Supplementary data

Assessment causality in associations between serum uric acid and risk of schizophrenia: a two-sample bidirectional Mendelian randomization study

Content:

42 determine whether the overall effect is driven by one specific genetic variant through

43 this analysis

44 Page 28 **References**

Proportion of the variance in schizophrenia

The proportion of variance (conceptually similar to the R^2) in schizophrenia was calculated for each single nucleotide polymorphism based on the formula below.[1]

$$R^2 = \frac{2\beta^2 \times \text{MAF} \times (1 - \text{MAF})}{2\beta^2 \times \text{MAF} \times (1 - \text{MAF}) + \left(se(\beta)\right)^2 \times 2N \times \text{MAF} \times (1 - \text{MAF})}$$

where β is the effect size (beta coefficient) for a given single nucleotide polymorphism, MAF is the minor allele frequency, se(β) is the standard error of effect size and N is the sample size.

F-statistic

The F-statistic of instrument variable was calculated for schizophrenia by using the formula below.[2]

$$\text{F} - \text{statistic} = \frac{R^2 \times (n - 1 - K)}{(1 - R^2) \times K}$$

where R^2 represents the proportion of variance in schizophrenia, n represents the sample size and K represents the number of instrument variables included in the model.

Table S1 Association of serum uric acid (UA) single nucleotide polymorphism (SNP) with smoking confounder queried from PhenoScanner V2[3]

SNP	Disease/trait	Beta	SE	*P*-value	Ancestry	PMID	Database
rs653178	Ever smoked	-0.006	0.001	2.12E-07	European	UKBB	PhenoScanner V2
rs653178	Past tobacco smoking	0.021	0.003	2.74E-11	European	UKBB	PhenoScanner V2
rs653178	Smoking status: previous	-0.007	0.001	2.57E-10	European	UKBB	PhenoScanner V2

Abbreviations: UA, uric acid; SNP, single nucleotide polymorphism; Beta, beta coefficient; SE, standard error.

62 **Table S2** SNP serum UA and SNP schizophrenia associations (per effect allele) of the instruments of serum UA before data harmonization

SNP	SNP-serum UA (exposure)					SNP-schizophrenia (outcome)				
	Effect	**SE**	**EA**	**OA**	***P*-value**	**Effect**[e]	**SE**	**EA**	**OA**	***P*-value**
rs10480300	0.035	0.006	T	C	4.10E-09	0.013	0.012	T	C	0.278
rs10821905	0.057	0.007	A	G	7.40E-17	0.003	0.014	A	G	0.809
rs11264341	-0.050	0.006	T	C	6.20E-19	0.023	0.011	T	C	0.036
rs1165151[f]	-0.091	0.005	T	G	7.00E-70	0.040	0.011	T	G	1.74E-04
rs1171614	-0.079	0.007	T	C	2.30E-28	0.012	0.014	T	C	0.391
rs1178977	0.047	0.007	A	G	1.20E-12	0.023	0.014	A	G	0.100
rs12498742	0.373	0.006	A	G	0[g]	-0.015	0.013	A	G	0.253
rs1260326	0.074	0.005	T	C	1.20E-44	-0.006	0.011	T	C	0.569
rs1394125	0.043	0.006	A	G	2.50E-13	0.001	0.012	A	G	0.951
rs1471633	0.059	0.005	A	C	1.20E-29	0.000	0.011	A	C	0.971
rs17050272	0.035	0.006	A	G	1.60E-10	0.014	0.011	A	G	0.203
rs17632159[h]	-0.039	0.006	C	G	3.50E-11	-0.022	0.012	C	G	0.061
rs17786744	-0.029	0.005	A	G	1.40E-08	0.021	0.011	A	G	0.051
rs2078267	-0.073	0.006	T	C	9.40E-38	-0.001	0.011	T	C	0.945
rs2231142	0.217	0.009	T	G	1.00E-134	-0.002	0.017	T	G	0.894

rs2941484	0.044	0.005	T	C	4.40E-17	0.005	0.011	T	C	0.625
rs3741414[f]	-0.072	0.007	T	C	2.20E-25	0.031	0.013	T	C	0.015
rs478607[f]	-0.047	0.007	A	G	4.40E-11	-0.031	0.015	A	G	0.030
rs653178[i]	-0.035	0.005	T	C	7.20E-12	-0.004	0.011	T	C	0.739
rs6598541	0.043	0.006	A	G	4.80E-15	0.005	0.011	A	G	0.644
rs675209	0.061	0.006	T	C	1.30E-23	0.014	0.012	T	C	0.254
rs6770152[f]	-0.044	0.005	T	G	2.60E-16	-0.031	0.011	T	G	0.004
rs7188445	-0.032	0.005	A	G	1.60E-09	-0.004	0.011	A	G	0.700
rs7193778	-0.046	0.008	T	C	8.20E-10	0.011	0.015	T	C	0.482
rs7224610	-0.042	0.005	A	C	5.40E-17	0.020	0.011	A	C	0.067
rs729761	-0.047	0.006	T	G	8.00E-16	0.021	0.012	T	G	0.089
rs7953704[f]	-0.029	0.005	A	G	2.56E-08	0.042	0.011	A	G	6.98E-05
rs7976059	0.032	0.005	T	G	1.93E-09	-0.013	0.011	T	G	0.231

Notes: [e]Odds ratios converted to beta coefficient by log transformation. [f]The excluded SNP in the second forward-direction MR (serum UA to schizophrenia), due to heterogeneities. [g]*P* value $<1 \times 10^{-700}$. [h]The excluded SNP, for being palindromic. [i]The excluded SNP, for being related with smoking confounder.

Abbreviations: SNP, single nucleotide polymorphism; UA, uric acid; Effect, effect size (beta coefficient) for a given SNP; SE, standard error of effect size; EA, effect allele; OA, other allele.

