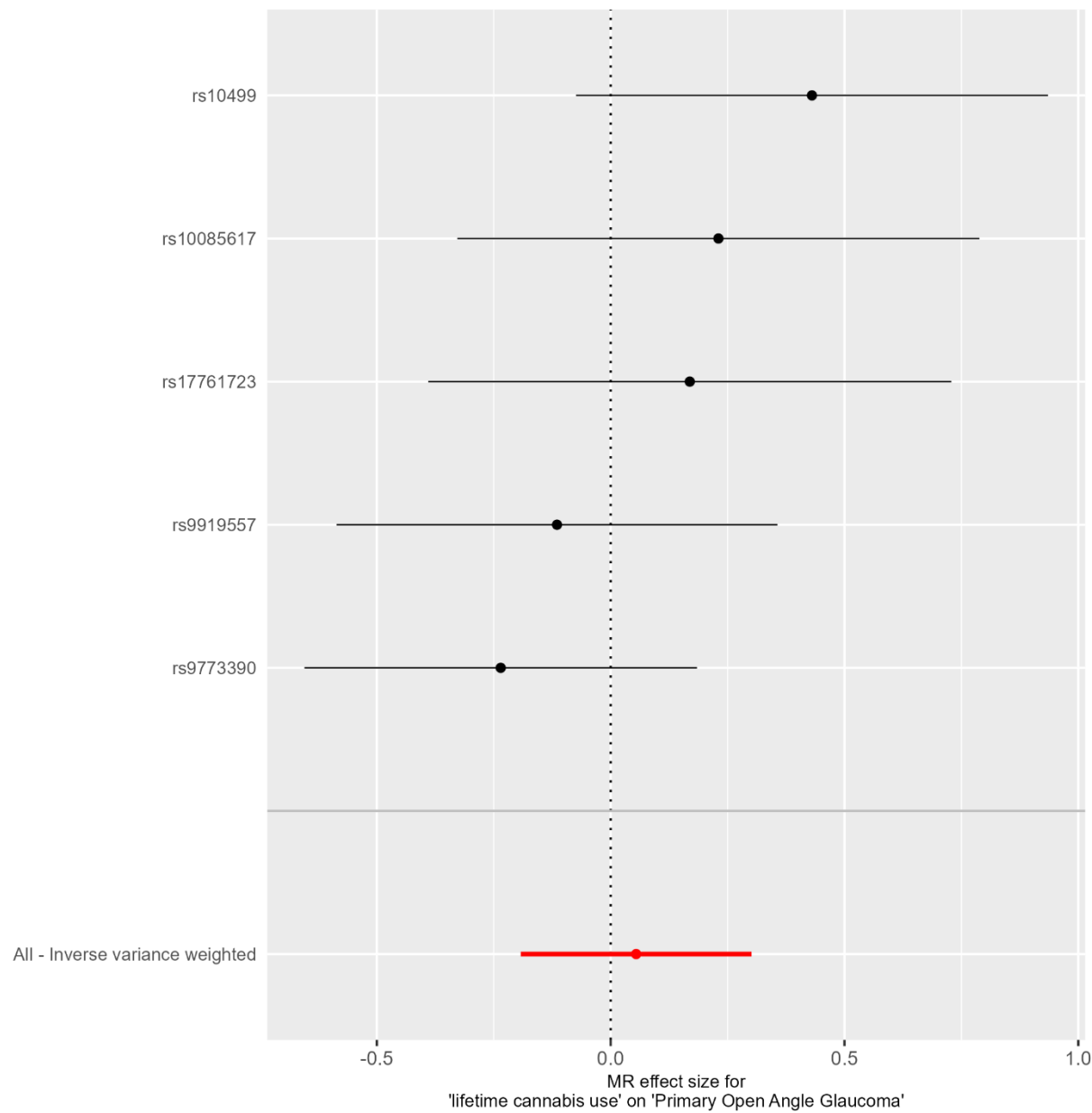


# **Cannabis use and the risk of primary open-angle glaucoma: a two-sample Mendelian randomization study**

**Authors:** Andreas