

## Supplementary data

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

#### Content:

|            |                                                                                                                                                            |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Page 4     | <b>Proportion of the variance in schizophrenia; F-statistic</b>                                                                                            |
| Page 5     | <b>Table S1</b> Association of serum uric acid (UA) single nucleotide polymorphism (SNP) with smoking confounder queried from PhenoScanner V2 <sup>3</sup> |
| Page 6-7   | <b>Table S2</b> SNP serum UA and SNP schizophrenia associations (per effect allele) of the instruments of serum UA before data harmonization               |
| Page 8-9   | <b>Table S3</b> SNP serum UA and SNP schizophrenia associations (per effect allele) of the instruments of serum UA after data harmonization                |
| Page 10-11 | <b>Table S4</b> Association of schizophrenia SNPs with smoking confounder queried from PhenoScanner V2 and GWAS Catalog <sup>3,4</sup>                     |
| Page 12-15 | <b>Table S5</b> SNP schizophrenia and SNP serum UA associations (per effect allele) of the instruments of schizophrenia before data harmonization          |
| Page 16-19 | <b>Table S6</b> SNP schizophrenia and SNP serum UA associations (per effect allele) of the instruments of schizophrenia after data harmonization           |
| Page 20    | <b>Table S7</b> Power (two-sided $\alpha = 0.05$ ) for Mendelian randomization analysis (SNPs–serum UA–schizophrenia)                                      |

Page 21-23 **Table S8** Summary of the 45 SNPs associated with schizophrenia used as instruments ( $P < 5E-08$ )

Page 24 **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.

Page 25 **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

Page 26 **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

Page 27 **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

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.<sup>1</sup>

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

where  $\beta$  is the effect size (beta coefficient) for a given single nucleotide polymorphism, MAF is the minor allele frequency,  $se(\beta)$  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.<sup>2</sup>

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

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.

60 **Table S1** Association of serum uric acid (UA) single nucleotide polymorphism (SNP) with smoking confounder queried from PhenoScanner V2<sup>3</sup>

| 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 |

61 **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 <sup>e</sup>         | 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 <sup>f</sup>  | -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 <sup>g</sup> | -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 <sup>h</sup> | -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 <sup>f</sup> | -0.072 | 0.007 | T | C | 2.20E-25 | 0.031  | 0.013 | T | C | 0.015    |
| rs478607 <sup>f</sup>  | -0.047 | 0.007 | A | G | 4.40E-11 | -0.031 | 0.015 | A | G | 0.030    |
| rs653178 <sup>i</sup>  | -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 <sup>f</sup> | -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 <sup>f</sup> | -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:** <sup>e</sup>Odds ratios converted to beta coefficient by log transformation. <sup>f</sup>The excluded SNP in the second forward-direction MR (serum UA to

schizophrenia), due to heterogeneities. <sup>g</sup> $P$  value  $< 1 \times 10^{-700}$ . <sup>h</sup>The excluded SNP, for being palindromic. <sup>i</sup>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.

68 **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 <sup>e</sup>         | 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 <sup>f</sup>  | 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 <sup>g</sup> | -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 <sup>h</sup> | 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 <sup>f</sup> | 0.072 | 0.007 | C | T | 2.20E-25 | -0.031 | 0.013 | C | T | 0.015    |
| rs478607 <sup>f</sup>  | 0.047 | 0.007 | G | A | 4.40E-11 | 0.031  | 0.015 | G | A | 0.030    |
| rs653178 <sup>i</sup>  | 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 <sup>f</sup> | 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 <sup>f</sup> | 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:** <sup>e</sup>Odds ratios converted to beta coefficient by log transformation. <sup>f</sup>The excluded SNP in the second forward-direction MR (serum UA to

schizophrenia), due to heterogeneities. <sup>g</sup> $P$  value  $< 1 \times 10^{-700}$ . <sup>h</sup>The excluded SNP, for being palindromic. <sup>i</sup>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<sup>3,4</sup>

| 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 |
| <b>SNP</b> | <b>Disease/trait</b>                                                   | <b>OR or BETA</b> | <b>95% CI (TEXT)</b>           | <b>P-value</b> | <b>Ancestry</b> | <b>PMID</b> | <b>Database</b> |
| rs11210892 | Smoking status (ever vs never smokers)                                 | 0.016             | 0.011-0.020<br>(unit decrease) | 4.00E-13       | European        | 30643258    | GWAS Catalog    |