Table S3 SNP serum UA and SNP schizophrenia associations (per effect allele) of the instruments of serum UA after data harmonization

SNP	SNP-serum UA (exposure)					SNP-schizophrenia (outcome)				
	Effect	**SE**	**EA**	**OA**	***P*-value**	**Effect** [e]	**SE**	**EA**	**OA**	***P*-value**
rs10480300	0.035	0.006	T	C	4.10E-09	0.013	0.012	T	C	0.278
rs10821905	0.057	0.007	A	G	7.40E-17	0.003	0.014	A	G	0.809
rs11264341	0.050	0.006	C	T	6.20E-19	-0.023	0.011	C	T	0.036
rs1165151[f]	0.091	0.005	G	T	7.00E-70	-0.040	0.011	G	T	1.74E-04
rs1171614	0.079	0.007	C	T	2.30E-28	-0.012	0.014	C	T	0.391
rs1178977	0.047	0.007	A	G	1.20E-12	0.023	0.014	A	G	0.100
rs12498742	0.373	0.006	A	G	0[g]	-0.015	0.013	A	G	0.253
rs1260326	0.074	0.005	T	C	1.20E-44	-0.006	0.011	T	C	0.569
rs1394125	0.043	0.006	A	G	2.50E-13	0.001	0.012	A	G	0.951
rs1471633	0.059	0.005	A	C	1.20E-29	0.000	0.011	A	C	0.971
rs17050272	0.035	0.006	A	G	1.60E-10	0.014	0.011	A	G	0.203
rs17632159[h]	0.039	0.006	G	C	3.50E-11	0.022	0.012	G	C	0.061
rs17786744	0.029	0.005	G	A	1.40E-08	-0.021	0.011	G	A	0.051
rs2078267	0.073	0.006	C	T	9.40E-38	0.001	0.011	C	T	0.945
rs2231142	0.217	0.009	T	G	1.00E-134	-0.002	0.017	T	G	0.894

rs2941484	0.044	0.005	T	C	4.40E-17	0.005	0.011	T	C	0.625
rs3741414[f]	0.072	0.007	C	T	2.20E-25	-0.031	0.013	C	T	0.015
rs478607[f]	0.047	0.007	G	A	4.40E-11	0.031	0.015	G	A	0.030
rs653178[i]	0.035	0.005	C	T	7.20E-12	0.004	0.011	C	T	0.739
rs6598541	0.043	0.006	A	G	4.80E-15	0.005	0.011	A	G	0.644
rs675209	0.061	0.006	T	C	1.30E-23	0.014	0.012	T	C	0.254
rs6770152[f]	0.044	0.005	G	T	2.60E-16	0.031	0.011	G	T	0.004
rs7188445	0.032	0.005	G	A	1.60E-09	0.004	0.011	G	A	0.700
rs7193778	0.046	0.008	C	T	8.20E-10	-0.011	0.015	C	T	0.482
rs7224610	0.042	0.005	C	A	5.40E-17	-0.020	0.011	C	A	0.067
rs729761	0.047	0.006	G	T	8.00E-16	-0.021	0.012	G	T	0.089
rs7953704[f]	0.029	0.005	G	A	2.56E-08	-0.042	0.011	G	A	6.98E-05
rs7976059	0.032	0.005	T	G	1.93E-09	-0.013	0.011	T	G	0.231

Notes: [e]Odds ratios converted to beta coefficient by log transformation. [f]The excluded SNP in the second forward-direction MR (serum UA to schizophrenia), due to heterogeneities. [g]*P* value $<1 \times 10^{-700}$. [h]The excluded SNP, for being palindromic. [i]The excluded SNP, for being related with smoking confounder.

Abbreviations: SNP, single nucleotide polymorphism; UA, uric acid; Effect, effect size (beta coefficient) for a given SNP; SE, standard error of effect size; EA, effect allele; OA, other allele.

74 **Table S4** Association of schizophrenia SNPs with smoking confounder queried from PhenoScanner V2 and GWAS Catalog[3,4]

SNP	Disease/trait	Beta	SE	*P*-value	Ancestry	PMID	Database
rs8042374	Nicotine dependence smoking cigarettes per day	-	-	9.50E-43	European	20418888	PhenoScanner V2
rs8042374	Nicotine dependence smoking cigarettes per day	-	-	1.52E-42	European	20418889	PhenoScanner V2
rs8042374	Current tobacco smoking	0.007	0.002	5.90E-06	European	UKBB	PhenoScanner V2
rs8042374	Difficulty not smoking for 1 day	0.084	0.010	2.24E-16	European	UKBB	PhenoScanner V2
rs8042374	Ever stopped smoking for 6+ months	-0.015	0.003	4.19E-07	European	UKBB	PhenoScanner V2
rs8042374	Light smokers, at least 100 smokes in lifetime	-0.021	0.003	9.10E-15	European	UKBB	PhenoScanner V2
rs8042374	Maternal smoking around birth	0.010	0.001	1.66E-11	European	UKBB	PhenoScanner V2
rs8042374	Number of cigarettes currently smoked daily	0.065	0.008	9.59E-16	European	UKBB	PhenoScanner V2
rs8042374	Number of cigarettes previously smoked daily	0.076	0.005	1.99E-47	European	UKBB	PhenoScanner V2