Katsimpris, Sebastian-Edgar Baumeister, Hansjörg Baurecht, Andrew J Tatham, Michael Nolde

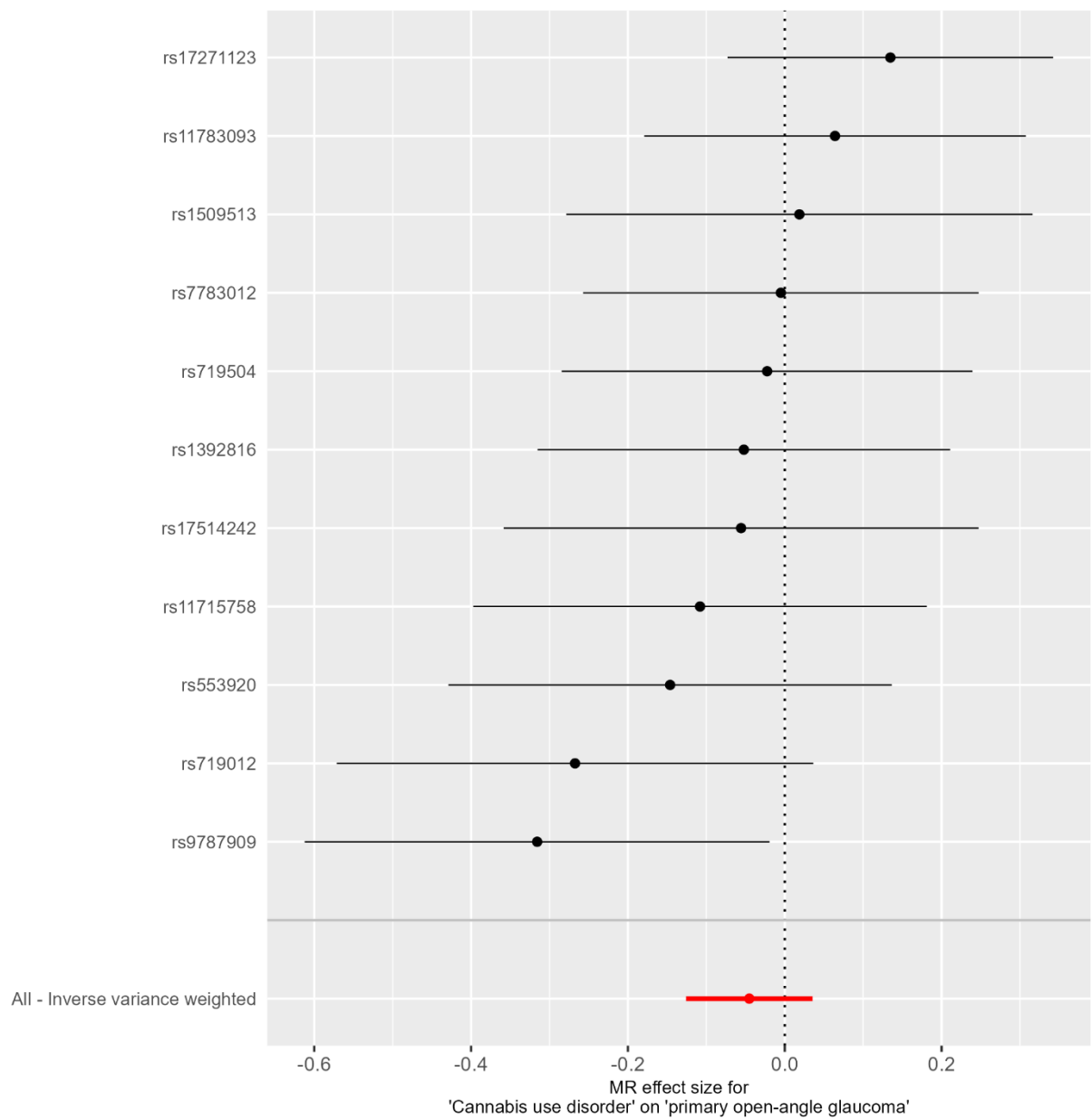
[Supplementary Figures and Tables](#)