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

76 **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 <sup>e</sup>         | 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 <sup>f</sup> | -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 <sup>g</sup> | 0.066                       | 0.011 | A  | T  | 3.61E-09 | -0.006                 | 0.006 | A  | T  | 0.318     |
| rs11210892 <sup>h</sup> | -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 <sup>g</sup> | -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 <sup>g</sup> | 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 <sup>g</sup>  | 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 <sup>g</sup> | -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 <sup>g</sup> | -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 <sup>h</sup> | 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 <sup>g</sup> | -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:** <sup>e</sup>Odds ratios converted to beta coefficient by log transformation. <sup>f</sup>The excluded SNP in the second reverse-direction MR (schizophrenia to serum UA), due to heterogeneities. <sup>g</sup>The excluded SNP, for being palindromic. <sup>h</sup>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 <sup>e</sup>         | 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 <sup>f</sup> | 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 <sup>g</sup> | 0.066                       | 0.011 | A  | T  | 3.61E-09 | -0.006                  | 0.006 | A  | T  | 0.318    |
| rs11210892 <sup>h</sup> | 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 <sup>g</sup> | 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 <sup>g</sup> | 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 <sup>g</sup>  | 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 <sup>g</sup> | 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 <sup>g</sup> | 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 <sup>h</sup> | 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 <sup>g</sup> | 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:** <sup>e</sup>Odds ratios converted to beta coefficient by log transformation. <sup>f</sup>The excluded SNP in the second reverse-direction MR (schizophrenia to serum UA), due to heterogeneities. <sup>g</sup>The excluded SNP, for being palindromic. <sup>h</sup>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.

86 **Table S7** Power (two-sided  $\alpha = 0.05$ ) for Mendelian randomization analysis (SNPs–serum UA–schizophrenia)

| Exposure | Actual <i>N</i><br>(Schizophrenia-<br>GWAS) | Proportion of<br>cases<br>(Schizophrenia-<br>GWAS) | Observational OR  | <i>R</i> <sup>2</sup> of instrument | <i>N</i> required for<br>80% power | Power at actual<br><i>N</i> |
|----------|---------------------------------------------|----------------------------------------------------|-------------------|-------------------------------------|------------------------------------|-----------------------------|
| serum UA | 150,064                                     | 0.25                                               | 0.72 <sup>i</sup> | 0.07 <sup>k</sup>                   | 6486                               | 100%                        |
| serum UA | 150,064                                     | 0.25                                               | 0.37 <sup>i</sup> | 0.07 <sup>k</sup>                   | 958                                | 100%                        |

87 **Notes:** Power was calculated using the online tool mRnd.<sup>5</sup>

88 <sup>i</sup>From chronic schizophrenia.<sup>6</sup> <sup>j</sup>From first episode schizophrenia.<sup>6</sup> <sup>k</sup>From Global Urate Genetics Consortium GWAS.<sup>7</sup>

89 **Abbreviations:** UA, uric acid; *R*<sup>2</sup>, variation explanation of instrument; *N*, sample size.

