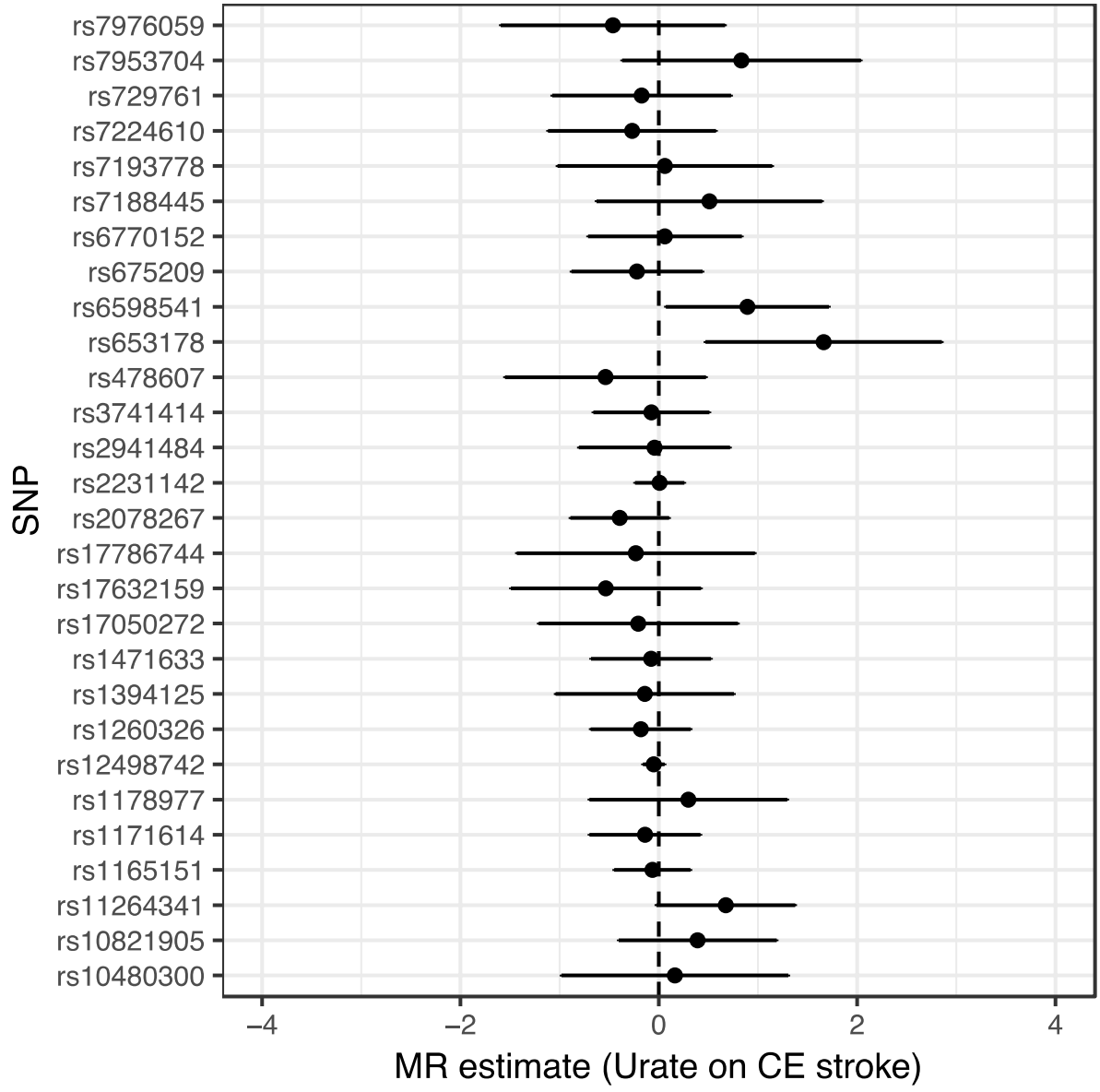
Each dot indicates the effect estimate of each SNP with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S6. Forest plot of the 28 MR estimates of the urate- any ischemic stroke relationship.



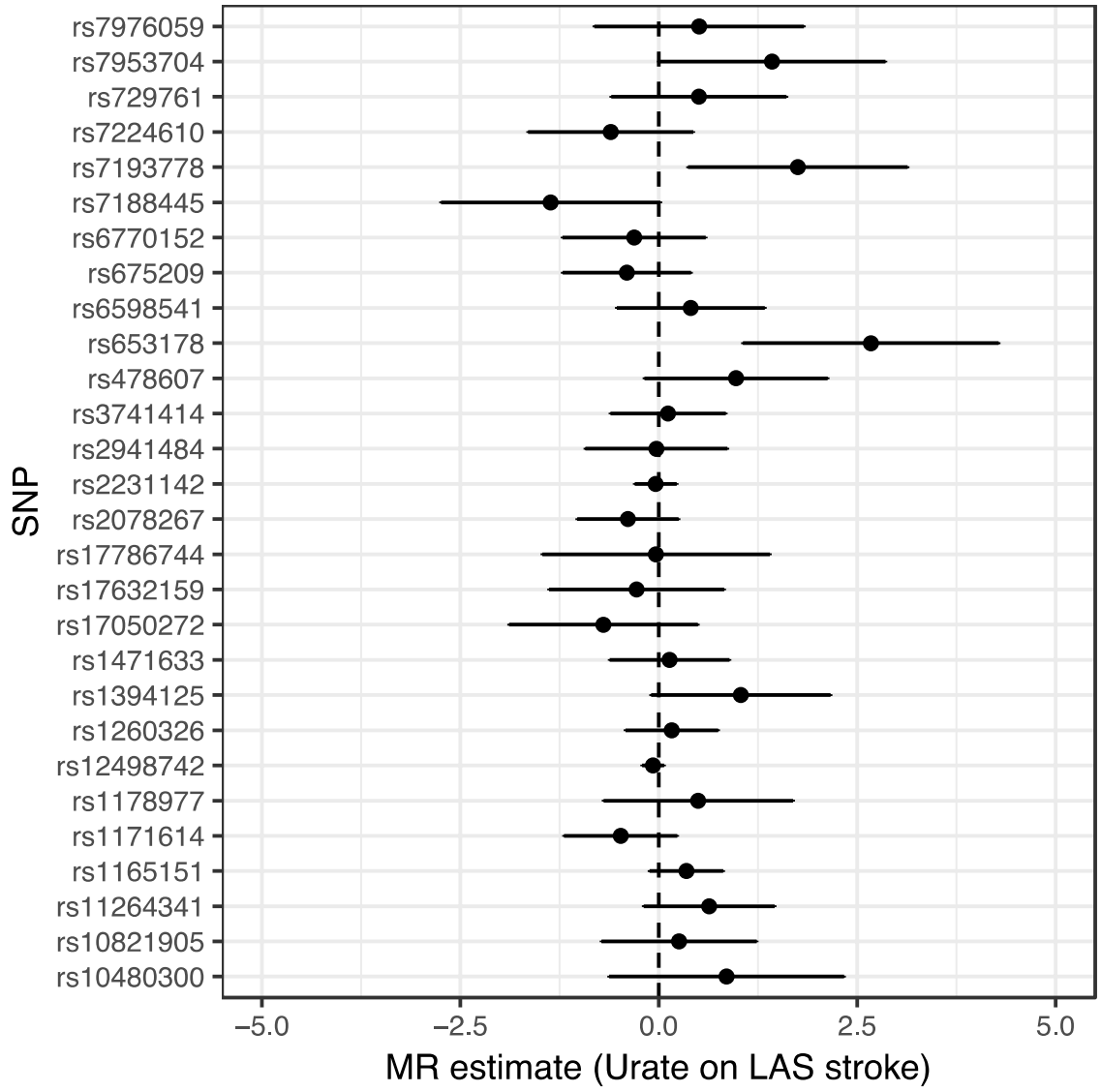
Each dot indicates the effect estimate (logOR) of each SNP with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S7. Forest plot of the 28 MR estimates of the urate- cardioembolic stroke ischemic stroke (CES) relationship.