**Supplementary Figure S1** Funnel plot of single SNP Wald ratio estimates for the effect of lifetime cannabis use on primary open-angle glaucoma



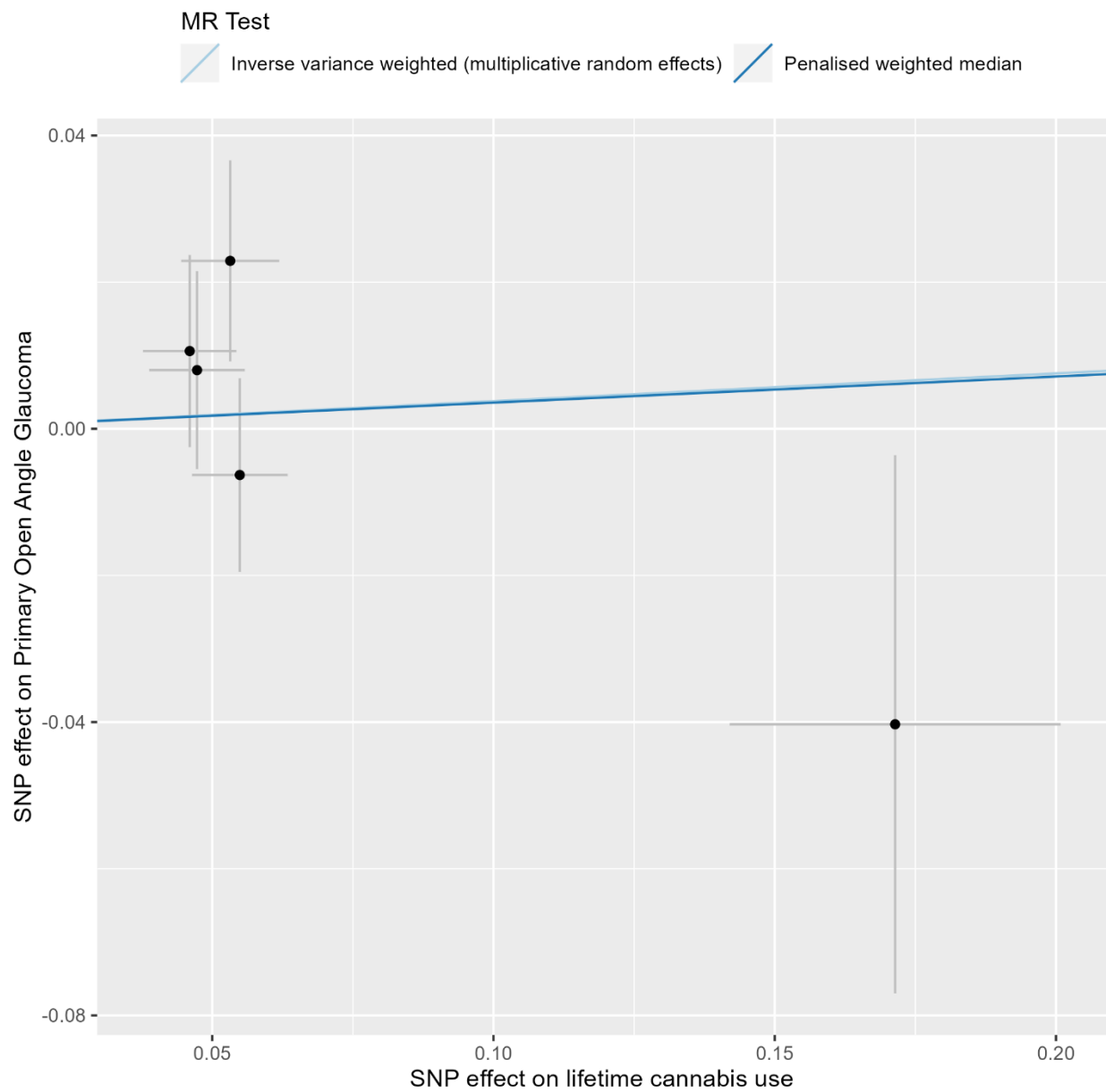
SNP: single-nucleotide polymorphism

**Supplementary Figure S2** Funnel plot of single SNP Wald ratio estimates for the effect of cannabis use disorder on primary open-angle glaucoma