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

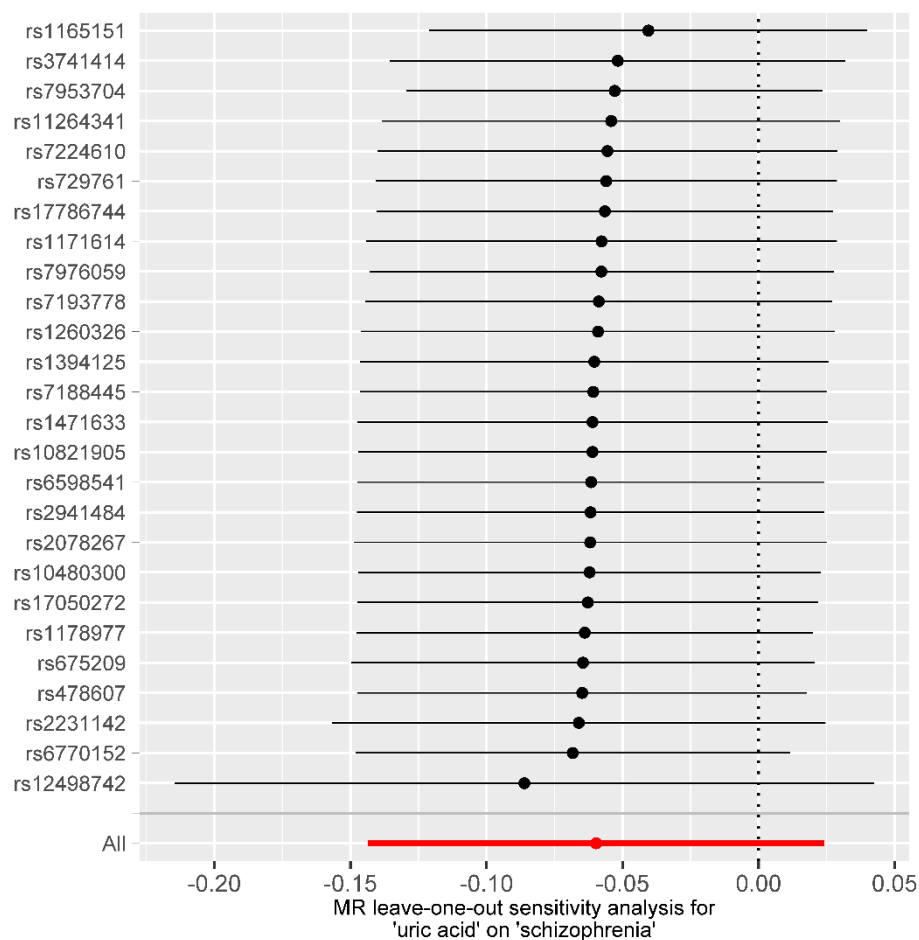
| SNP                     | Chr | Position | Effect <sup>e</sup> | SE    | EA | OA | EAF   | P-value  | N      | MAF   | R <sup>2</sup> | F     |
|-------------------------|-----|----------|---------------------|-------|----|----|-------|----------|--------|-------|----------------|-------|
| rs1023500               | 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 <sup>f</sup> | 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 |

