**Depression and risk of gastrointestinal disorders: a comprehensive two-sample Mendelian randomization study**

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# Supplementary Method

## Univariable Mendelian randomization

Under the instrument strength independent of direct effect (InSIDE) assumption that the association of IVs with exposure is independent of the direct effect, MR-Egger's test gives consistent estimates of the causal effect. Furthermore, estimates of intercept in MR-Egger regression can be used to evaluate the directional pleiotropy of IVs(Bowden, Davey Smith, & Burgess, 2015). The simple median method gives a consistent estimate of the causal effect when at least 50% of the genetic variants are valid instrumental variables(Bowden, Davey Smith, Haycock, & Burgess, 2016). The weighted median approach provides consistent and robust estimates even if more than 50% of the IVs are invalid(Bowden et al., 2016). We performed weighted mode MR which provides an effect estimate based on the assumption that the most common effect of the genetic variants stems from valid instruments(Hartwig, Davey Smith, & Bowden, 2017). MR-RAPS offer robust effect estimates with weak instrumental bias(Qingyuan Zhao, Jingshu Wang, Gibran Hemani, Jack Bowden, & Dylan S Small, 2020). MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) is mainly used to detect outlier IVs (*P* < 0.05) for removal to correct potential directional horizontal pleiotropy and resolve detected heterogeneity(Verbanck, Chen, Neale, & Do, 2018).

## Sensitivity analyses

As a sensitivity analysis and to test for potential violations of the relevance assumption, we calcu­lated F-statistics and the R2 for MDD. Other sensitivity analyses included MR-Egger(Bowden et al., 2015), simple median(Bowden et al., 2016), weighted median(Bowden et al., 2016), weighted mode(Hartwig et al., 2017), MR-RAPS(Qingyuan Zhao, Jingshu Wang, Gibran Hemani, Jack Bowden, & Dylan S. Small, 2020), Mendelian randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO)(Verbanck et al., 2018) methods, which are robust to some of the assumptions of the IVW approach (described in **Supplementary Method**). These results were also pooled across studies, as explained above. Consistency across different MR methods would indicate that the independence and exclusion restriction assumptions are less likely to be broken.

We further assessed the validity of the independence assumption by conducting MR analyses using negative control outcomes (i.e. skin color, ease of skin tanning). Evidence of association between MDD and these negative control outcomes would imply possible bias related to population stratification that has not been adequately accounted for by GWAS adjustments(Sanderson, Richardson, Hemani, & Davey Smith, 2021). We also assessed the genetically predicted association of MDD on GID risk factors (i.e. body mass index, waist circumference, pack years of smoking, time spent doing vigorous physical activity, C-reactive protein level, years of schooling, alcohol intake frequency, household income, and Townsend deprivation index) to detect poten­tial violations of the exclusion restriction assumption. GWAS data for negative control outcomes and GID risk factors were obtained using the University of Bristol’s IEU OpenGWAS API. Furthermore, we searched the GWAS catalog and PhenoScanner to exclude IVs with genome-wide significance for GID or potential confounding traits (***Table S5***) and re-ran the MR to detect poten­tial violations of the independence assumption.

Where associations between genetically predicted MDD and GID were identified, we additionally produced informative plots to illustrate the results. Scatter plots visualize SNP-outcome associations against SNP-exposure associations that can provide an immediate picture of the causal effect estimates of different MR methods. Forest plots are primarily used to assess the presence of heterogeneity in IVs. Funnel plots allow a visual assessment of the degree of pleiotropy balance of the instruments used, with symmetry providing evidence against directional pleiotropy. The leave-one-out plots were produced to assess whether the effects were likely to be driven by a single SNP. Additionally, Cochran’s Q statistics and I square were used to quantifying global heterogeneity across SNP-specific MR estimates(Bowden et al., 2019) and MR-Egger intercept tests were performed to detect horizontal pleiotropy(Bowden et al., 2015). We also used Causal Analysis using Summary Effect Estimates (CAUSE) (Morrison, Knoblauch, Marcus, Stephens, & He, 2020), a method that uses genome-wide summary statistics to disentangle causality from correlated horizontal pleiotropy (i.e. SNPs are associated with MDD and GID through a shared heritable factor), while taking into account uncorrelated horizontal pleiotropy (i.e. SNPs are associated with MDD through separate mechanisms).