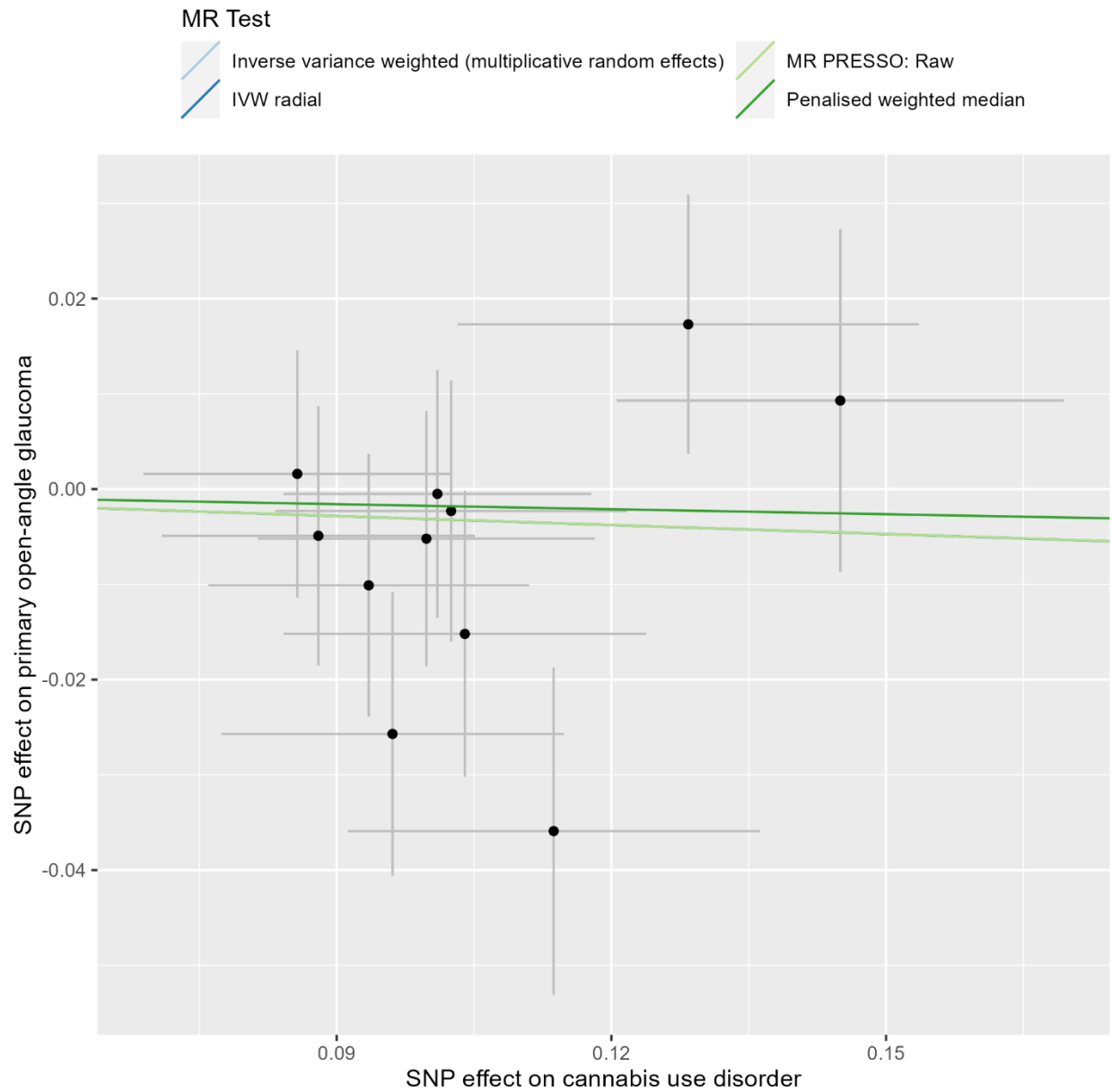
SNP, single-nucleotide polymorphism

**Supplementary Figure S3** Scatter plot of SNP-primary open-angle glaucoma associations vs SNP-lifetime cannabis use associations



SNP: single-nucleotide polymorphism

**Supplementary Figure S4** Scatter plot of SNP-primary open-angle glaucoma associations vs SNP-cannabis use disorder associations



SNP: single-nucleotide polymorphism

**Supplementary Table S1** Phenotypic descriptive statistics of studies included in the exposure, confounder/outcome risk factor, and outcome genome-wide association studies

| GWAS / Study                  | Phenotype                   |            |                           |                              |
|-------------------------------|-----------------------------|------------|---------------------------|------------------------------|
| (Gharahkhani et al., 2021)    | Primary open angle glaucoma |            |                           |                              |
|                               | N cases                     | N controls | Age (mean $\pm$ SD) cases | Age (mean $\pm$ SD) controls |
| NEIGHBOR/MEEI                 | 2606                        | 2606       | 65.7 $\pm$ 13.4           | 68.3 $\pm$ 11.4              |
| EPIC-Norfolk Eye Study        | 664                         | 5630       | 61.5 $\pm$ 7.9            | 55.6 $\pm$ 7.9               |
| ANZRAG                        | 3071                        | 6750       | NA                        | NA                           |
| UKBB POAG ICD10 code          | 1448                        | 22107      | 62.67 $\pm$ 5.6           | 56.36 $\pm$ 7.9              |
| Kaiser Permanente GERA Cohort | 3819                        | 47961      | 79.6 $\pm$ 9.4            | 69.7 $\pm$ 13.0              |
| KCL                           | 576                         | 287        | 70.5 $\pm$ 13.5           | 80.3 $\pm$ 4.3               |
| BMES                          | 107                         | 600        | 68.9 $\pm$ 7.9            | 63.8 $\pm$ 8.3               |
| Southampton                   | 941                         | 1557       | >40                       | >40                          |
| GHS                           | 47                          | 2731       | 62.21 $\pm$ 10.63         | 55.66 $\pm$ 10.86            |