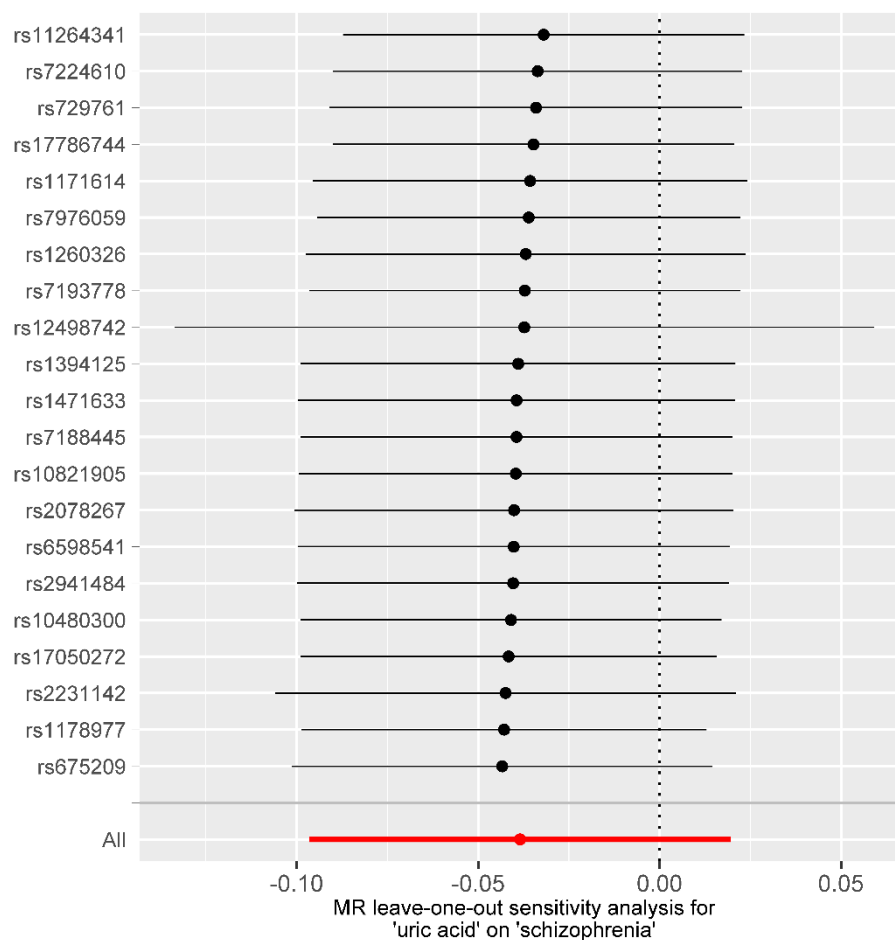
**Notes:** <sup>e</sup>Odds ratios converted to beta coefficient by log transformation. <sup>f</sup>The excluded SNP in the second reverse-direction MR (schizophrenia to serum UA), due to heterogeneities.

**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*<sup>2</sup>, the proportion of variance in schizophrenia.



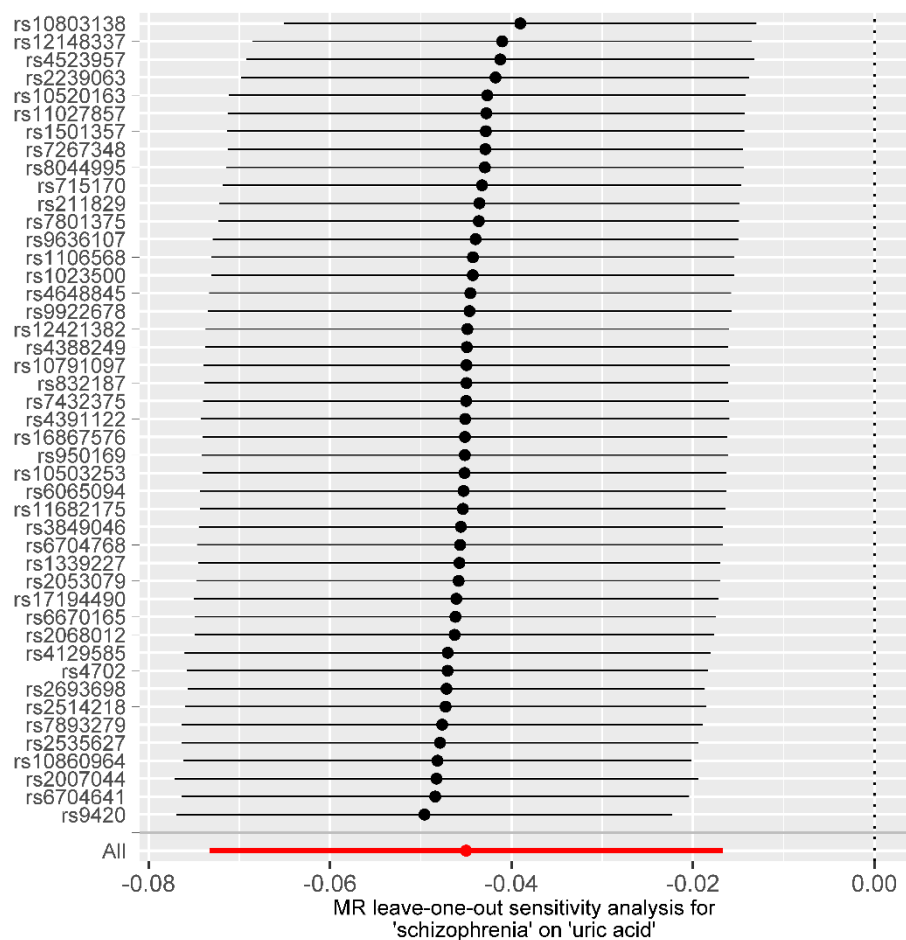
**Figure S1** Leave-one-out analysis depicting uric acid (UA) (before removal of the 5 single nucleotide polymorphisms (SNPs) with potential pleiotropic effects)-to-schizophrenia Mendelian randomization (MR) results (inverse variance weighted (IVW) method) after excluding each of the genetic variants 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.