## Secondary analyses

As a secondary analysis, linkage disequilibrium score regression (LDSC)(Bulik-Sullivan et al., 2015) was used to identify genome-wide genetic correla­tions between MDD and GID. Genetic correlations were estimated using full GWAS summary statistics for the MDD and GID, as well as the 1000 Genomes Project European LD reference panel. Additionally, reversed MR analyses were conducted to assess the causality and directionality of the link between GID and MDD.

Finally, MDD and GID share several risk factors, including but not limited to obesity(Emerenziani et al., 2019), diabetes(Verne & Sninsky, 1998) and insomnia(Ali, Choe, Awab, Wagener, & Orr, 2013). In order to address the potential confounding/mediating factors may interfere with this association, we performed an IVW-MVMR to estimate their direct effects on GID independent of body mass index (BMI), type 2 diabetes (T2D) and insomnia(Sanderson, Davey Smith, Windmeijer, & Bowden, 2019; Sanderson, Spiller, & Bowden, 2021).

# Supplementary Results

## Gastroesophageal reflux disease

Leave-one-out analysis revealed that the effect was not driven by a single SNP (***Figure S1***). ***Figure S1*** shows the effect of genetic instruments on MDD against their effect on GERD. Moreover, there was no detectable evidence of uncorrelated horizontal pleiotropy (MR-Egger intercept = -0.0027, p = 0.767; ***Table S6***), but with moderate heterogeneity across indi­vidual SNP estimates (Cochran’s Q = 66.11, p = 0.0043, I square=0.41; ***Table S6***).

## Irritable bowel syndrome

Leave-one-out analysis revealed that the effect was not driven by a single SNP (***Figure S1***). ***Figure S1*** shows the effect of genetic instruments on MDD against their effect on IBS. Moreover, there was no detectable evidence of uncorrelated horizontal pleiotropy (MR-Egger intercept = -0.0064, p = 0.53; ***Table S6***), but with moderate heterogeneity across indi­vidual SNP estimates (Cochran’s Q = 73.45, p = 0.0014, I square=0.442; ***Table S6***).

## Peptic ulcer disease

Leave-one-out analysis revealed that the effect was not driven by a single SNP (***Figure S1***). ***Figure S1*** shows the effect of genetic instruments on MDD against their effect on PUD. Moreover, there was no detectable evidence of uncorrelated horizontal pleiotropy (MR-Egger intercept = -0.0043, p = 0.747; ***Table S6***), but with low heterogeneity across indi­vidual SNP estimates (Cochran’s Q = 46.26 , p = 0.264, I square = 0.114; ***Table S6***).

## Non-alcoholic fatty liver disease

Leave-one-out analysis revealed that the effect was not driven by a single SNP (***Figure S1***). ***Figure S1*** shows the effect of genetic instruments on MDD against their effect on NAFLD. Moreover, there was no detectable evidence of uncorrelated horizontal pleiotropy (MR-Egger intercept = -0.0112, p = 0.551; ***Table S6***), but with low heterogeneity across indi­vidual SNP estimates (Cochran’s Q = 45.61, p = 0.2863, I square = 0.101; ***Table S6***).