| HPFS illumina                 | 116                         | 527        | 58.3 $\pm$ 8.4            | 51.5 $\pm$ 8.0               |
| HPFS Affy                     | 34                          | 1297       | 58.7 $\pm$ 8.0            | 52.8 $\pm$ 7.9               |
| NHS illumina                  | 266                         | 1692       | 55.8 $\pm$ 6.4            | 53.2 $\pm$ 6.5               |
| NHS Affy                      | 46                          | 1992       | 55.7 $\pm$ 6.0            | 53.0 $\pm$ 6.7               |
| ERF                           | 110                         | 1999       | NA                        | NA                           |
| Rotterdam Study I             | 198                         | 1282       | NA                        | NA                           |
| FINNGEN                       | 1824                        | 93036      | 65.6 $\pm$ 11.9           | 57.8 $\pm$ 16.1              |
| Geisinger 60K                 | 664                         | 5904       | >18                       | >18                          |
| Geisinger 30K                 | 140                         | 1622       | >18                       | >18                          |
| (Pasman et al., 2018)         | Lifetime cannabis use       |            |                           |                              |
|                               | N                           | Female (%) | Age (Mean)                | Cannabis users (%)           |
| ALSPAC                        | 2,976                       | 55.7       | 17.75                     | 41.6                         |
| BLTS                          | 721                         | 57.1       | 26.2                      | 59.5                         |
| CADD                          | 853                         | 30.2       | 24.9                      | 79.3                         |
| EGCUT1                        | 2,765                       | 54.5       | 33.8                      | 1.3                          |
| EGCUT2                        | 970                         | 51.2       | 31.1                      | 4.8                          |
| FinnTwin                      | 1,029                       | 51.7       | 22.8                      | 27.4                         |