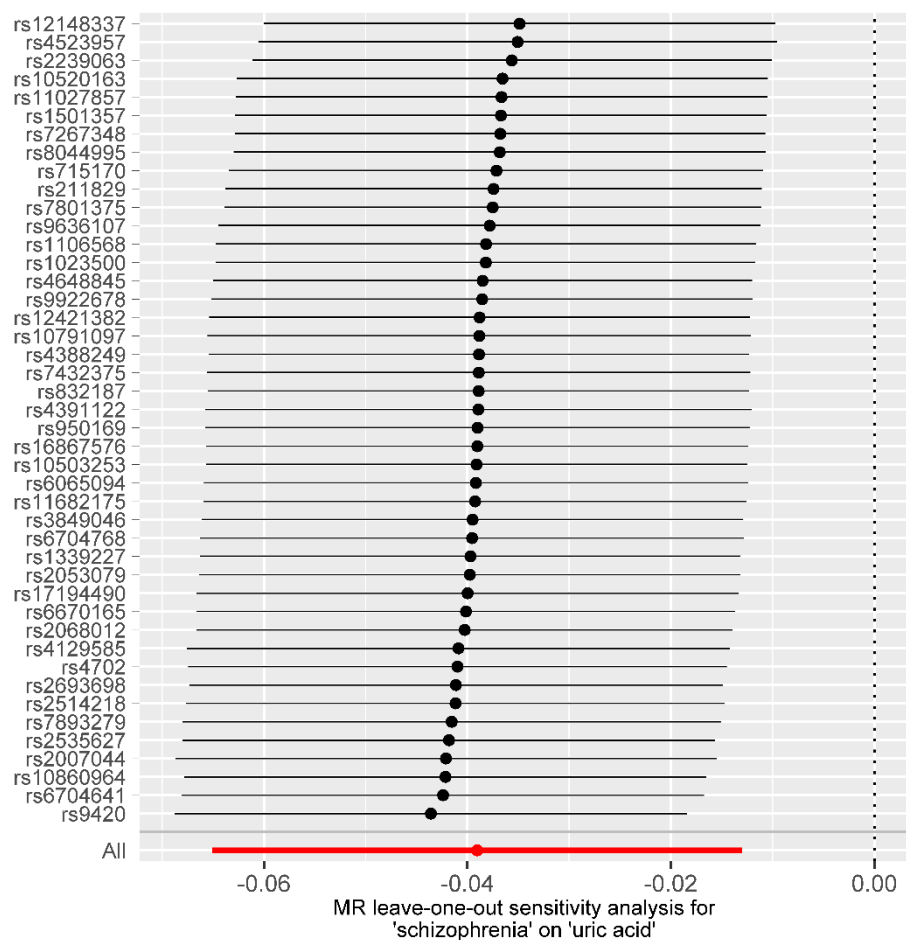
**Figure S2** Leave-one-out analysis depicting serum UA (after removal of the 5 SNPs with potential pleiotropic effects)-to-schizophrenia MR results (IVW method) after excluding each of the genetic variants from the analysis one at a time. We could determine whether the overall effect is driven by one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

## References

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