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# Supplementary Table

## Table S1. List of instrucment variables used for major depressive disorder

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | A1 | A2 | BETA | SE | P | N | Trait | EAF | R2 | F |
| rs8025231 | A | C | -0.0339 | 0.0048 | 2.36E-12 | 480359 | MDD | 0.57 | 0.000563 | 270.7279 |
| rs1432639 | A | C | 0.039 | 0.005 | 4.55E-15 | 480359 | MDD | 0.63 | 0.000709 | 340.85 |
| rs1806153 | T | G | 0.0361 | 0.0059 | 1.18E-09 | 480359 | MDD | 0.22 | 0.000447 | 214.947 |
| rs4261101 | A | G | -0.0285 | 0.005 | 1.04E-08 | 480359 | MDD | 0.37 | 0.000379 | 181.9963 |
| rs9427672 | A | G | -0.0321 | 0.0058 | 3.12E-08 | 480359 | MDD | 0.24 | 0.000376 | 180.6279 |
| rs34192913 | I | D | 0.0278 | 0.0051 | 4.61E-08 | 480359 | MDD | 0.34 | 0.000347 | 166.6696 |
| rs12129573 | A | C | 0.034498 | 0.005 | 4.01E-12 | 480359 | MDD | 0.37 | 0.000555 | 266.6652 |
| rs7856424 | T | C | -0.0306 | 0.0053 | 8.48E-09 | 480359 | MDD | 0.29 | 0.000386 | 185.3368 |
| rs12552 | A | G | 0.042897 | 0.0048 | 6.07E-19 | 480359 | MDD | 0.44 | 0.000907 | 435.9889 |
| rs11643192 | A | C | 0.027002 | 0.0049 | 3.36E-08 | 480359 | MDD | 0.41 | 0.000353 | 169.5038 |
| rs115507122 | C | G | -0.0418 | 0.0063 | 3.3E-11 | 480359 | MDD | 0.18 | 0.000516 | 247.9084 |
| rs12958048 | A | G | 0.033802 | 0.0051 | 3.61E-11 | 480359 | MDD | 0.33 | 0.000505 | 242.8246 |
| rs5869436 | I | D | -0.0323 | 0.005 | 7.87E-11 | 480359 | MDD | 0.58 | 0.000508 | 244.2239 |
| rs61867293 | T | C | -0.0374 | 0.0061 | 6.97E-10 | 480359 | MDD | 0.2 | 0.000448 | 215.1145 |
| rs915057 | A | G | -0.03 | 0.0049 | 7.61E-10 | 480359 | MDD | 0.42 | 0.000438 | 210.6547 |
| rs11135349 | A | C | -0.0294 | 0.0048 | 1.09E-09 | 480359 | MDD | 0.48 | 0.000431 | 207.3286 |
| rs4904738 | T | C | -0.0289 | 0.0049 | 2.57E-09 | 480359 | MDD | 0.57 | 0.00041 | 196.7989 |
| rs7430565 | A | G | -0.0288 | 0.0048 | 2.87E-09 | 480359 | MDD | 0.58 | 0.000404 | 194.2029 |
| rs10149470 | A | G | -0.029 | 0.0049 | 3.05E-09 | 480359 | MDD | 0.49 | 0.00042 | 201.9435 |
| rs34215985 | C | G | -0.0373 | 0.0063 | 3.13E-09 | 480359 | MDD | 0.24 | 0.000507 | 243.8857 |
| rs200343480 | D | I | 0.028996 | 0.0049 | 3.77E-09 | 480359 | MDD | 0.49 | 0.00042 | 201.932 |
| rs11682175 | T | C | -0.0281 | 0.0048 | 4.68E-09 | 480359 | MDD | 0.52 | 0.000394 | 189.4343 |
| rs10959913 | T | G | 0.033396 | 0.0057 | 5.06E-09 | 480359 | MDD | 0.76 | 0.000407 | 195.5181 |
| rs4869056 | A | G | -0.0287 | 0.005 | 6.8E-09 | 480359 | MDD | 0.63 | 0.000384 | 184.5026 |
| rs8063603 | A | G | -0.0308 | 0.0053 | 6.87E-09 | 480359 | MDD | 0.65 | 0.000432 | 207.4195 |
| rs116755193 | T | C | -0.0292 | 0.005 | 7.01E-09 | 480359 | MDD | 0.38 | 0.000402 | 193.0977 |