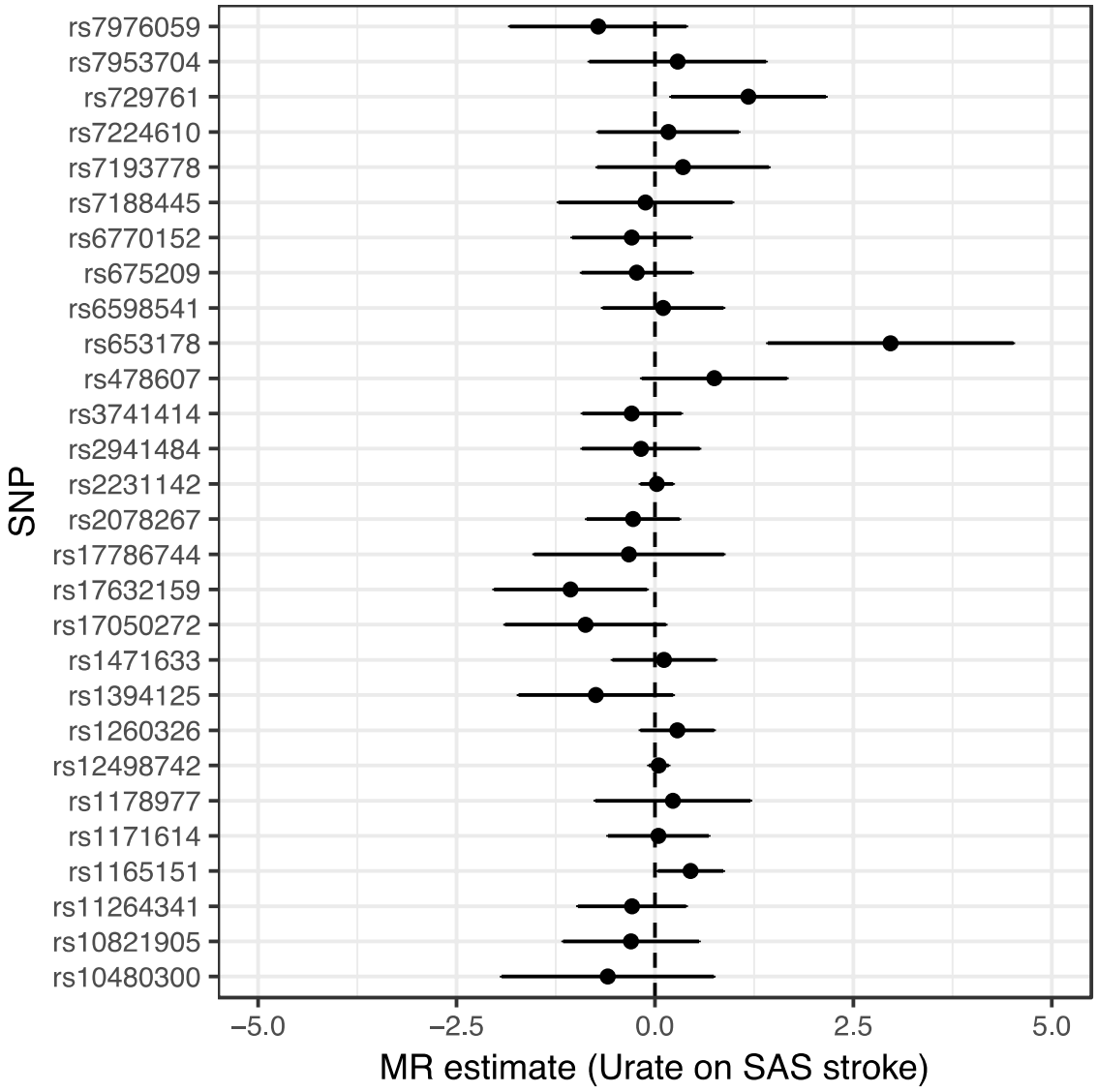
Each dot indicates the effect estimate (logOR) of each SNP with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S8. Forest plot of the 28 MR estimates of the urate- large-artery atherosclerotic ischemic stroke (LAS) relationship.



Each dot indicates the effect estimate (logOR) of each SNP with horizontal lines represent the 95% confidence interval (CI) of this estimate.

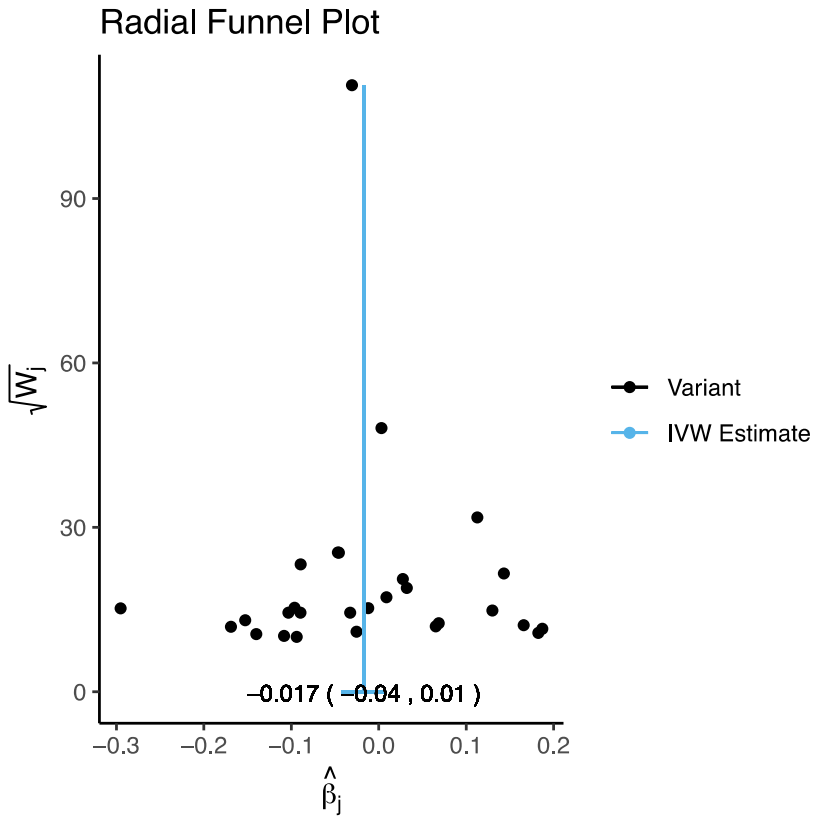
Figure S9. Forest plot of the 28 MR estimates of the urate- small-artery stroke ischemic stroke (SAS) relationship.



Each dot indicates the effect estimate (logOR) of each SNP with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S10. Funnel plot (A) and radial plot (B) for the urate-cognitive performance relationship.

(A)



(B)