|                        |                       |          |       |       |
|------------------------|-----------------------|----------|-------|-------|
| HUVH                   | 981                   | 29.8     | 35.6  | 20.1  |
| MCTFR                  | 6,241                 | 53.5     | 37.2  | 59.3  |
| NTR                    | 4,653                 | 66.2     | 36.9  | 26.9  |
| QIMR                   | 6,778                 | 53.8     | 45.2  | 51.4  |
| TRAILS                 | 1,226                 | 46.9     | 19.0  | 50.5  |
| Utrecht                | 1,173                 | 53.5     | 20.6  | 54.1  |
| Yale Penn EA           | 1,964                 | 40.2     | 38.2  | 91.6  |
| Radar                  | 338                   | 44.4     | 19.54 | 58.8  |
| SYS                    | 551                   | 56       | 49.52 | 52.45 |
| TwinsUK                | 2,070                 | 92.6     | 57.7  | 11.7  |
| Yale Penn AA           | 2,660                 | 46.4     | 41.6  | 81.8  |
| 23andme                | 22,683                | 55.3     | 54    | 43.2  |
| UKB                    | 126,785               | 56.3     | 55    | 22.3  |
| <hr/>                  |                       |          |       |       |
| (Johnson et al., 2020) | Cannabis use disorder |          |       |       |
|                        | Cases                 | Controls |       |       |
| CATS                   | 958                   | 453      |       |       |
| CADD                   | 397                   | 699      |       |       |
| CHDS                   | 201                   | 420      |       |       |
| FSCD                   | 226                   | 314      |       |       |
| COGENE Nico            | 306                   | 607      |       |       |
| COGENE SAGE            | 228                   | 830      |       |       |
| GEDIGSMS               | 81                    | 491      |       |       |
| BLTS                   | 170                   | 1216     |       |       |
| MCTFR                  | 449                   | 1625     |       |       |
| Yale Penn 1            | 916                   | 833      |       |       |
| Yale Penn 2            | 557                   | 497      |       |       |
| bigCOGA                | 2206                  | 5053     |       |       |
| CEDAR                  | 64                    | 148      |       |       |
| OZ-ALC                 | 593                   | 4893     |       |       |
| VTSABD                 | 99                    | 734      |       |       |
| IASPSAD                | 104                   | 613      |       |       |

|                      |                 |                     |            |
|----------------------|-----------------|---------------------|------------|
| Add health           | 722             | 4071                |            |
| iPSYCH               | 2758            | 53326               |            |
| deCODE               | 6033            | 280396              |            |
| <hr/>                |                 |                     |            |
| (Pulit et al., 2019) | Body mass index |                     |            |
|                      | N               | BMI (Mean $\pm$ SD) | Female (%) |
| <hr/>                |                 |                     |            |
| UKB + GIANT          | 806,834         | 27.4 (4.8)          | 54         |
| <hr/>                |                 |                     |            |

**Supplementary Table S2** Associations of single nucleotide polymorphisms for lifetime cannabis use and cannabis use disorder