| rs5758265 | A | G | 0.031004 | 0.0054 | 7.55E-09 | 480359 | MDD | 0.28 | 0.000388 | 186.251 |
| rs17727765 | T | C | -0.0508 | 0.0088 | 8.51E-09 | 480359 | MDD | 0.92 | 0.00038 | 182.5332 |
| rs7198928 | T | C | 0.028403 | 0.005 | 1E-08 | 480359 | MDD | 0.62 | 0.00038 | 182.6656 |
| rs2389016 | T | C | 0.0305 | 0.0053 | 1.02E-08 | 480359 | MDD | 0.28 | 0.000375 | 180.2396 |
| rs62099069 | A | T | -0.0279 | 0.0049 | 1.31E-08 | 480359 | MDD | 0.42 | 0.000379 | 182.1814 |
| rs12666117 | A | G | 0.027401 | 0.0048 | 1.35E-08 | 480359 | MDD | 0.47 | 0.000374 | 179.7494 |
| rs11663393 | A | G | 0.0278 | 0.0049 | 1.65E-08 | 480359 | MDD | 0.45 | 0.000383 | 183.8334 |
| rs1354115 | A | C | 0.027596 | 0.0049 | 2.37E-08 | 480359 | MDD | 0.62 | 0.000359 | 172.4283 |
| rs1226412 | T | C | 0.033203 | 0.0059 | 2.38E-08 | 480359 | MDD | 0.79 | 0.000366 | 175.77 |
| rs7200826 | T | C | 0.030704 | 0.0055 | 2.43E-08 | 480359 | MDD | 0.25 | 0.000354 | 169.8762 |
| rs4143229 | A | C | -0.0509 | 0.0091 | 2.51E-08 | 480359 | MDD | 0.92 | 0.000381 | 183.2904 |
| rs10950398 | A | G | 0.027498 | 0.0049 | 2.55E-08 | 480359 | MDD | 0.41 | 0.000366 | 175.7942 |
| rs1833288 | A | G | 0.030199 | 0.0054 | 2.63E-08 | 480359 | MDD | 0.72 | 0.000368 | 176.7015 |
| rs7029033 | T | C | 0.051805 | 0.0093 | 2.74E-08 | 480359 | MDD | 0.07 | 0.000349 | 167.9054 |
| rs9402472 | A | G | 0.032699 | 0.0059 | 2.78E-08 | 480359 | MDD | 0.24 | 0.00039 | 187.4436 |
| rs4074723 | A | C | -0.027 | 0.0049 | 3.12E-08 | 480359 | MDD | 0.41 | 0.000353 | 169.493 |
| rs159963 | A | C | -0.027 | 0.0049 | 3.19E-08 | 480359 | MDD | 0.56 | 0.000359 | 172.6472 |
| rs1392816 | T | C | -0.0998 | 0.0184 | 6.14E-08 | 351174 | CUD | 0.3757 | 0.004672 | 1648.464 |
| rs719504 | A | G | 0.1025 | 0.0192 | 9E-08 | 350403 | CUD | 0.3499 | 0.00478 | 1682.86 |
| rs11715758 | A | G | -0.0935 | 0.0175 | 8.91E-08 | 355885 | CUD | 0.3777 | 0.00411 | 1468.574 |
| rs72818514 | T | C | -0.1828 | 0.0342 | 9.33E-08 | 355548 | CUD | 0.0517 | 0.003277 | 1168.799 |
| rs553920 | T | C | 0.104 | 0.0198 | 1.6E-07 | 353969 | CUD | 0.2296 | 0.003826 | 1359.604 |
| rs7783012 | A | G | 0.101 | 0.0168 | 1.84E-09 | 357019 | CUD | 0.5239 | 0.005089 | 1826.097 |
| rs11783093 | T | C | -0.145 | 0.0244 | 2.68E-09 | 355028 | CUD | 0.1541 | 0.005481 | 1956.748 |
| rs719012 | T | C | 0.0961 | 0.0187 | 2.87E-07 | 356928 | CUD | 0.2644 | 0.003592 | 1286.83 |
| rs1509513 | A | G | 0.0857 | 0.0168 | 3.18E-07 | 356900 | CUD | 0.5457 | 0.003642 | 1304.418 |
| rs9787909 | A | C | 0.1137 | 0.0225 | 4.52E-07 | 354449 | CUD | 0.829 | 0.003665 | 1303.91 |
| rs17271123 | T | G | 0.1284 | 0.0252 | 3.54E-07 | 291017 | CUD | 0.4125 | 0.007991 | 2344.183 |
| rs17514242 | C | G | -0.088 | 0.0171 | 2.56E-07 | 357037 | CUD | 0.6491 | 0.003528 | 1263.967 |