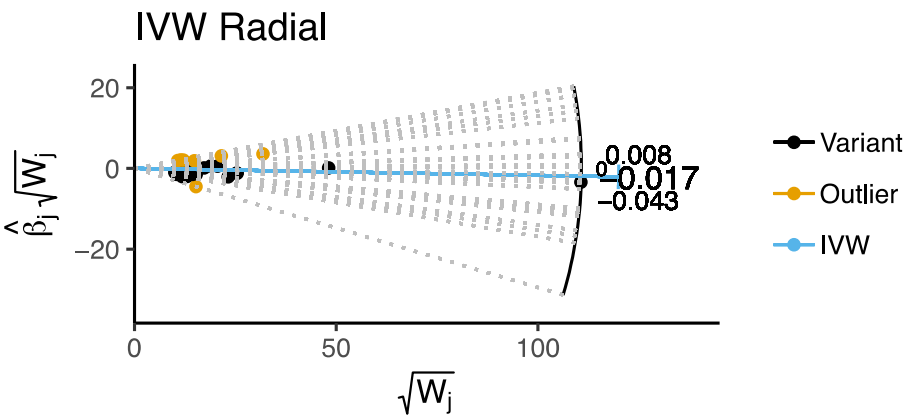
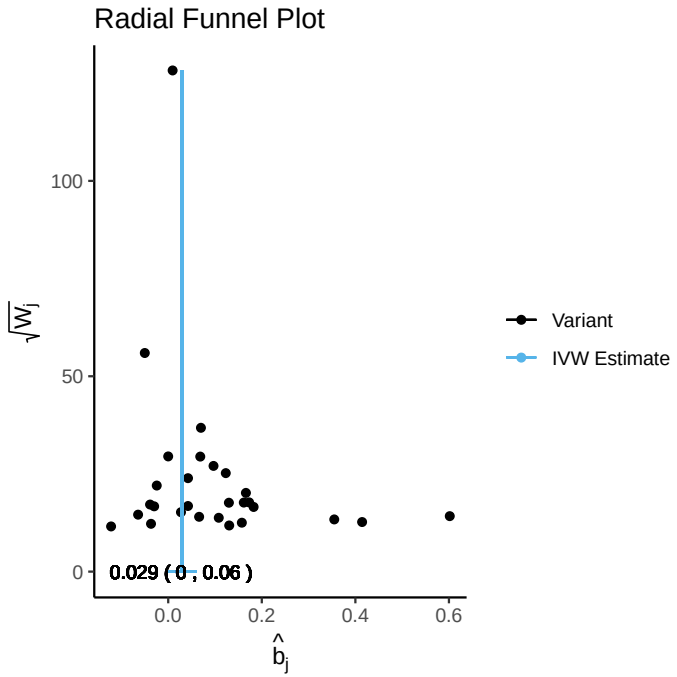


Figure S11. Funnel plot (A) and radial plot (B) for the urate-Alzheimer's disease relationship.

(A)



(B)

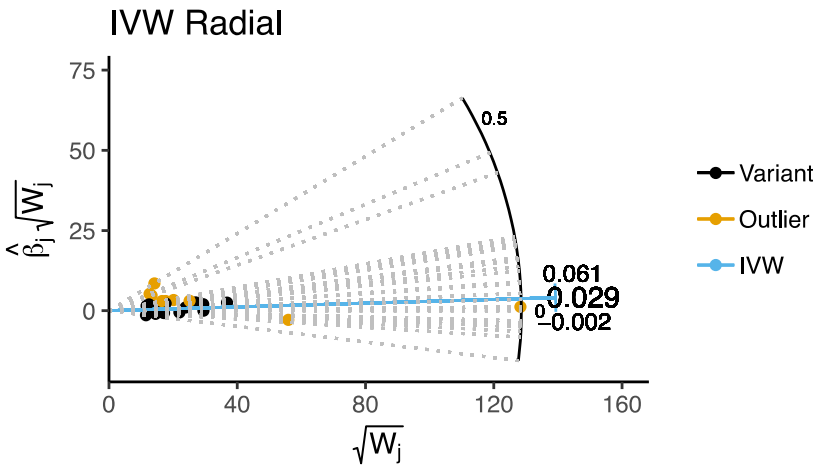
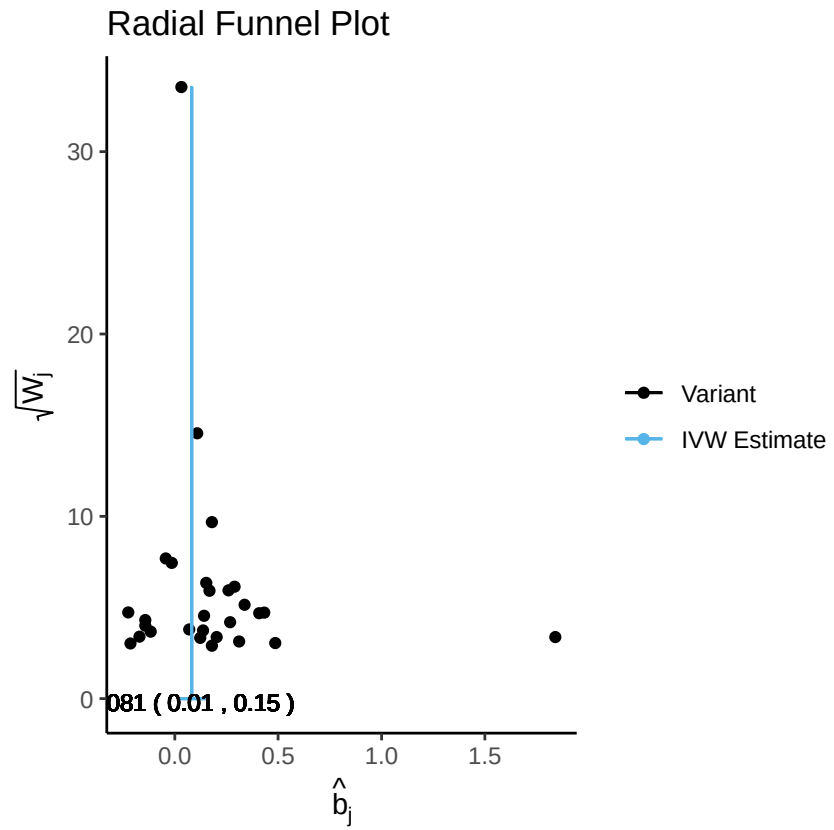


Figure S12. Funnel plot (A) and radial plot (B) for the urate-coronary heart disease (CHD) relationship.

(A)



(B)

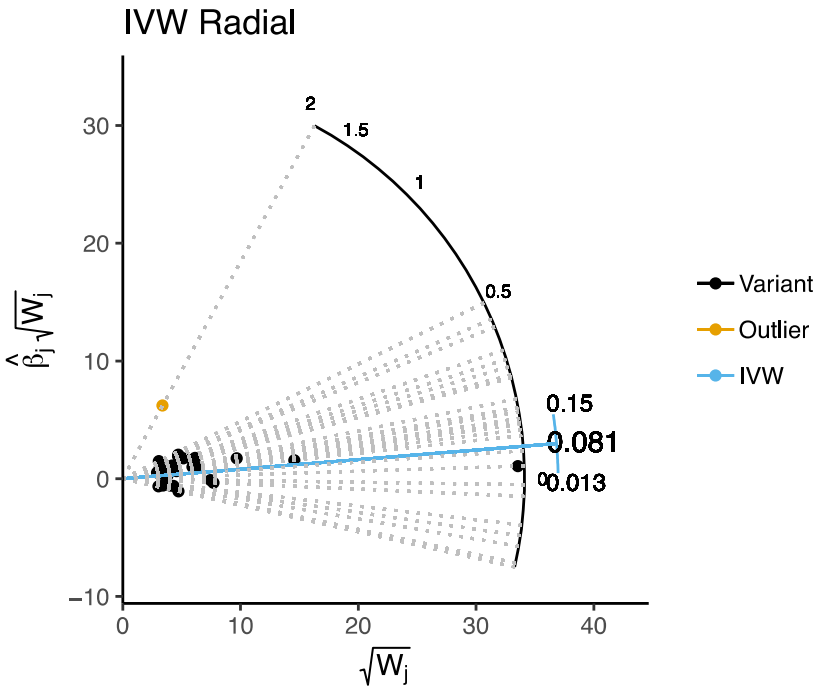


Figure S13. Funnel plot (A) and radial plot (B) for the urate-myocardial infarction (MI) relationship.