rs8042374	Number of unsuccessful stop-smoking attempts	0.024	0.005	1.48E-06	European	UKBB	PhenoScanner V2
rs8042374	Pack years adult smoking as proportion of life span exposed to smoking	0.065	0.005	7.68E-35	European	UKBB	PhenoScanner V2
rs8042374	Pack years of smoking preview only	0.061	0.005	1.46E-30	European	UKBB	PhenoScanner V2
rs8042374	Time from waking to first cigarette	-0.083	0.013	1.90E-10	European	UKBB	PhenoScanner V2
rs8042374	Cigarettes per day	0.981	0.096	2.38E-24	European	20418890	PhenoScanner V2
rs11210892	Current tobacco smoking	-0.009	0.001	7.85E-10	European	UKBB	PhenoScanner V2
rs11210892	Maternal smoking around birth	-0.006	0.001	4.68E-07	European	UKBB	PhenoScanner V2
rs11210892	Past tobacco smoking	0.017	0.003	3.81E-07	European	UKBB	PhenoScanner V2
rs11210892	Smoking status: current	-0.005	0.001	1.97E-10	European	UKBB	PhenoScanner V2
SNP	**Disease/trait**	**OR or BETA**	**95% CI (TEXT)**	***P*-value**	**Ancestry**	**PMID**	**Database**
rs11210892	Smoking status (ever vs never smokers)	0.016	0.011-0.020 (unit decrease)	4.00E-13	European	30643258	GWAS Catalog

Abbreviations: UA, uric acid; SNP, single nucleotide polymorphism; Beta, beta coefficient; SE, standard error; 95% CI, 95% confidence interval.

Table S5 SNP schizophrenia and SNP serum UA associations (per effect allele) of the instruments of schizophrenia before data harmonization

SNP	SNP-schizophrenia(exposure)					SNP-serum UA (outcome)				
	Effect [e]	SE	EA	OA	*P*-value	Effect	SE	EA	OA	*P*-value
rs1023500	0.073	0.013	T	C	3.43E-08	-0.006	0.007	T	C	0.394
rs10503253	0.071	0.012	A	C	1.06E-08	-0.003	0.007	A	C	0.718
rs10520163	0.063	0.010	T	C	1.47E-09	-0.010	0.006	T	C	0.088
rs10791097	0.074	0.010	T	G	1.09E-12	-0.003	0.006	T	G	0.571
rs10803138[f]	-0.069	0.012	A	G	2.03E-08	0.023	0.006	A	G	4.531E-04
rs10860964	0.059	0.011	T	C	4.84E-08	0.008	0.006	T	C	0.201
rs11027857	0.062	0.010	A	G	2.55E-09	-0.010	0.006	A	G	0.102
rs1106568	-0.068	0.012	A	G	9.47E-09	0.006	0.006	A	G	0.393
rs11139497[g]	0.066	0.011	A	T	3.61E-09	-0.006	0.006	A	T	0.318
rs11210892[h]	-0.069	0.011	A	G	3.39E-10	-0.001	0.006	A	G	0.936
rs11682175	-0.070	0.010	T	C	1.47E-11	0.002	0.006	T	C	0.708
rs12148337	0.058	0.010	T	C	1.79E-08	-0.015	0.005	T	C	0.007
rs12325245[g]	-0.084	0.015	A	T	1.87E-08	0.007	0.008	A	T	0.384
rs12421382	-0.061	0.011	T	C	3.7E-08	0.003	0.006	T	C	0.618
rs12522290[g]	0.081	0.014	C	G	1.99E-08	-0.002	0.008	C	G	0.769

rs1339227	-0.060	0.011	T	C	2.69E-08	0.000	0.006	T	C	0.988
rs1501357	-0.077	0.013	T	C	5.05E-09	0.012	0.007	T	C	0.101
rs16867576	0.097	0.017	A	G	4.61E-09	-0.004	0.008	A	G	0.663
rs17194490	0.096	0.014	T	G	2.69E-11	0.000	0.008	T	G	0.970
rs2007044	-0.092	0.011	A	G	3.22E-18	-0.002	0.006	A	G	0.677
rs2053079	-0.071	0.012	A	G	4.49E-09	0.000	0.006	A	G	0.953
rs2068012	-0.070	0.012	T	C	1.41E-08	-0.003	0.008	T	C	0.681
rs211829	0.059	0.011	T	C	3.71E-08	-0.007	0.006	T	C	0.212
rs215411[g]	0.062	0.011	A	T	3.06E-08	0.001	0.006	A	T	0.900
rs2239063	0.065	0.012	A	C	1.93E-08	-0.014	0.006	A	C	0.026
rs2514218	-0.075	0.011	T	C	2.75E-11	-0.003	0.006	T	C	0.660
rs2535627	0.068	0.010	T	C	4.26E-11	0.005	0.005	T	C	0.431
rs2693698	-0.063	0.011	A	G	4.8E-09	-0.004	0.006	A	G	0.485
rs2851447[g]	-0.089	0.012	C	G	1.86E-14	-0.009	0.007	C	G	0.203
rs3849046	0.061	0.010	T	C	4.67E-09	-0.001	0.005	T	C	0.852
rs4129585	0.083	0.010	A	C	1.74E-15	0.001	0.005	A	C	0.922
rs4240748[g]	-0.059	0.011	C	G	4.59E-08	0.003	0.006	C	G	0.601
rs4388249	0.073	0.013	T	C	3.05E-08	-0.004	0.007	T	C	0.639