\* R2 represents the proportion of the variance in the exposure explained by the genetic variant (SNP). It was calculated by means of the following formula: R2= (2β^2×MAF×(1-MAF))/(2β^2×MAF×(1-MAF)+2N×MAF×(1-MAF)×SE^2 )

\* F represents the strength of the instrument. It was calculated by means of the following formula: F= (R^2×(N-2))/(1-R^2)

## Table S2. Harmonized instruments used in the univariable MR analyses for UKB outcome datasets

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table S2a. Harmonized instruments used in the MR analyses investigating the potential causal effect of genetic predicted major depressive disorder (MDD) on gastroesophageal reflux disease (GERD) | | | | | | | | | |
| SNP | A1 | A2 | EAF | beta.MDD | se.MDD | pval.MDD | beta.GERD | se.GERD | pval.GERD |
| rs10149470 | A | G | 0.49 | -0.028996361 | 0.0049 | 3.05E-09 | 0.0041 | 0.0059 | 0.4909 |
| rs10950398 | A | G | 0.41 | 0.027498429 | 0.0049 | 2.55E-08 | 0.018 | 0.0061 | 0.003014 |
| rs10959913 | T | G | 0.76 | 0.033396091 | 0.0057 | 5.06E-09 | 0.0065 | 0.007 | 0.3541 |
| rs11135349 | A | C | 0.48 | -0.029397915 | 0.0048 | 1.09E-09 | -0.0013 | 0.0059 | 0.8224 |
| rs11643192 | A | C | 0.41 | 0.027002139 | 0.0049 | 3.36E-08 | -0.0008 | 0.0061 | 0.8975 |
| rs11663393 | A | G | 0.45 | 0.027799975 | 0.0049 | 1.65E-08 | 0.0177 | 0.0059 | 0.002734 |
| rs116755193 | T | C | 0.38 | -0.029202266 | 0.005 | 7.01E-09 | 0.0027 | 0.006 | 0.6481 |
| rs11682175 | T | C | 0.52 | -0.028101165 | 0.0048 | 4.68E-09 | -0.0032 | 0.0059 | 0.5929 |
| rs12129573 | A | C | 0.37 | 0.034498041 | 0.005 | 4.01E-12 | 0.0146 | 0.0062 | 0.01798 |
| rs1226412 | T | C | 0.79 | 0.033202641 | 0.0059 | 2.38E-08 | 0.003 | 0.0073 | 0.6809 |
| rs12552 | A | G | 0.44 | 0.042896641 | 0.0048 | 6.07E-19 | 0.0117 | 0.006 | 0.04883 |
| rs12666117 | A | G | 0.47 | 0.027401137 | 0.0048 | 1.35E-08 | 0.0213 | 0.0059 | 0.000328 |
| rs12958048 | A | G | 0.33 | 0.033802214 | 0.0051 | 3.61E-11 | 0.0137 | 0.0063 | 0.02877 |
| rs1354115 | A | C | 0.62 | 0.027595712 | 0.0049 | 2.37E-08 | 0.0079 | 0.0061 | 0.1983 |
| rs1432639 | A | C | 0.63 | 0.038999535 | 0.005 | 4.55E-15 | 0.0115 | 0.006 | 0.05608 |
| rs159963 | A | C | 0.56 | -0.027001276 | 0.0049 | 3.19E-08 | -0.0191 | 0.006 | 0.001442 |