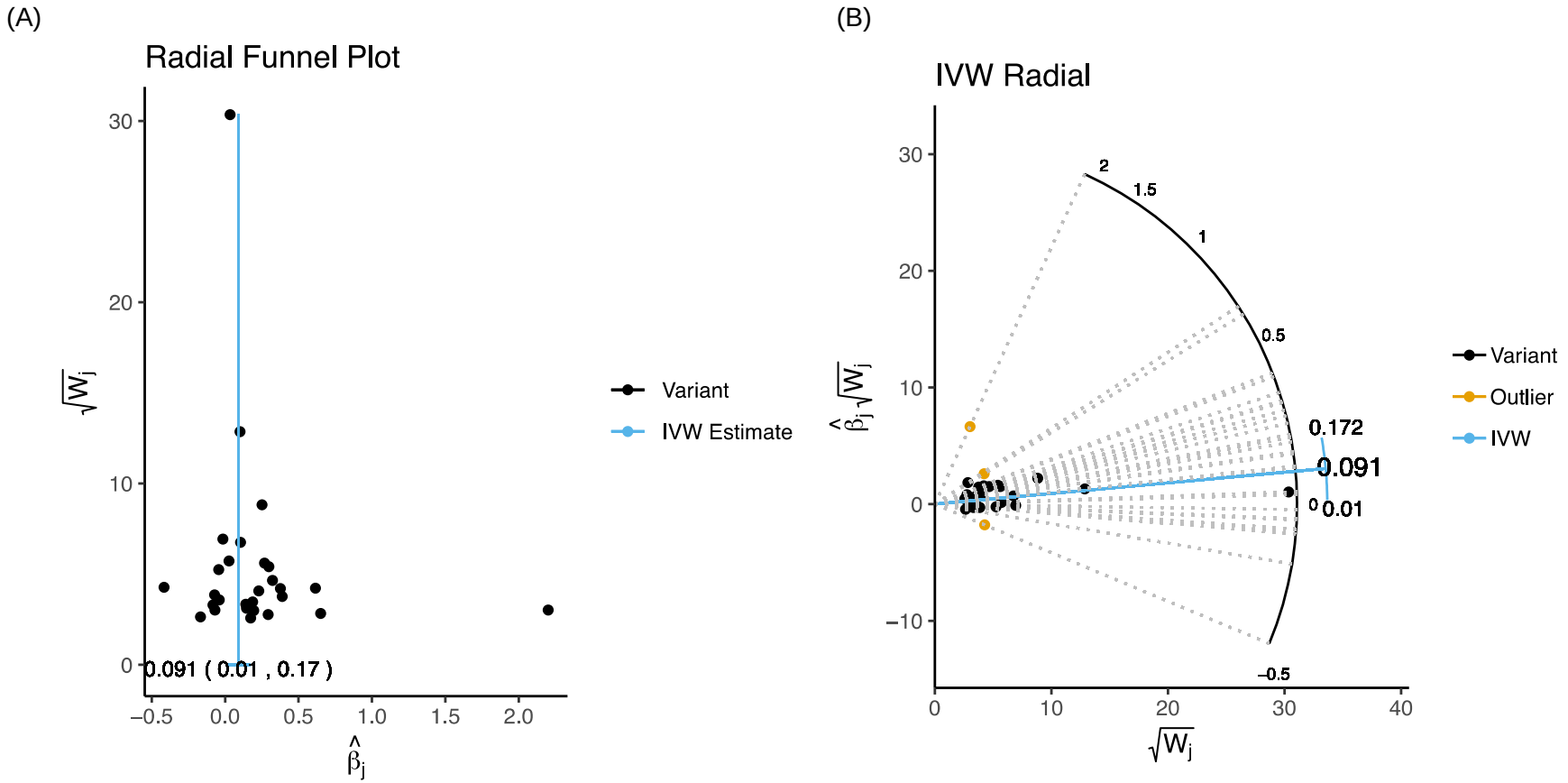


Figure S14. Funnel plot (A) and radial plot (B) for the urate- systolic blood pressure (SBP) relationship.

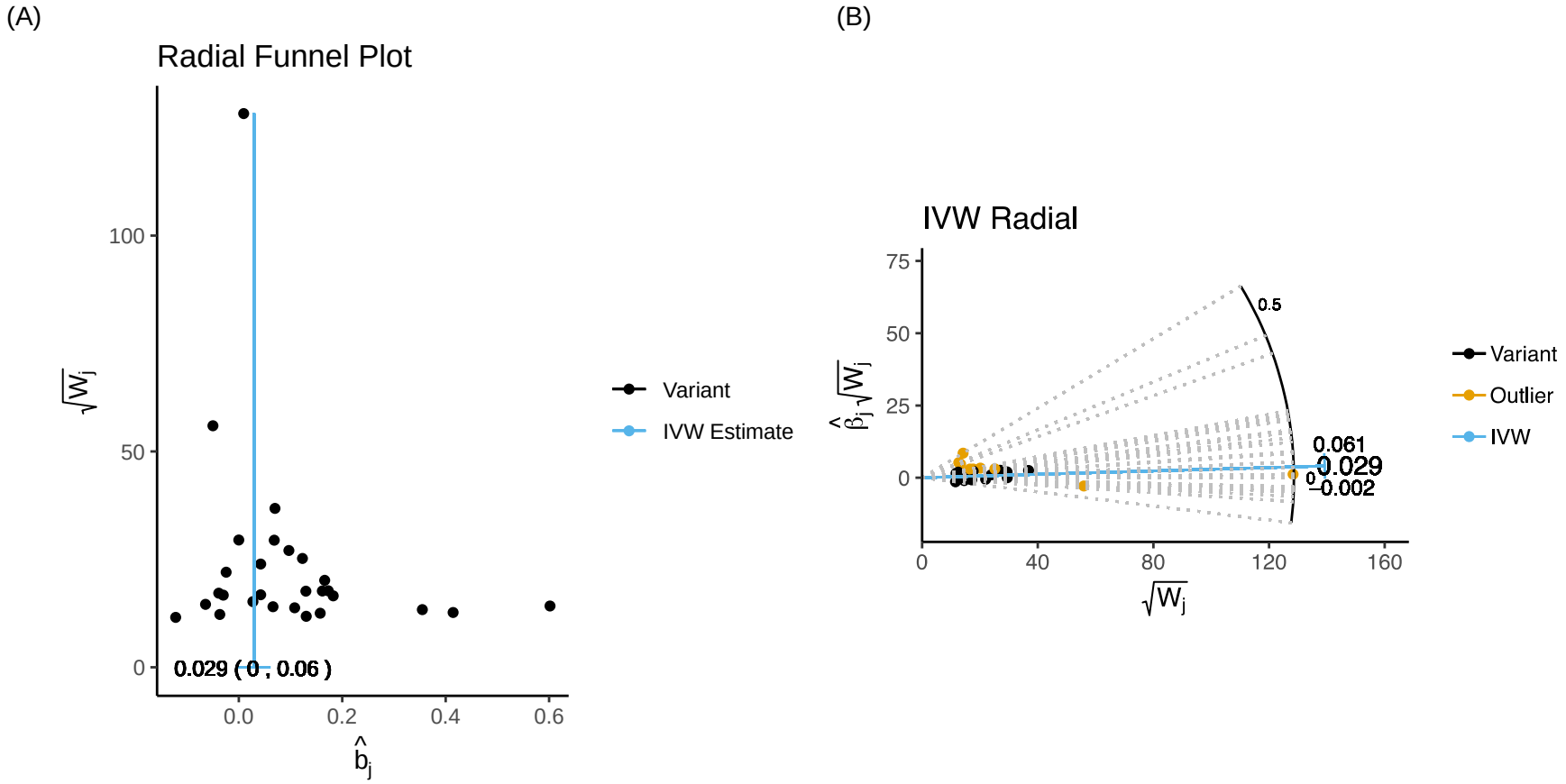


Figure S15. Funnel plot (A) and radial plot (B) for the urate-any ischemic stroke relationship.