rs4391122	-0.081	0.010	A	G	1.1E-14	0.003	0.005	A	G	0.552
rs4523957	0.069	0.011	T	G	2.86E-10	-0.014	0.006	T	G	0.024
rs4648845	0.070	0.011	T	C	8.7E-10	-0.006	0.008	T	C	0.497
rs4702	-0.081	0.011	A	G	8.3E-14	-0.003	0.006	A	G	0.706
rs6065094	-0.074	0.011	A	G	1.46E-11	0.003	0.006	A	G	0.662
rs6670165	0.072	0.013	T	C	4.45E-08	0.002	0.007	T	C	0.805
rs6704641	0.078	0.014	A	G	8.33E-09	0.009	0.007	A	G	0.194
rs6704768	-0.073	0.010	A	G	2.32E-12	0.002	0.005	A	G	0.783
rs715170	-0.067	0.012	T	C	1.27E-08	0.009	0.006	T	C	0.156
rs7267348	-0.065	0.012	T	C	4.56E-08	0.011	0.006	T	C	0.090
rs7432375	-0.069	0.011	A	G	7.26E-11	0.003	0.005	A	G	0.586
rs7801375	-0.079	0.014	A	G	4.42E-08	0.010	0.007	A	G	0.222
rs7893279	0.117	0.017	T	G	1.97E-12	0.004	0.008	T	G	0.624
rs8042374[h]	0.089	0.012	A	G	2.44E-13	-0.004	0.006	A	G	0.604
rs8044995	0.078	0.014	A	G	1.51E-08	-0.012	0.007	A	G	0.123
rs832187	-0.060	0.011	T	C	1.43E-08	0.003	0.006	T	C	0.635
rs9420	0.066	0.011	A	G	2.24E-09	0.011	0.006	A	G	0.070
rs950169	-0.080	0.012	T	C	1.62E-11	0.003	0.006	T	C	0.604

rs9636107	-0.073	0.010	A	G	3.34E-12	0.006	0.005	A	G	0.311
rs9841616[g]	-0.078	0.014	A	T	2.35E-08	0.015	0.007	A	T	0.042
rs9922678	0.065	0.011	A	G	1.28E-08	-0.004	0.006	A	G	0.512

Notes: [e]Odds ratios converted to beta coefficient by log transformation. [f]The excluded SNP in the second reverse-direction MR (schizophrenia to serum UA), due to heterogeneities. [g]The excluded SNP, for being palindromic. [h]The excluded SNP, for being related with smoking confounder.

Abbreviations: SNP, single nucleotide polymorphism; UA, uric acid; Effect, effect size (beta coefficient) for a given SNP; SE, standard error of effect size; EA, effect allele; OA, other allele.

81 **Table S6** SNP schizophrenia and SNP serum UA associations (per effect allele) of the instruments of schizophrenia after data harmonization

SNP	SNP-schizophrenia(exposure)					SNP- serum UA (outcome)				
	Effect [e]	SE	EA	OA	*P*-value	Effect	SE	EA	OA	*P*-value
rs1023500	0.073	0.013	T	C	3.43E-08	-0.006	0.007	T	C	0.394
rs10503253	0.071	0.012	A	C	1.06E-08	-0.003	0.007	A	C	0.718
rs10520163	0.063	0.010	T	C	1.47E-09	-0.010	0.006	T	C	0.088
rs10791097	0.074	0.010	T	G	1.09E-12	-0.003	0.006	T	G	0.571
rs10803138[f]	0.069	0.012	G	A	2.03E-08	-0.023	0.006	G	A	4.53E-04
rs10860964	0.059	0.011	T	C	4.84E-08	0.008	0.006	T	C	0.201
rs11027857	0.062	0.010	A	G	2.55E-09	-0.010	0.006	A	G	0.102
rs1106568	0.068	0.012	G	A	9.47E-09	-0.006	0.006	G	A	0.393
rs11139497[g]	0.066	0.011	A	T	3.61E-09	-0.006	0.006	A	T	0.318
rs11210892[h]	0.069	0.011	G	A	3.39E-10	0.001	0.006	G	A	0.936
rs11682175	0.070	0.010	C	T	1.47E-11	-0.002	0.006	C	T	0.708
rs12148337	0.058	0.010	T	C	1.79E-08	-0.015	0.005	T	C	0.007
rs12325245[g]	0.084	0.015	T	A	1.87E-08	-0.007	0.008	T	A	0.384
rs12421382	0.061	0.011	C	T	3.7E-08	-0.003	0.006	C	T	0.618
rs12522290[g]	0.081	0.014	C	G	1.99E-08	-0.002	0.008	C	G	0.769

rs1339227	0.060	0.011	C	T	2.69E-08	0.000	0.006	C	T	0.988
rs1501357	0.077	0.013	C	T	5.05E-09	-0.012	0.007	C	T	0.101
rs16867576	0.097	0.017	A	G	4.61E-09	-0.004	0.008	A	G	0.663
rs17194490	0.096	0.014	T	G	2.69E-11	0.000	0.008	T	G	0.970
rs2007044	0.092	0.011	G	A	3.22E-18	0.002	0.006	G	A	0.677
rs2053079	0.071	0.012	G	A	4.49E-09	0.000	0.006	G	A	0.953
rs2068012	0.070	0.012	C	T	1.41E-08	0.003	0.008	C	T	0.681
rs211829	0.059	0.011	T	C	3.71E-08	-0.007	0.006	T	C	0.212
rs215411[g]	0.062	0.011	A	T	3.06E-08	0.001	0.006	A	T	0.900
rs2239063	0.065	0.012	A	C	1.93E-08	-0.014	0.006	A	C	0.026
rs2514218	0.075	0.011	C	T	2.75E-11	0.003	0.006	C	T	0.660
rs2535627	0.068	0.010	T	C	4.26E-11	0.005	0.005	T	C	0.431
rs2693698	0.063	0.011	G	A	4.8E-09	0.004	0.006	G	A	0.485
rs2851447[g]	0.089	0.012	G	C	1.86E-14	0.009	0.007	G	C	0.203
rs3849046	0.061	0.010	T	C	4.67E-09	-0.001	0.005	T	C	0.852
rs4129585	0.083	0.010	A	C	1.74E-15	0.001	0.005	A	C	0.922
rs4240748[g]	0.059	0.011	G	C	4.59E-08	-0.003	0.006	G	C	0.601
rs4388249	0.073	0.013	T	C	3.05E-08	-0.004	0.007	T	C	0.639