| rs17727765 | T | C | 0.92 | -0.05079868 | 0.0088 | 8.51E-09 | -0.0019 | 0.0111 | 0.8662 |
| rs1806153 | T | G | 0.22 | 0.036100466 | 0.0059 | 1.18E-09 | 0.0295 | 0.007 | 2.50E-05 |
| rs1833288 | A | G | 0.72 | 0.030199374 | 0.0054 | 2.63E-08 | 0.0109 | 0.0067 | 0.1006 |
| rs200343480 | C | CAG | 0.49 | 0.028995537 | 0.0049 | 3.77E-09 | 0.0199 | 0.0061 | 0.001011 |
| rs2389016 | T | C | 0.28 | 0.030500107 | 0.0053 | 1.02E-08 | 0.0204 | 0.0065 | 0.001583 |
| rs34192913 | AT | A | 0.34 | 0.027799975 | 0.0051 | 4.61E-08 | 0.004 | 0.0064 | 0.5293 |
| rs4074723 | A | C | 0.41 | -0.027001276 | 0.0049 | 3.12E-08 | -0.0078 | 0.006 | 0.1908 |
| rs4143229 | A | C | 0.92 | -0.050903897 | 0.0091 | 2.51E-08 | -0.0217 | 0.0116 | 0.06154 |
| rs4261101 | A | G | 0.37 | -0.028502361 | 0.005 | 1.04E-08 | -0.0001 | 0.0061 | 0.9839 |
| rs4869056 | A | G | 0.63 | -0.028697873 | 0.005 | 6.80E-09 | -0.0059 | 0.0061 | 0.3325 |
| rs4904738 | T | C | 0.57 | -0.028903717 | 0.0049 | 2.57E-09 | -0.0151 | 0.006 | 0.01165 |
| rs5758265 | A | G | 0.28 | 0.031004359 | 0.0054 | 7.55E-09 | 0.0156 | 0.0065 | 0.01702 |
| rs5869436 | TA | T | 0.58 | -0.032295945 | 0.005 | 7.87E-11 | -0.0027 | 0.0062 | 0.6583 |
| rs61867293 | T | C | 0.2 | -0.037400771 | 0.0061 | 6.97E-10 | -0.0075 | 0.0075 | 0.3162 |
| rs7029033 | T | C | 0.07 | 0.051804664 | 0.0093 | 2.74E-08 | 0.0182 | 0.0118 | 0.1227 |
| rs7198928 | T | C | 0.62 | 0.028402795 | 0.005 | 1.00E-08 | -0.0069 | 0.0061 | 0.2552 |
| rs7200826 | T | C | 0.25 | 0.030703778 | 0.0055 | 2.43E-08 | -0.0002 | 0.0067 | 0.9807 |
| rs7430565 | A | G | 0.58 | -0.02880079 | 0.0048 | 2.87E-09 | -0.0006 | 0.006 | 0.9258 |
| rs7856424 | T | C | 0.29 | -0.030603548 | 0.0053 | 8.48E-09 | -0.0077 | 0.0065 | 0.2386 |
| rs8025231 | A | C | 0.57 | -0.033898104 | 0.0048 | 2.36E-12 | -0.0156 | 0.0059 | 0.008268 |
| rs8063603 | A | G | 0.65 | -0.030799472 | 0.0053 | 6.87E-09 | -0.0016 | 0.0064 | 0.7985 |
| rs915057 | A | G | 0.42 | -0.029995398 | 0.0049 | 7.61E-10 | -0.0018 | 0.006 | 0.7654 |
| rs9402472 | A | G | 0.24 | 0.032699497 | 0.0059 | 2.78E-08 | 0.0137 | 0.0069 | 0.04799 |
| rs9427672 | A | G | 0.24 | -0.032099728 | 0.0058 | 3.12E-08 | 0.0016 | 0.0069 | 0.8151 |