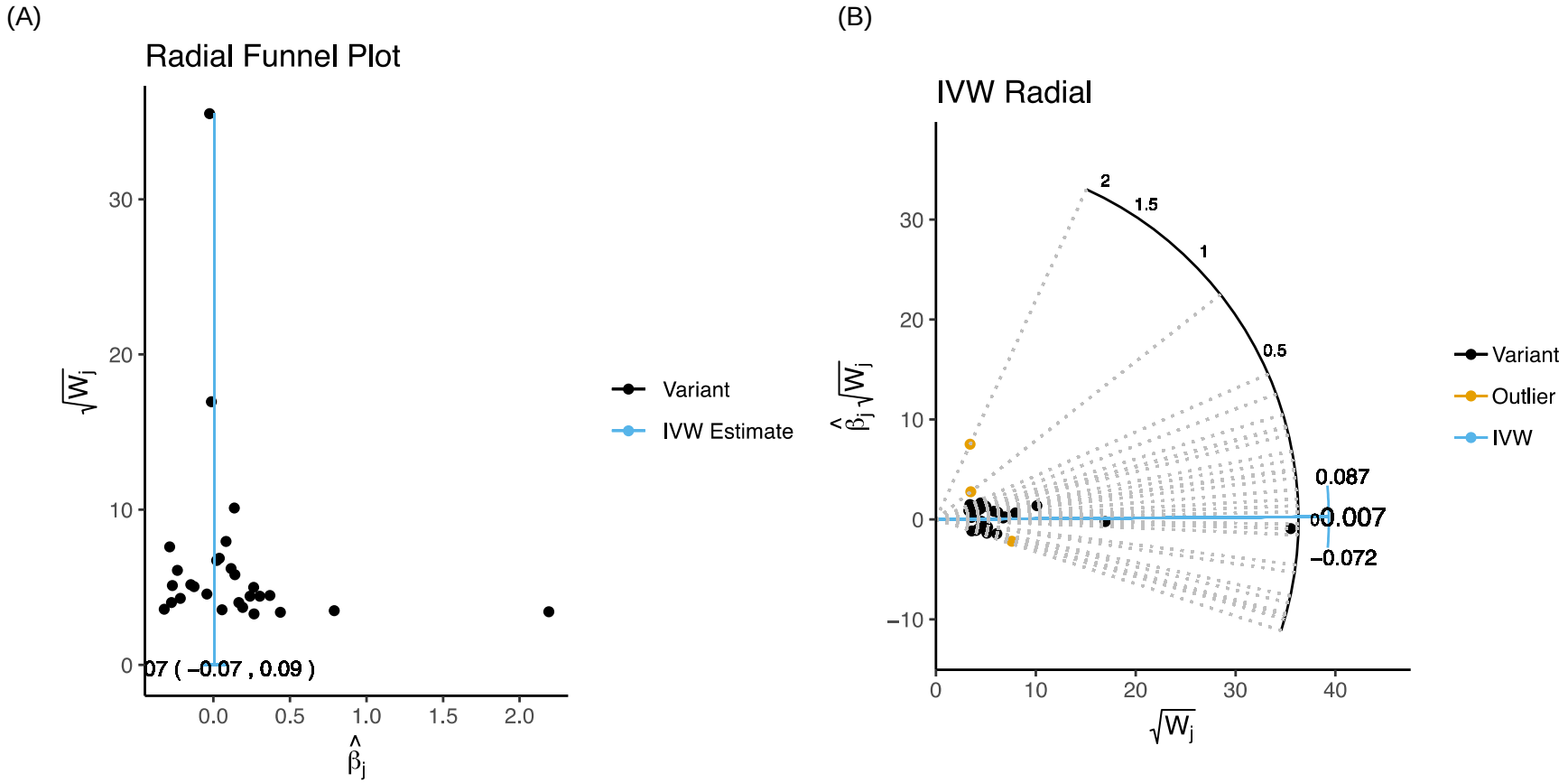


Figure S16. Funnel plot (A) and radial plot (B) for the urate- cardioembolic ischemic stroke (CES) relationship.

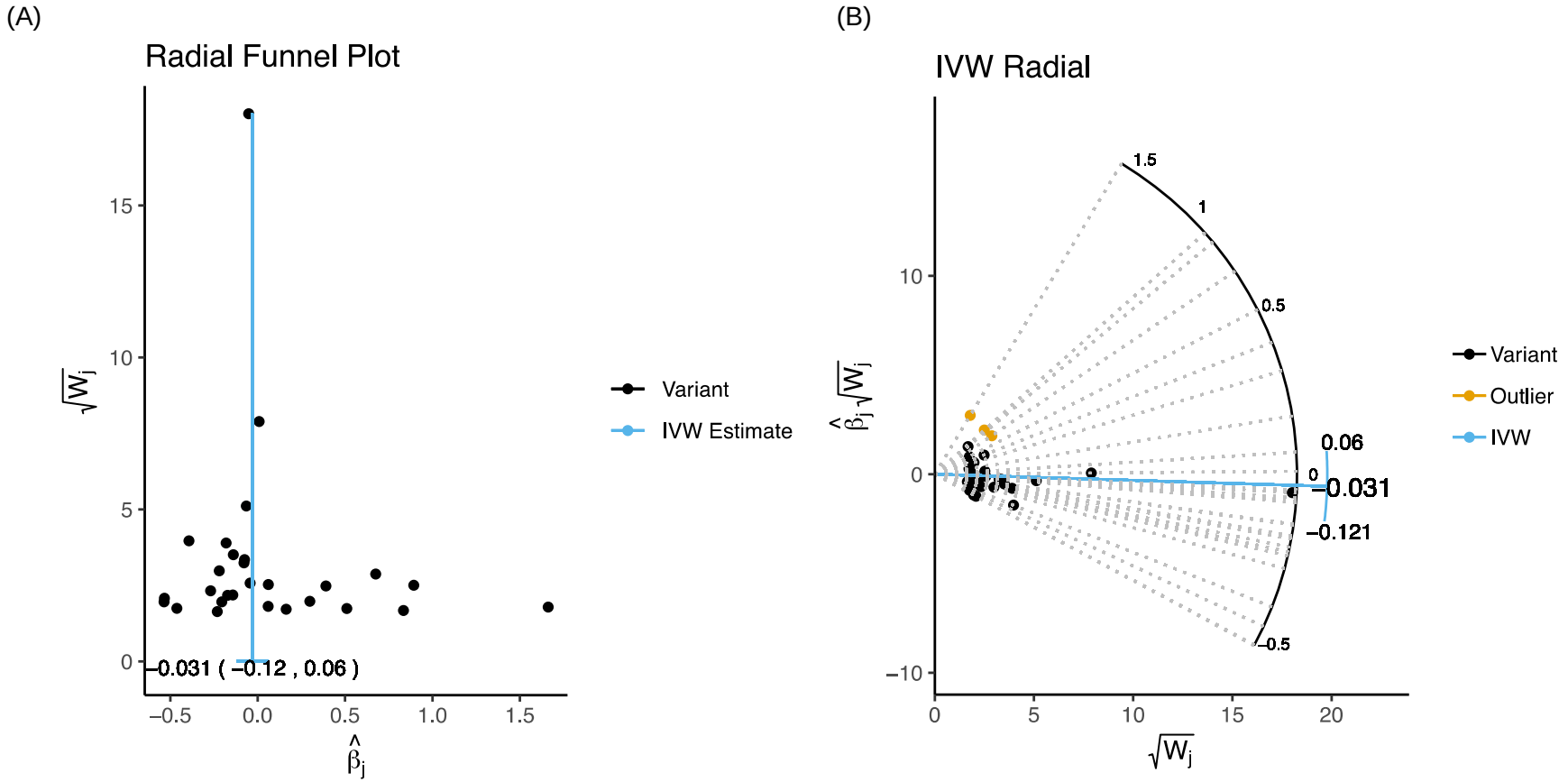


Figure S17. Funnel plot (A) and radial plot (B) for the urate- large-artery atherosclerotic ischemic stroke (LAS) relationship.