rs4391122	0.081	0.010	G	A	1.1E-14	-0.003	0.005	G	A	0.552
rs4523957	0.069	0.011	T	G	2.86E-10	-0.014	0.006	T	G	0.024
rs4648845	0.070	0.011	T	C	8.7E-10	-0.006	0.008	T	C	0.497
rs4702	0.081	0.011	G	A	8.3E-14	0.003	0.006	G	A	0.706
rs6065094	0.074	0.011	G	A	1.46E-11	-0.003	0.006	G	A	0.662
rs6670165	0.072	0.013	T	C	4.45E-08	0.002	0.007	T	C	0.805
rs6704641	0.078	0.014	A	G	8.33E-09	0.009	0.007	A	G	0.194
rs6704768	0.073	0.010	G	A	2.32E-12	-0.002	0.005	G	A	0.783
rs715170	0.067	0.012	C	T	1.27E-08	-0.009	0.006	C	T	0.156
rs7267348	0.065	0.012	C	T	4.56E-08	-0.011	0.006	C	T	0.090
rs7432375	0.069	0.011	G	A	7.26E-11	-0.003	0.005	G	A	0.586
rs7801375	0.079	0.014	G	A	4.42E-08	-0.010	0.007	G	A	0.222
rs7893279	0.117	0.017	T	G	1.97E-12	0.004	0.008	T	G	0.624
rs8042374[h]	0.089	0.012	A	G	2.44E-13	-0.004	0.006	A	G	0.604
rs8044995	0.078	0.014	A	G	1.51E-08	-0.012	0.007	A	G	0.123
rs832187	0.060	0.011	C	T	1.43E-08	-0.003	0.006	C	T	0.635
rs9420	0.066	0.011	A	G	2.24E-09	0.011	0.006	A	G	0.070
rs950169	0.080	0.012	C	T	1.62E-11	-0.003	0.006	C	T	0.604

rs9636107	0.073	0.010	G	A	3.34E-12	-0.006	0.005	G	A	0.311
rs9841616[g]	0.078	0.014	T	A	2.35E-08	-0.015	0.007	T	A	0.042
rs9922678	0.065	0.011	A	G	1.28E-08	-0.004	0.006	A	G	0.512

Notes: [e]Odds ratios converted to beta coefficient by log transformation. [f]The excluded SNP in the second reverse-direction MR (schizophrenia to serum UA), due to heterogeneities. [g]The excluded SNP, for being palindromic. [h]The excluded SNP, for being related with smoking confounder.

Abbreviations: SNP, single nucleotide polymorphism; UA, uric acid; Effect, effect size (beta coefficient) for a given SNP; SE, standard error of effect size; EA, effect allele; OA, other allele.

Table S7 Power (two-sided α = 0.05) for Mendelian randomization analysis (SNPs–serum UA–schizophrenia)

Exposure	Actual *N* (Schizophrenia-GWAS)	Proportion of cases (Schizophrenia-GWAS)	Observational OR	R^2 of instrument	*N* required for 80% power	Power at actual *N*
serum UA	150,064	0.25	0.72[i]	0.07[k]	6486	100%
serum UA	150,064	0.25	0.37[j]	0.07[k]	958	100%

Notes: Power was calculated using the online tool mRnd.[5]

[i]From chronic schizophrenia.[6] [j]From first episode schizophrenia.[6] [k]From Global Urate Genetics Consortium GWAS.[7]

Abbreviations: UA, uric acid; R^2, variation explanation of instrument; *N*, sample size.

Table S8 Summary of the 45 SNPs associated with schizophrenia used as instruments (*P*<5E-08)

SNP	Chr	Position	Effect [e]	SE	EA	OA	EAF	*P*-value	*N*	MAF	R^2	F
rs1023500	22	42340844	0.073	0.013	T	C	0.817	3.43E-08	150064	0.183	0.0002	30.50
rs10503253	8	4180844	0.071	0.012	A	C	0.223	1.06E-08	150064	0.223	0.0002	32.69
rs10520163	4	1.71E+08	0.063	0.010	T	C	0.493	1.47E-09	150064	0.493	0.0002	36.94
rs10791097	11	1.31E+08	0.074	0.010	T	G	0.479	1.09E-12	150064	0.479	0.0003	51.19
rs10803138[f]	1	2.44E+08	-0.069	0.012	A	G	0.232	2.03E-08	150064	0.232	0.0002	31.38
rs10860964	12	1.04E+08	0.059	0.011	T	C	0.650	4.84E-08	150064	0.350	0.0002	29.99
rs11027857	11	24403620	0.062	0.010	A	G	0.515	2.55E-09	150064	0.485	0.0002	35.88
rs1106568	4	1.77E+08	-0.068	0.012	A	G	0.747	9.47E-09	150064	0.253	0.0002	33.03
rs11682175	2	57987593	-0.070	0.010	T	C	0.520	1.47E-11	150064	0.480	0.0003	45.92
rs12148337	15	70589272	0.058	0.010	T	C	0.478	1.79E-08	150064	0.478	0.0002	31.49
rs12421382	11	1.09E+08	-0.061	0.011	T	C	0.318	3.70E-08	150064	0.318	0.0002	30.45
rs1339227	6	73155701	-0.060	0.011	T	C	0.347	2.69E-08	150064	0.347	0.0002	31.07
rs1501357	5	45364875	-0.077	0.013	T	C	0.794	5.05E-09	150064	0.206	0.0002	34.19
rs16867576	5	88746331	0.097	0.017	A	G	0.889	4.61E-09	150064	0.111	0.0002	34.28
rs17194490	3	2547786	0.096	0.014	T	G	0.169	2.69E-11	150064	0.169	0.0003	44.54
rs2007044	12	2344960	-0.092	0.011	A	G	0.602	3.22E-18	150064	0.398	0.0005	76.27