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| Table S2b. Harmonized instruments used in the MR analyses investigating the potential causal effect of genetic predicted major depressive disorder (MDD) on irritable bowel syndrome (IBS) | | | | | | | | | |
| SNP | **A1** | **A2** | **EAF** | **beta.MDD** | **se.MDD** | **pval.MDD** | **beta.IBS** | **se.IBS** | **pval.IBS** |
| rs10149470 | A | G | 0.49 | -0.029 | 0.0049 | 3.05E-09 | -0.0061 | 0.0069 | 0.3774 |
| rs10950398 | A | G | 0.41 | 0.027498 | 0.0049 | 2.55E-08 | 0.0053 | 0.0078 | 0.4955 |
| rs10959913 | T | G | 0.76 | 0.033396 | 0.0057 | 5.06E-09 | -0.0102 | 0.009 | 0.256 |
| rs11135349 | A | C | 0.48 | -0.0294 | 0.0048 | 1.09E-09 | -0.0167 | 0.0068 | 0.01461 |
| rs115507122 | C | G | 0.18 | -0.0418 | 0.0063 | 3.3E-11 | -0.035 | 0.0088 | 7.03E-05 |
| rs11643192 | A | C | 0.41 | 0.027002 | 0.0049 | 3.36E-08 | 0.0247 | 0.007 | 0.000392 |
| rs11663393 | A | G | 0.45 | 0.0278 | 0.0049 | 1.65E-08 | 0.0144 | 0.0068 | 0.03489 |
| rs116755193 | T | C | 0.38 | -0.0292 | 0.005 | 7.01E-09 | -0.0017 | 0.0069 | 0.8021 |
| rs11682175 | T | C | 0.52 | -0.0281 | 0.0048 | 4.68E-09 | -0.0158 | 0.0068 | 0.02078 |
| rs12129573 | A | C | 0.37 | 0.034498 | 0.005 | 4.01E-12 | -0.01 | 0.0072 | 0.1657 |
| rs1226412 | T | C | 0.79 | 0.033203 | 0.0059 | 2.38E-08 | 0.0123 | 0.0085 | 0.146 |
| rs12552 | A | G | 0.44 | 0.042897 | 0.0048 | 6.07E-19 | 0.0238 | 0.0069 | 0.000547 |
| rs12666117 | A | G | 0.47 | 0.027401 | 0.0048 | 1.35E-08 | 0.0233 | 0.0069 | 0.000683 |
| rs12958048 | A | G | 0.33 | 0.033802 | 0.0051 | 3.61E-11 | 0.0222 | 0.0072 | 0.002127 |
| rs1354115 | A | C | 0.62 | 0.027596 | 0.0049 | 2.37E-08 | 0.0051 | 0.0071 | 0.4707 |
| rs1432639 | A | C | 0.63 | 0.039 | 0.005 | 4.55E-15 | 0.0096 | 0.0069 | 0.1663 |
| rs159963 | A | C | 0.56 | -0.027 | 0.0049 | 3.19E-08 | -0.0219 | 0.0069 | 0.001606 |
| rs17727765 | T | C | 0.92 | -0.0508 | 0.0088 | 8.51E-09 | -0.0277 | 0.0129 | 0.03228 |
| rs1806153 | T | G | 0.22 | 0.0361 | 0.0059 | 1.18E-09 | 0.0161 | 0.0081 | 0.04678 |
| rs1833288 | A | G | 0.72 | 0.030199 | 0.0054 | 2.63E-08 | 0.0087 | 0.0078 | 0.2649 |
| rs200343480 | C | CAG | 0.49 | 0.028996 | 0.0049 | 3.77E-09 | 0.0132 | 0.0081 | 0.1027 |
| rs2389016 | T | C | 0.28 | 0.0305 | 0.0053 | 1.02E-08 | 0.0159 | 0.0075 | 0.0343 |
| rs34192913 | AT | A | 0.34 | 0.0278 | 0.0051 | 4.61E-08 | 0.0023 | 0.0086 | 0.788 |
| rs34215985 | C | G | 0.24 | -0.0373 | 0.0063 | 3.13E-09 | -0.019 | 0.0085 | 0.02536 |
| rs4074723 | A | C | 0.41 | -0.027 | 0.0049 | 3.12E-08 | -0.0027 | 0.007 | 0.6938 |
| rs4143229 | A | C | 0.92 | -0.0509 | 0.0091 | 2.51E-08 | -0.0378 | 0.0131 | 0.00389 |
| rs4261101 | A | G | 0.37 | -0.0285 | 0.005 | 1.04E-08 | -0.0023 | 0.0071 | 0.7499 |
| rs4869056 | A | G | 0.63 | -0.0287 | 0.005 | 6.8E-09 | -0.0059 | 0.0071 | 0.4011 |
| rs4904738 | T | C | 0.57 | -0.0289 | 0.0049 | 2.57E-09 | -0.0228 | 0.0069 | 0.000921 |
| rs5758265 | A | G | 0.28 | 0.031004 | 0.0054 | 7.55E-09 | 0.0351 | 0.0075 | 3.29E-06 |
| rs5869436 | TA | T | 0.58 | -0.0323 | 0.005 | 7.87E-11 | -0.019 | 0.0083 | 0.02178 |
| rs61867293 | T | C | 0.2 | -0.0374 | 0.0061 | 6.97E-10 | -0.0021 | 0.0086 | 0.8061 |
| rs7029033 | T | C | 0.07 | 0.051805 | 0.0093 | 2.74E-08 | 0.0174 | 0.0132 | 0.1888 |
| rs7198928 | T | C | 0.62 | 0.028403 | 0.005 | 1E-08 | 0.0065 | 0.007 | 0.3548 |
| rs7200826 | T | C | 0.25 | 0.030704 | 0.0055 | 2.43E-08 | -0.0022 | 0.0078 | 0.7755 |
| rs7430565 | A | G | 0.58 | -0.0288 | 0.0048 | 2.87E-09 | -0.0038 | 0.0069 | 0.5855 |
| rs7856424 | T | C | 0.29 | -0.0306 | 0.0053 | 8.48E-09 | -0.0024 | 0.0075 | 0.7501 |
| rs8025231 | A | C | 0.57 | -0.0339 | 0.0048 | 2.36E-12 | -0.0092 | 0.0069 | 0.1807 |
| rs8063603 | A | G | 0.65 | -0.0308 | 0.0053 | 6.87E-09 | -0.0071 | 0.0074 | 0.3357 |
| rs915057 | A | G | 0.42 | -0.03 | 0.0049 | 7.61E-10 | -0.0036 | 0.0069 | 0.602 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | 0.0085 | 0.008 | 0.2888 |
| rs9427672 | A | G | 0.24 | -0.0321 | 0.0058 | 3.12E-08 | -0.0238 | 0.0081 | 0.003351 |