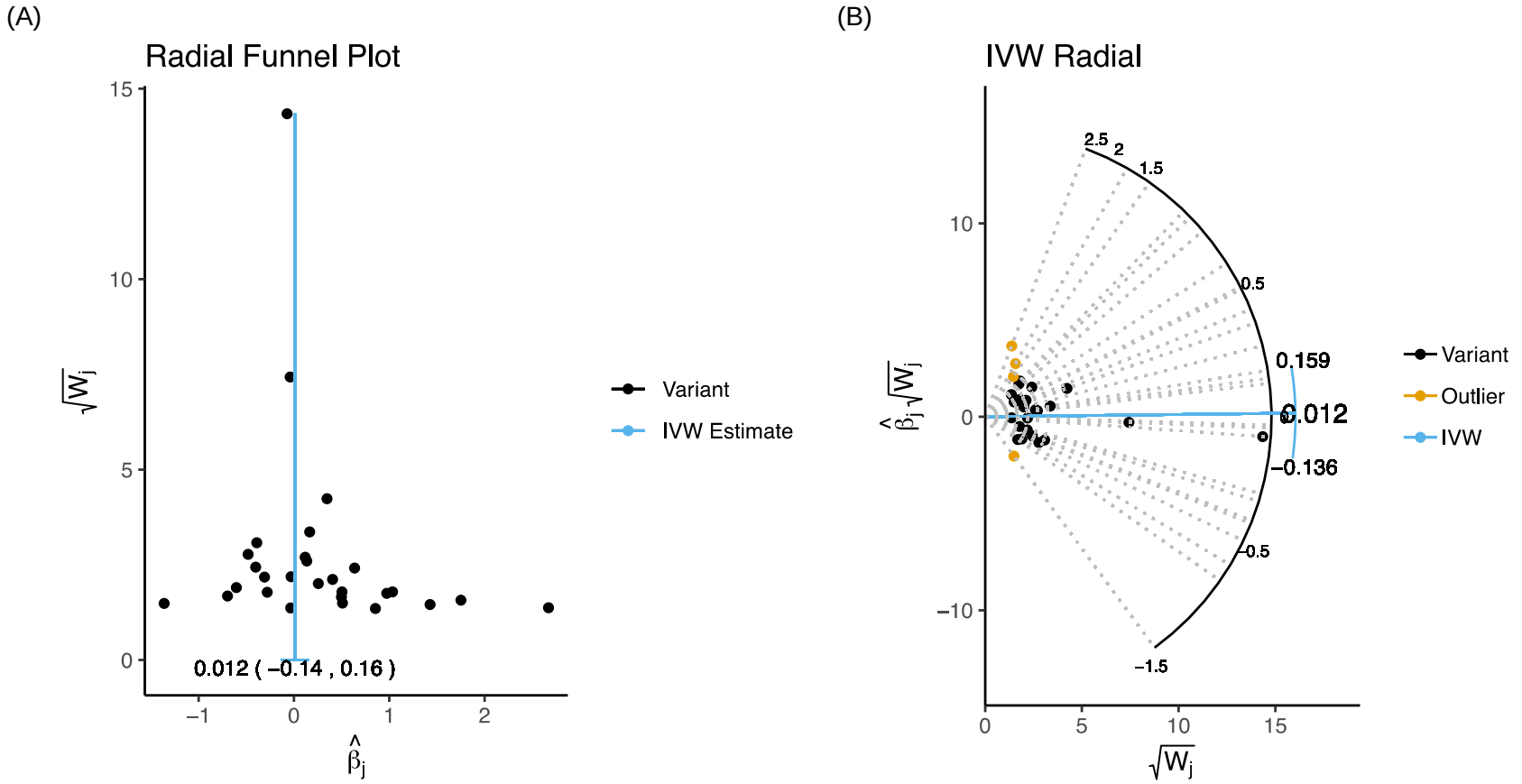
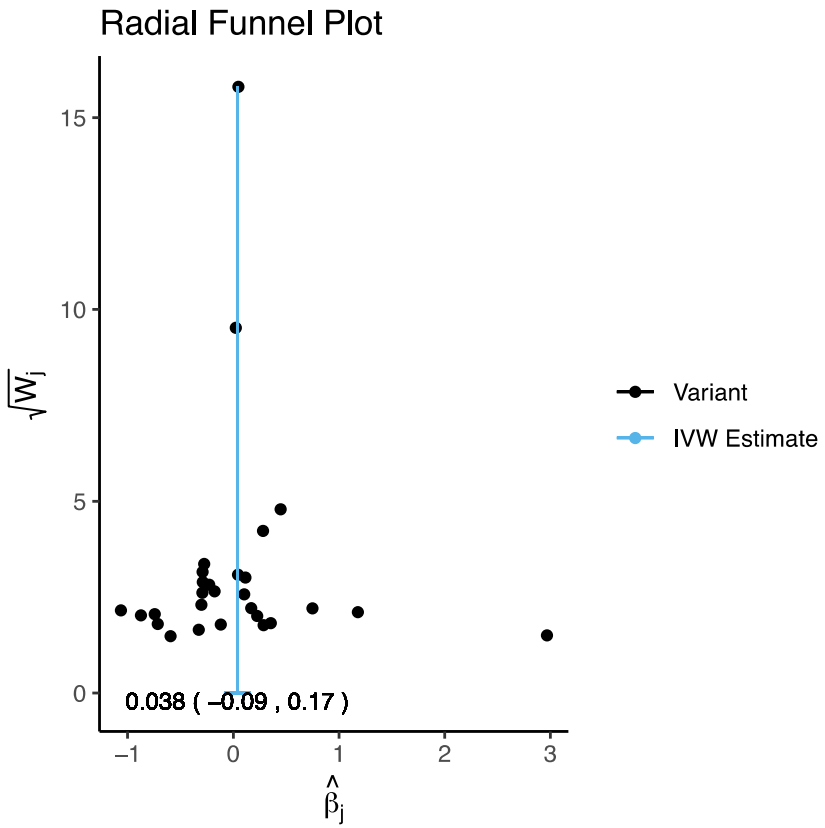


Figure S18. Funnel plot (A) and radial plot (B) for the urate- small-artery ischemic stroke (SVS) relationship.

(A)



(B)