rs2053079	19	30987423	-0.071	0.012	A	G	0.755	4.49E-09	150064	0.245	0.0002	34.62
rs2068012	14	30190316	-0.070	0.012	T	C	0.760	1.41E-08	150064	0.240	0.0002	32.20
rs211829	7	1.1E+08	0.059	0.011	T	C	0.641	3.71E-08	150064	0.359	0.0002	30.51
rs2239063	12	2511831	0.065	0.012	A	C	0.729	1.93E-08	150064	0.271	0.0002	31.85
rs2514218	11	1.13E+08	-0.075	0.011	T	C	0.310	2.75E-11	150064	0.310	0.0003	44.40
rs2535627	3	52845105	0.068	0.010	T	C	0.545	4.26E-11	150064	0.455	0.0003	43.84
rs2693698	14	99719219	-0.063	0.011	A	G	0.412	4.80E-09	150064	0.412	0.0002	34.35
rs3849046	5	1.38E+08	0.061	0.010	T	C	0.542	4.67E-09	150064	0.458	0.0002	34.63
rs4129585	8	1.43E+08	0.083	0.010	A	C	0.447	1.74E-15	150064	0.447	0.0004	63.84
rs4388249	5	1.09E+08	0.073	0.013	T	C	0.212	3.05E-08	150064	0.212	0.0002	30.58
rs4391122	5	60598543	-0.081	0.010	A	G	0.505	1.10E-14	150064	0.495	0.0004	60.21
rs4523957	17	2208899	0.069	0.011	T	G	0.642	2.86E-10	150064	0.358	0.0003	39.96
rs4648845	1	2387101	0.070	0.011	T	C	0.533	8.70E-10	150064	0.467	0.0003	37.48
rs4702	15	91426560	-0.081	0.011	A	G	0.547	8.30E-14	150064	0.453	0.0004	55.78
rs6065094	20	37453194	-0.075	0.011	A	G	0.307	1.46E-11	150064	0.307	0.0003	45.87
rs6670165	1	1.77E+08	0.072	0.013	T	C	0.196	4.45E-08	150064	0.196	0.0002	29.76
rs6704641	2	2E+08	0.078	0.014	A	G	0.819	8.33E-09	150064	0.181	0.0002	33.21
rs6704768	2	2.34E+08	-0.073	0.010	A	G	0.540	2.32E-12	150064	0.460	0.0003	48.73

rs715170	18	53795514	-0.067	0.012	T	C	0.261	1.27E-08	150064	0.261	0.0002	32.49
rs7267348	20	48131036	-0.065	0.012	T	C	0.741	4.56E-08	150064	0.259	0.0002	29.97
rs7432375	3	1.36E+08	-0.069	0.011	A	G	0.421	7.26E-11	150064	0.421	0.0003	42.74
rs7801375	7	1.32E+08	-0.079	0.014	A	G	0.146	4.42E-08	150064	0.146	0.0002	30.02
rs7893279	10	18745105	0.117	0.017	T	G	0.899	1.97E-12	150064	0.101	0.0003	49.50
rs8044995	16	68189340	0.078	0.014	A	G	0.173	1.51E-08	150064	0.173	0.0002	32.03
rs832187	3	63833050	-0.060	0.011	T	C	0.607	1.43E-08	150064	0.393	0.0002	32.47
rs9420	11	57510294	0.066	0.011	A	G	0.327	2.24E-09	150064	0.327	0.0002	36.00
rs950169	15	84706461	-0.080	0.012	T	C	0.247	1.62E-11	150064	0.247	0.0003	45.31
rs9636107	18	53200117	-0.073	0.010	A	G	0.490	3.34E-12	150064	0.490	0.0003	48.86
rs9922678	16	9946319	0.065	0.011	A	G	0.299	1.28E-08	150064	0.299	0.0002	32.58

Notes: [e]Odds ratios converted to beta coefficient by log transformation. [f]The excluded SNP in the second reverse-direction MR (schizophrenia to serum UA), due to heterogeneities.

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome; Effect, effect size (beta coefficient) for a given SNP; SE, standard error of effect size; EA, effect allele; OA, other allele; EAF, effect allele frequency; *N*, sample size; MAF, minor allele frequency; R^2, the proportion of variance in schizophrenia.