| SNP                   | Estimates for exposure |    |       |        |       |         | Estimates for primary open angle glaucoma |        |       |       |
|-----------------------|------------------------|----|-------|--------|-------|---------|-------------------------------------------|--------|-------|-------|
|                       | EA                     | OA | EAF   | BETA   | SE    | P       | F                                         | BETA   | SE    | P     |
| Lifetime cannabis use |                        |    |       |        |       |         |                                           |        |       |       |
| rs10085617            | A                      | T  | 0.416 | 0.046  | 0.008 | 2.9e-08 | 30.7                                      | 0.011  | 0.013 | 0.209 |
| rs10499               | A                      | G  | 0.651 | 0.053  | 0.009 | 1.1e-09 | 37.4                                      | 0.023  | 0.014 | 0.047 |
| rs17761723            | T                      | C  | 0.346 | 0.047  | 0.009 | 3.2e-08 | 31.0                                      | 0.008  | 0.014 | 0.277 |
| rs9773390             | T                      | C  | 0.933 | -0.171 | 0.029 | 5.7e-09 | 34.0                                      | 0.040  | 0.037 | 0.136 |
| rs9919557             | T                      | C  | 0.614 | -0.055 | 0.009 | 9.9e-11 | 41.7                                      | 0.006  | 0.013 | 0.317 |
| Cannabis use disorder |                        |    |       |        |       |         |                                           |        |       |       |
| rs11715758            | A                      | G  | 0.622 | -0.094 | 0.018 | 8.9e-08 | 28.5                                      | 0.010  | 0.014 | 0.232 |
| rs11783093            | T                      | C  | 0.846 | -0.145 | 0.024 | 2.7e-09 | 35.3                                      | -0.009 | 0.018 | 0.303 |
| rs1392816             | T                      | C  | 0.624 | -0.100 | 0.018 | 6.1e-08 | 29.4                                      | 0.005  | 0.013 | 0.349 |
| rs1509513             | A                      | G  | 0.546 | 0.086  | 0.017 | 3.2e-07 | 26.0                                      | 0.002  | 0.013 | 0.451 |
| rs17271123            | T                      | G  | 0.587 | 0.128  | 0.025 | 3.5e-07 | 26.0                                      | 0.017  | 0.014 | 0.102 |
| rs17514242            | C                      | G  | 0.649 | -0.088 | 0.017 | 2.6e-07 | 26.5                                      | 0.005  | 0.014 | 0.359 |
| rs553920              | T                      | C  | 0.770 | 0.104  | 0.020 | 1.6e-07 | 27.6                                      | -0.015 | 0.015 | 0.155 |
| rs719012              | T                      | C  | 0.264 | 0.096  | 0.019 | 2.9e-07 | 26.4                                      | -0.026 | 0.015 | 0.042 |
| rs719504              | A                      | G  | 0.650 | 0.102  | 0.019 | 9.0e-08 | 28.5                                      | -0.002 | 0.014 | 0.433 |
| rs7783012             | A                      | G  | 0.476 | 0.101  | 0.017 | 1.8e-09 | 36.1                                      | 0.000  | 0.013 | 0.485 |
| rs9787909             | A                      | C  | 0.829 | 0.114  | 0.022 | 4.5e-07 | 25.5                                      | -0.036 | 0.017 | 0.018 |

EA, effect allele. OA, other allele. EAF, effect allele frequency. SE, standard error.

**Supplementary Table S3** Association ( $P < 5 \times 10^{-8}$ ) of the single nucleotide polymorphisms used as instruments with confounders or outcome risk factors in PhenoScanner (accessed on 2022/11/20 using the phenoscanner function of the R MendelianRandomization package)

| SNP                   | Phenotypes                                 | PMID     |
|-----------------------|--------------------------------------------|----------|
| Lifetime cannabis use |                                            |          |
| rs10499               | Mean corpuscular volume                    | 27863252 |
| rs10499               | Red blood cell count                       | 27863252 |
| rs10499               | Hip circumference                          | 25673412 |
| rs10499               | Waist circumference                        | 25673412 |
| rs10499               | Crohns disease                             | 26192919 |
| Cannabis use disorder |                                            |          |
| rs11715758            | High light scatter percentage of red cells | 27863252 |
| rs11715758            | High light scatter reticulocyte count      | 27863252 |
| rs11715758            | Immature fraction of reticulocytes         | 27863252 |
| rs11715758            | Reticulocyte count                         | 27863252 |
| rs11715758            | Reticulocyte fraction of red cells         | 27863252 |
| rs7783012             | Years of educational attainment            | 27225129 |
| rs7783012             | Age first birth                            | 27798627 |

PMID, PubMed ID. Body mass index was considered as a relevant confounder or risk factor for primary open angle glaucoma.