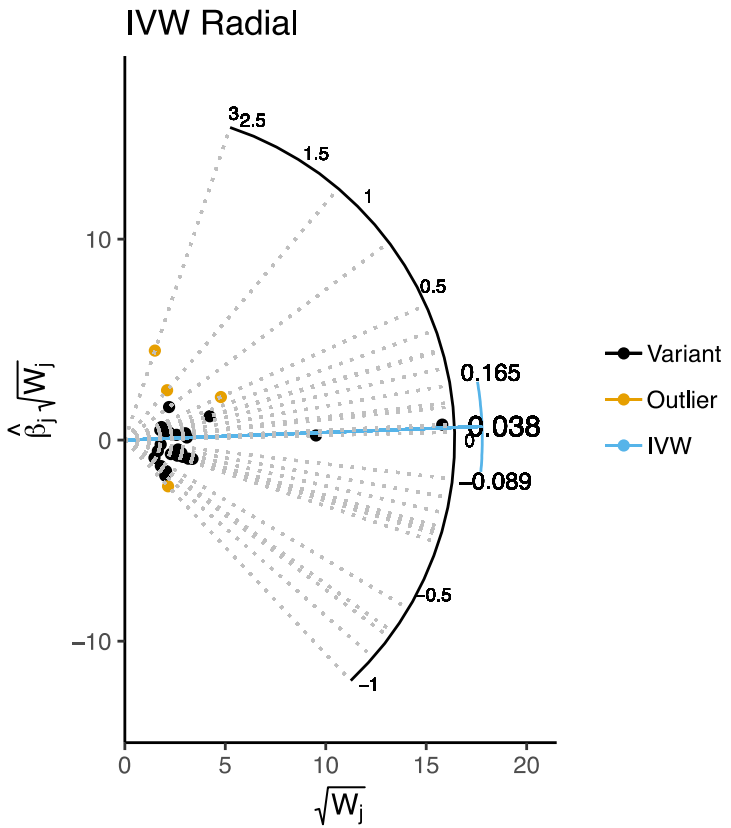
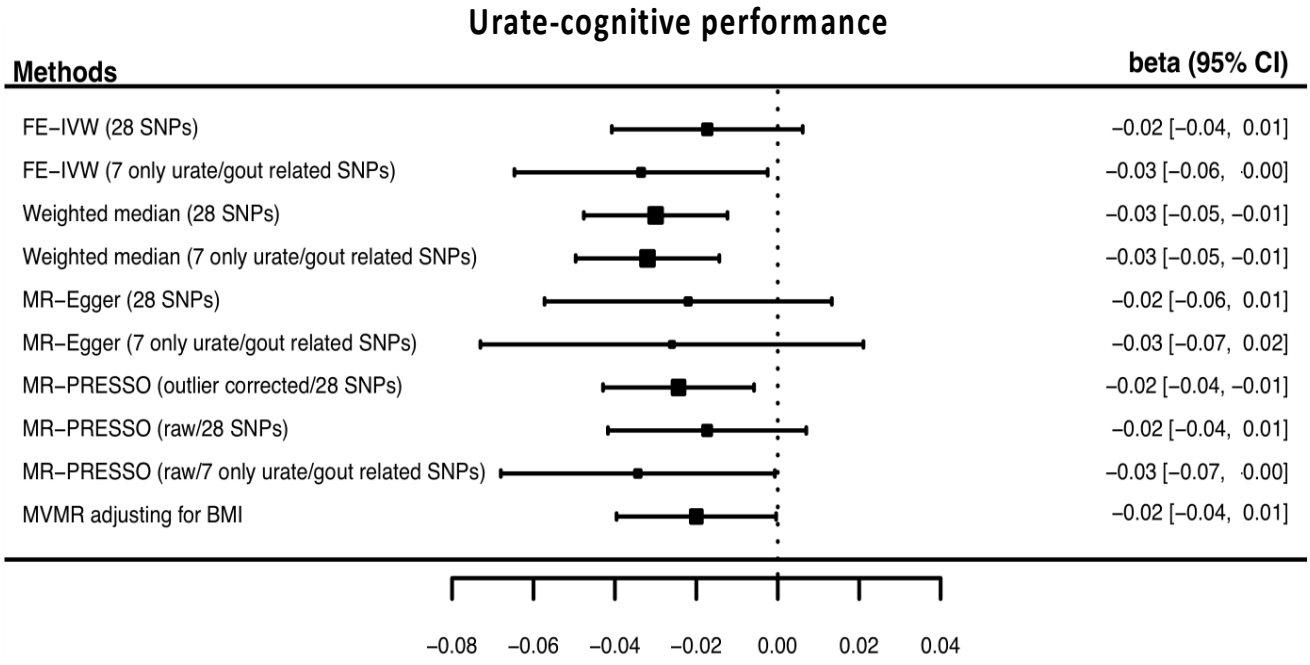
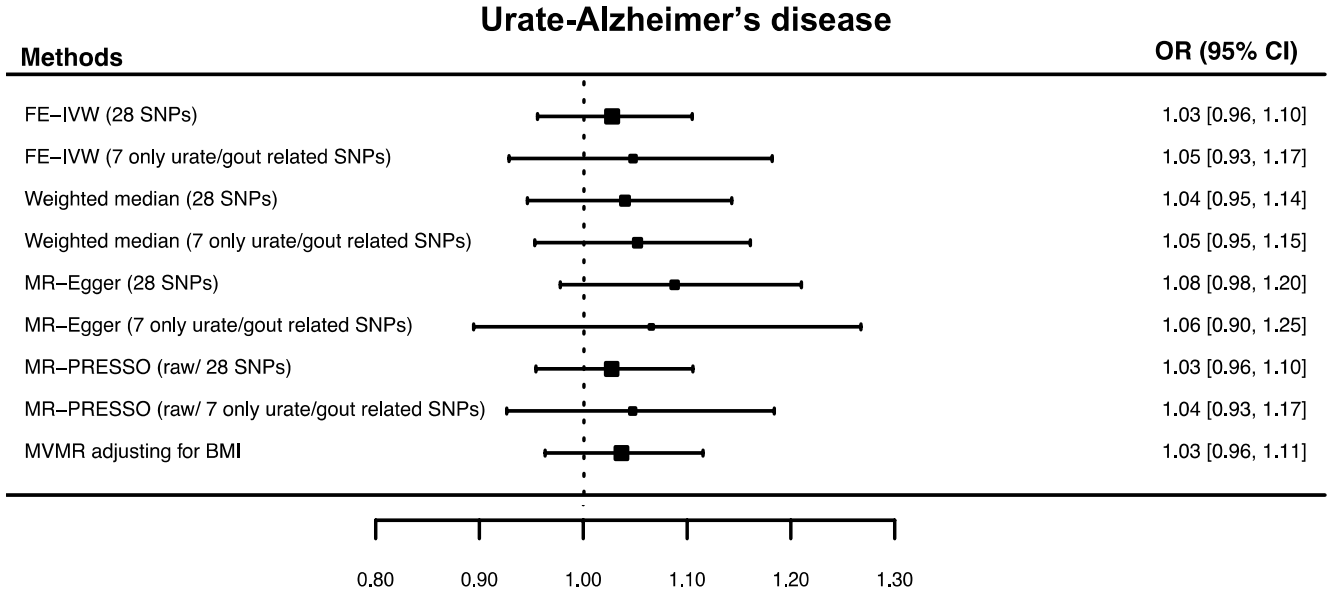


Figure S19. Forest plot for the association of uric acid with cognitive performance.



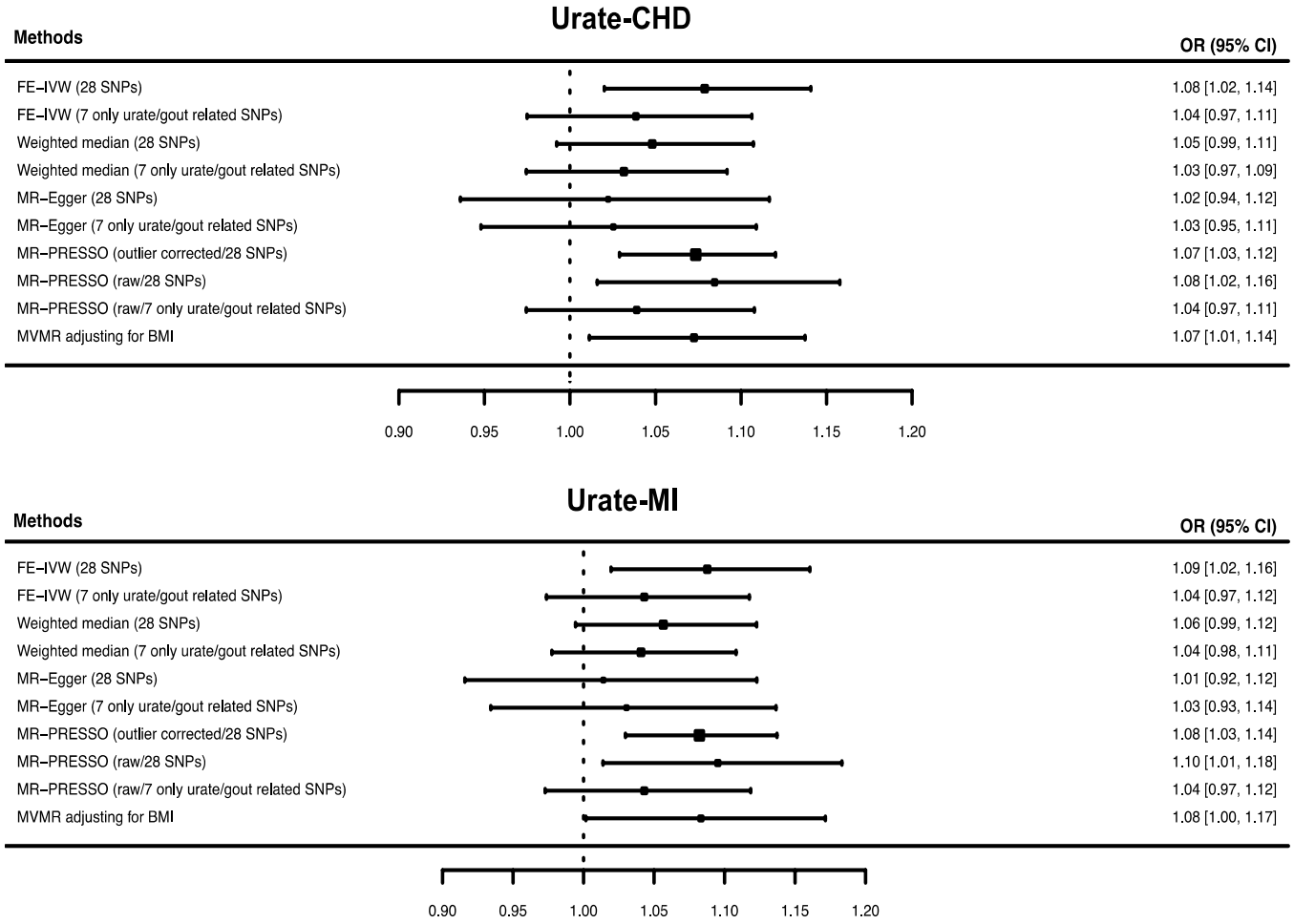
All methods performed in this study are included. Each box indicates the effect estimate (beta) calculated by each method with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S20. Forest plot for the association of uric acid with Alzheimer's disease.