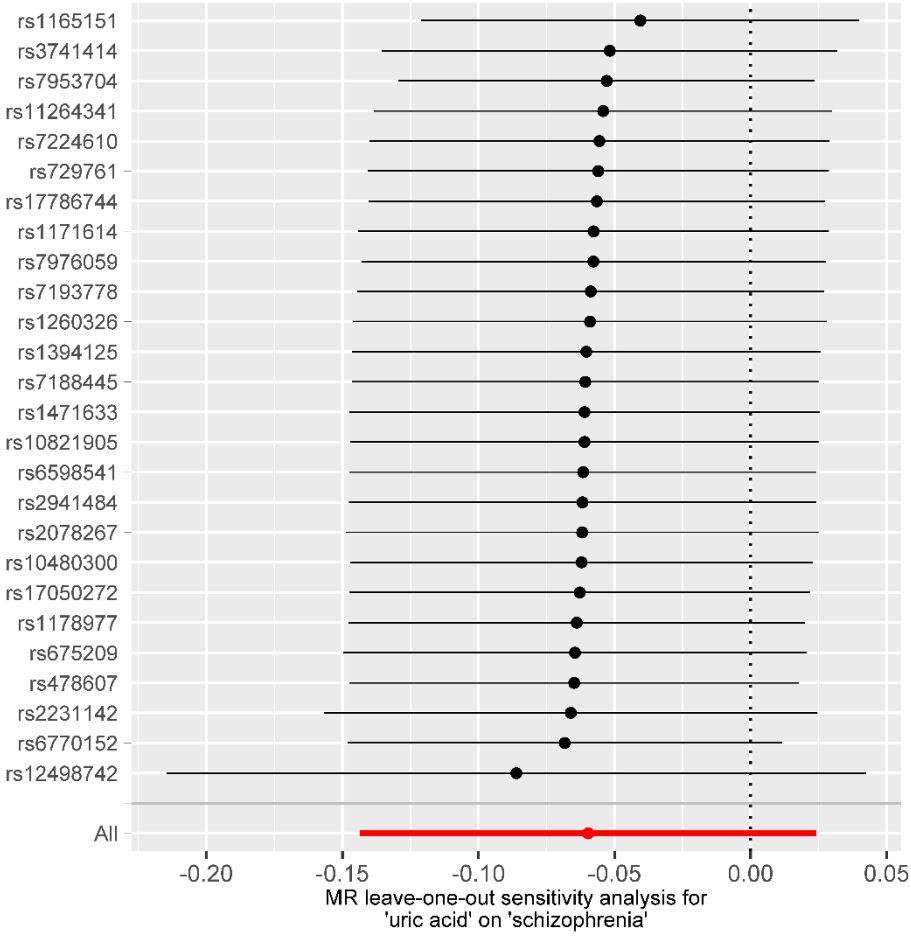

Figure S1 Leave-one-out analysis depicting uric acid (UA) (before removal of the 5 single nucleotide polymorphisms (SNPs) with potential pleiotropic effects)-to-schizophrenia Mendelian randomization (MR) results (inverse variance weighted (IVW) method) after excluding each of the genetic variants from the analysis one at a time. We could determine whether the overall effect is driven by one specific genetic variant through this analysis.

Abbreviation: MR, Mendelian randomization.

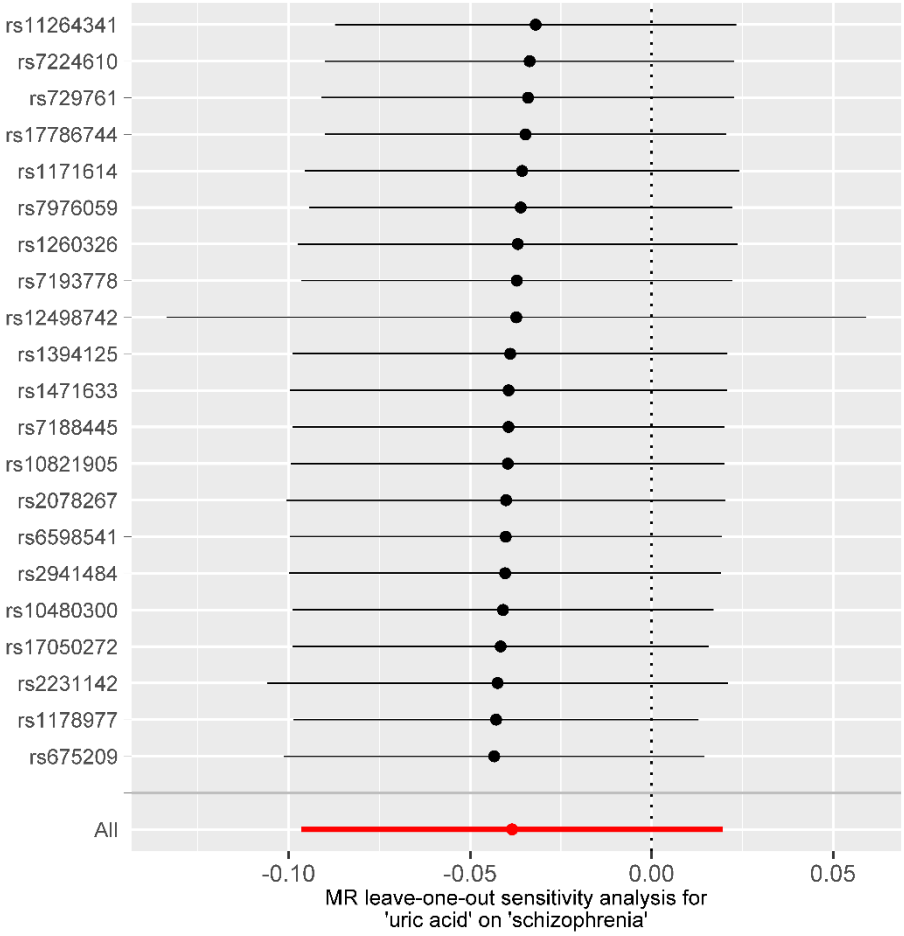

Figure S2 Leave-one-out analysis depicting serum UA (after removal of the 5 SNPs with potential pleiotropic effects)-to-schizophrenia MR results (IVW method) after excluding each of the genetic variants from the analysis one at a time. We could determine whether the overall effect is driven by one specific genetic variant through this analysis.

Abbreviation: MR, Mendelian randomization.