**Supplementary Table S4** Heterogeneity of Wald ratios and MR-Egger test for directional pleiotropy

| Lifetime cannabis use                    |            | Heterogeneity      |       |                               |
|------------------------------------------|------------|--------------------|-------|-------------------------------|
|                                          | Q          | Degrees of Freedom | P     | I <sub>G</sub> X <sup>2</sup> |
| Lifetime cannabis use                    | 2.8        | 4                  | 0.592 | 0.1                           |
| Cannabis use disorder                    | 9.9        | 10                 | 0.45  | 0.036                         |
| MR-Egger test for directional pleiotropy |            |                    |       |                               |
|                                          | Intercept  | Standard error     | P     |                               |
| Lifetime cannabis use                    | 2.927e-02  | 0.018              | 0.197 |                               |
| Cannabis use disorder                    | -3.637e-02 | 0.029              | 0.239 |                               |

**Supplementary Table S5** Inverse variance weighted estimates in leave-one-out analysis in primary analysis

| SNP excluded          | SNP        | OR   | (95% CI)    | P value |
|-----------------------|------------|------|-------------|---------|
| Lifetime cannabis use | rs10085617 | 1.02 | (0.83;1.25) | 0.885   |
|                       | rs10499    | 0.98 | (0.84;1.14) | 0.757   |
|                       | rs17761723 | 1.02 | (0.83;1.26) | 0.830   |
|                       | rs9773390  | 1.12 | (0.95;1.32) | 0.169   |
|                       | rs9919557  | 1.07 | (0.87;1.32) | 0.507   |
| Cannabis use disorder | rs11715758 | 0.97 | (0.92;1.03) | 0.369   |
|                       | rs11783093 | 0.96 | (0.9;1.02)  | 0.179   |
|                       | rs1392816  | 0.97 | (0.91;1.03) | 0.326   |
|                       | rs1509513  | 0.97 | (0.91;1.03) | 0.257   |
|                       | rs17271123 | 0.95 | (0.9;1)     | 0.042   |
|                       | rs17514242 | 0.97 | (0.91;1.03) | 0.321   |
|                       | rs553920   | 0.98 | (0.92;1.03) | 0.408   |
|                       | rs719012   | 0.98 | (0.93;1.03) | 0.472   |
|                       | rs719504   | 0.97 | (0.91;1.03) | 0.293   |
|                       | rs7783012  | 0.97 | (0.91;1.03) | 0.272   |
|                       | rs9787909  | 0.98 | (0.94;1.03) | 0.514   |

## References

- Gharahkhani, P., Jorgenson, E., Hysi, P., Khawaja, A. P., Pendergrass, S., Han, X., . . . FinnGen, s. (2021). Genome-wide meta-analysis identifies 127 open-angle glaucoma loci with consistent effect across ancestries. *Nature Communications*, 12(1), 1258. doi:10.1038/s41467-020-20851-4
- Johnson, E. C., Demontis, D., Thorgeirsson, T. E., Walters, R. K., Polimanti, R., Hatoum, A. S., . . . Agrawal, A. (2020). A large-scale genome-wide association study meta-analysis of cannabis use disorder. *Lancet Psychiatry*, 7(12), 1032-1045. doi:10.1016/s2215-0366(20)30339-4
- Pasman, J. A., Verweij, K. J. H., Gerring, Z., Stringer, S., Sanchez-Roige, S., Treur, J. L., . . . International Cannabis, C. (2018). GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal effect of schizophrenia liability. *Nature Neuroscience*, 21(9), 1161-1170. doi:10.1038/s41593-018-0206-1
- Pulit, S. L., Stoneman, C., Morris, A. P., Wood, A. R., Glastonbury, C. A., Tyrrell, J., . . . Lindgren, C. M. (2019). Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Human Molecular Genetics*, 28(1), 166-174. doi:10.1093/hmg/ddy327