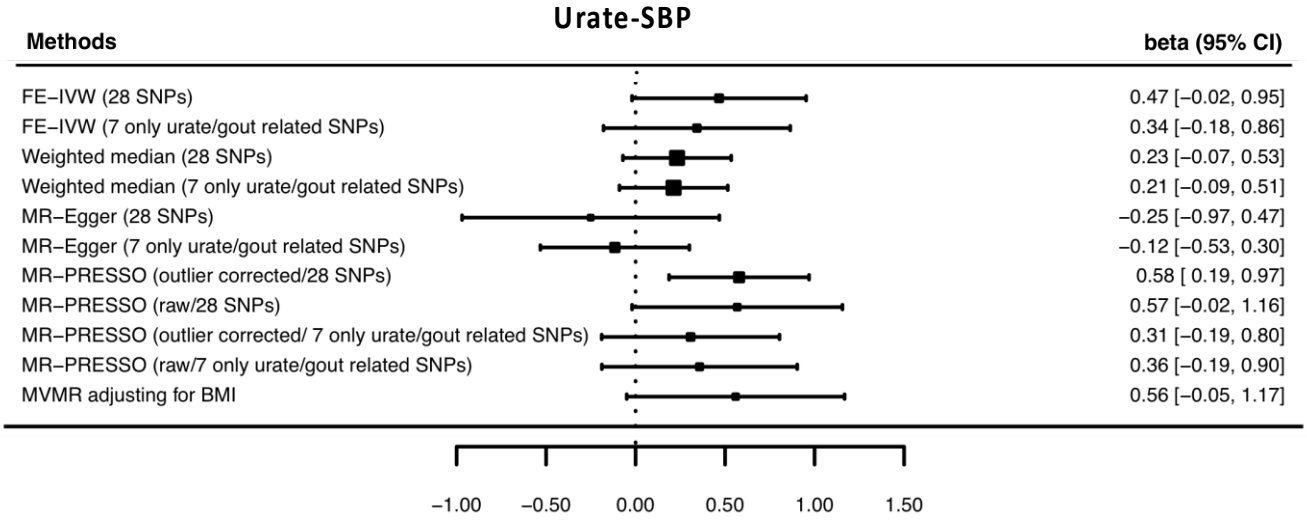
All methods performed in this study are included. Each box indicates the effect estimate (odds ratio [OR]) calculated by each method with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S21. Forest plots for the association of uric acid with coronary heart disease (CHD), myocardial infarction (MI).



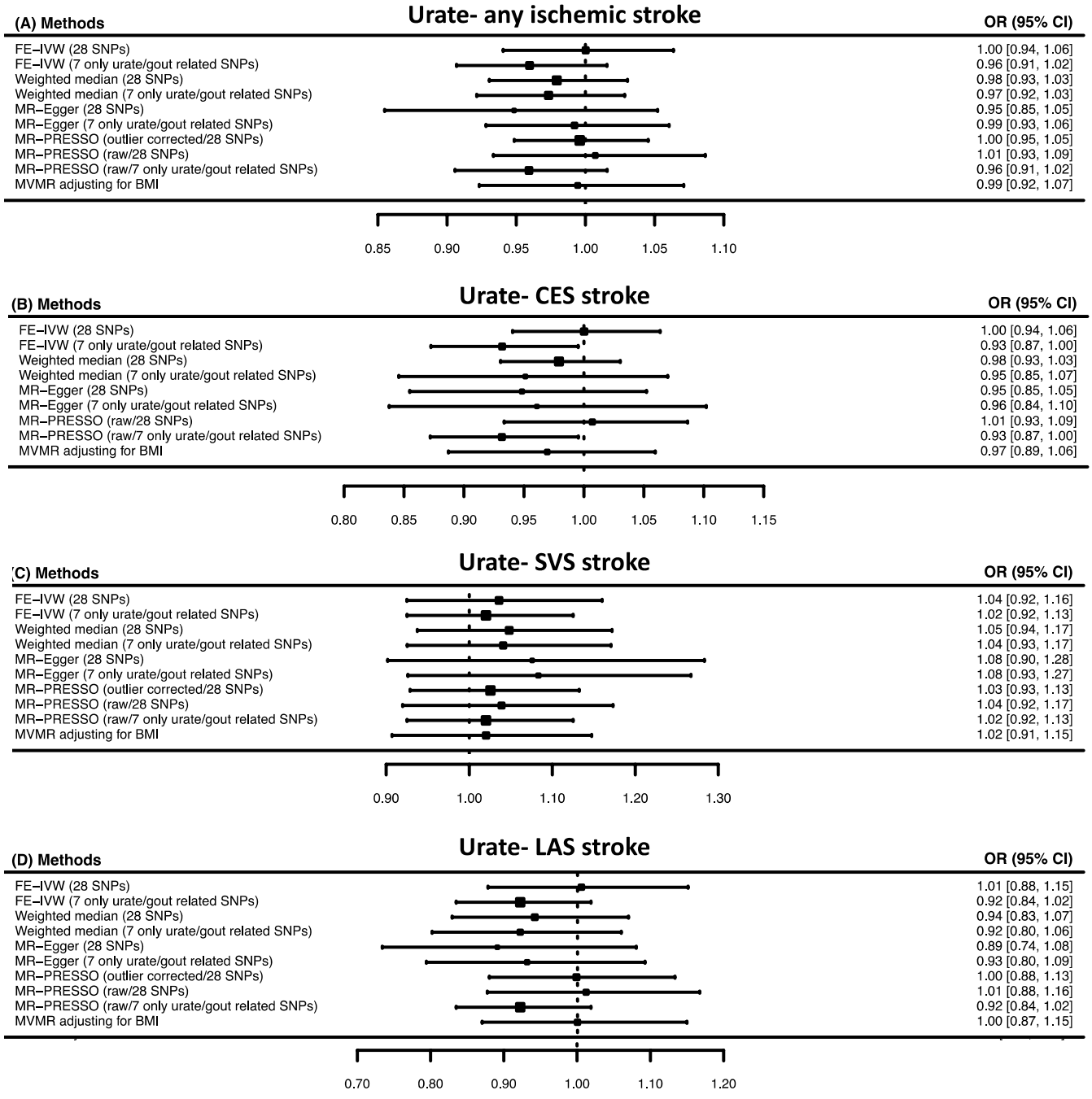
All methods performed in this study are included. Each box indicates the effect estimate (odds ratio [OR]) calculated by each method with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S22. Forest plot for the association of uric acid with systolic blood pressure (SBP).



All methods performed in this study are included. Each box indicates the effect estimate (beta) calculated by each method with horizontal lines represent the 95% confidence interval (CI) of this estimate.

Figure S23. Forest plots for the association of uric acid with ischemic stroke (any type) and its subtypes (cardioembolic stroke [CES], stroke caused by small-vessel disease (small-vessel stroke [SVS] and large-artery atherosclerotic stroke [LAS]).



All methods performed in this study are included. Each box indicates the effect estimate (odds ratio [OR]) calculated by each method with horizontal lines represent the 95% confidence interval (CI) of this estimate.

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