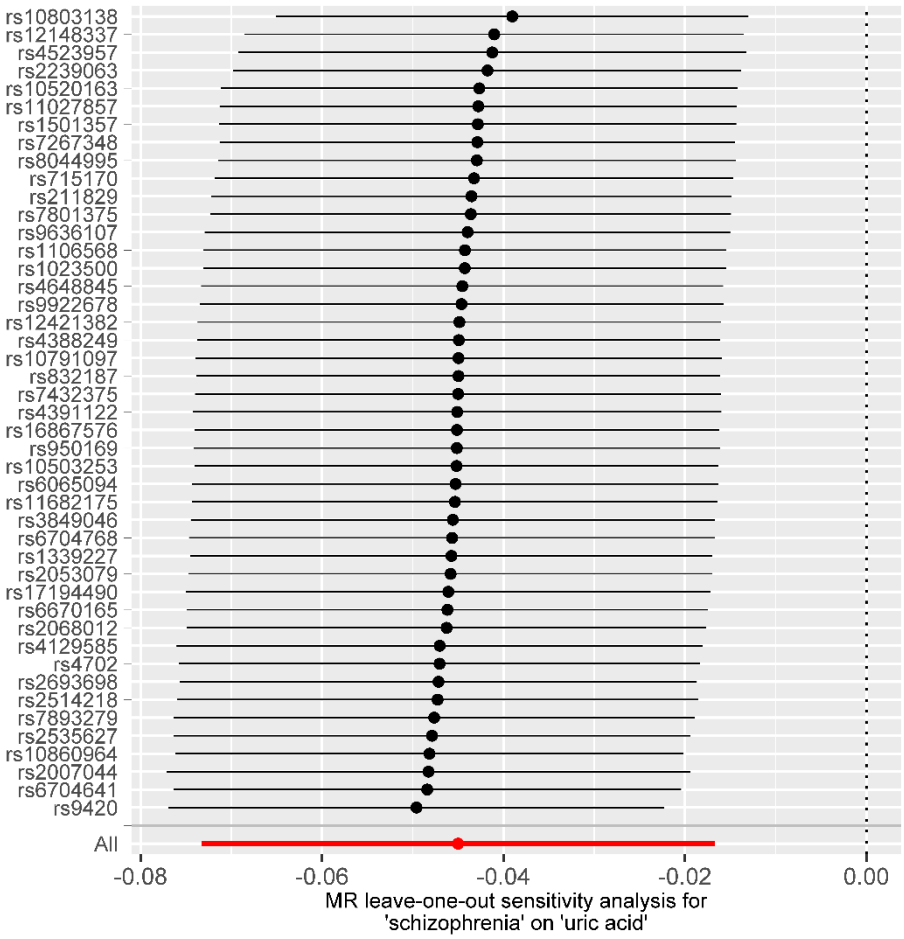

Figure S3 Leave-one-out analysis depicting schizophrenia (before removal of the SNP with potential pleiotropic effects)-to-serum UA MR results (IVW method) after excluding each of the genetic variants from the analysis one at a time. We could determine whether the overall effect is driven by one specific genetic variant through this analysis.

Abbreviation: MR, Mendelian randomization.

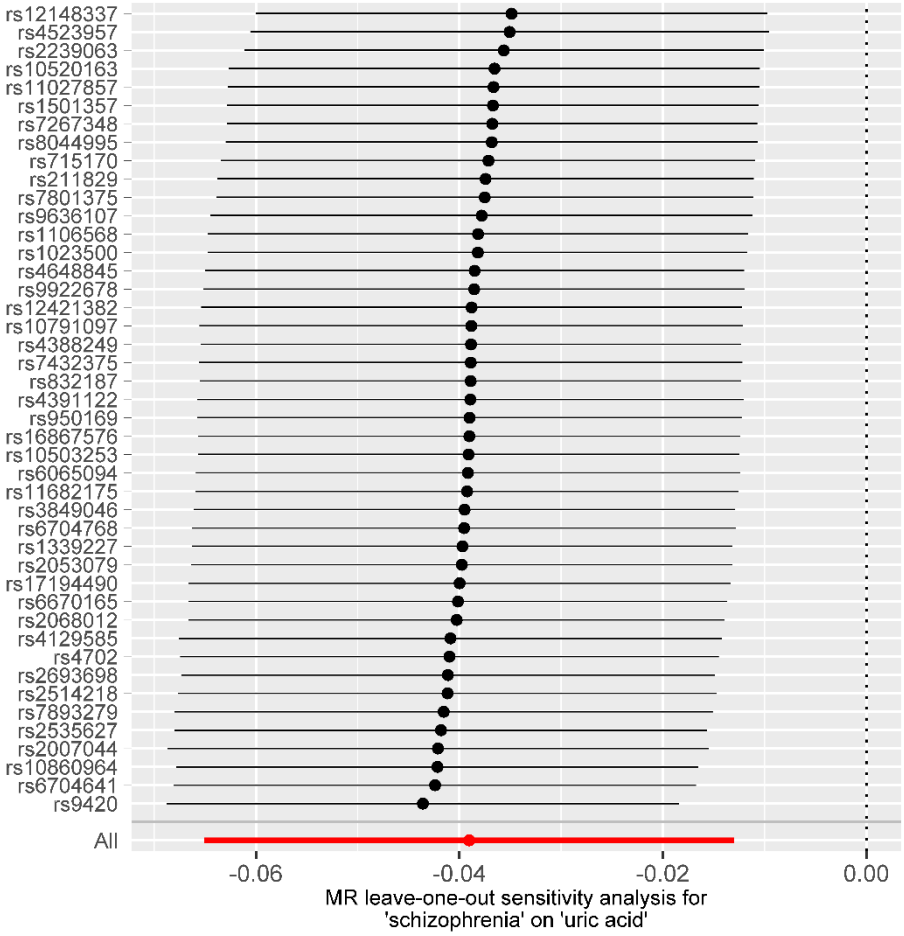

Figure S4 Leave-one-out analysis depicting schizophrenia (after removal of the SNP with potential pleiotropic effects)-to-serum UA MR results (IVW method) after excluding each of the genetic variants from the analysis one at a time. We could determine whether the overall effect is driven by one specific genetic variant through this analysis.

Abbreviation: MR, Mendelian randomization.

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