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| Table S2c. Harmonized instruments used in the MR analyses investigating the potential causal effect of genetic predicted major depressive disorder (MDD) on peptic ulcer disease (PUD) | | | | | | | | | |
| SNP | **A1** | **A2** | **EAF** | **beta.MDD** | **se.MDD** | **pval.MDD** | **beta.PUD** | **se.PUD** | **pval.PUD** |
| rs10149470 | A | G | 0.49 | -0.029 | 0.0049 | 3.05E-09 | -0.00492 | 0.011131 | 0.66 |
| rs10950398 | A | G | 0.41 | 0.027498 | 0.0049 | 2.55E-08 | 0.013378 | 0.011225 | 0.23 |
| rs10959913 | T | G | 0.76 | 0.033396 | 0.0057 | 5.06E-09 | 0.015791 | 0.013258 | 0.23 |
| rs11135349 | A | C | 0.48 | -0.0294 | 0.0048 | 1.09E-09 | -0.01052 | 0.011145 | 0.35 |
| rs115507122 | C | G | 0.18 | -0.0418 | 0.0063 | 3.3E-11 | -0.01443 | 0.013854 | 0.3 |
| rs11643192 | A | C | 0.41 | 0.027002 | 0.0049 | 3.36E-08 | -0.01724 | 0.01147 | 0.13 |
| rs11663393 | A | G | 0.45 | 0.0278 | 0.0049 | 1.65E-08 | -0.00793 | 0.017131 | 0.64 |
| rs116755193 | T | C | 0.38 | -0.0292 | 0.005 | 7.01E-09 | 0.013334 | 0.01129 | 0.24 |
| rs11682175 | T | C | 0.52 | -0.0281 | 0.0048 | 4.68E-09 | -0.00882 | 0.01159 | 0.45 |
| rs12129573 | A | C | 0.37 | 0.034498 | 0.005 | 4.01E-12 | 0.029146 | 0.01161 | 0.012 |
| rs1226412 | T | C | 0.79 | 0.033203 | 0.0059 | 2.38E-08 | 0.015397 | 0.013892 | 0.27 |
| rs12552 | A | G | 0.44 | 0.042897 | 0.0048 | 6.07E-19 | 0.010034 | 0.011268 | 0.37 |
| rs12666117 | A | G | 0.47 | 0.027401 | 0.0048 | 1.35E-08 | 0.008898 | 0.011289 | 0.43 |
| rs12958048 | A | G | 0.33 | 0.033802 | 0.0051 | 3.61E-11 | 0.016512 | 0.011836 | 0.16 |
| rs1354115 | A | C | 0.62 | 0.027596 | 0.0049 | 2.37E-08 | 0.016544 | 0.011547 | 0.15 |
| rs1432639 | A | C | 0.63 | 0.039 | 0.005 | 4.55E-15 | -0.00671 | 0.011356 | 0.55 |
| rs159963 | A | C | 0.56 | -0.027 | 0.0049 | 3.19E-08 | -0.01349 | 0.011402 | 0.24 |
| rs17727765 | T | C | 0.92 | -0.0508 | 0.0088 | 8.51E-09 | -0.00955 | 0.021228 | 0.65 |
| rs1806153 | T | G | 0.22 | 0.0361 | 0.0059 | 1.18E-09 | 0.029094 | 0.013131 | 0.027 |
| rs1833288 | A | G | 0.72 | 0.030199 | 0.0054 | 2.63E-08 | 0.001262 | 0.01302 | 0.92 |
| rs200343480 | C | CAG | 0.49 | 0.028996 | 0.0049 | 3.77E-09 | 0.014932 | 0.0113 | 0.19 |
| rs2389016 | T | C | 0.28 | 0.0305 | 0.0053 | 1.02E-08 | 0.004581 | 0.012163 | 0.71 |
| rs34192913 | AT | A | 0.34 | 0.0278 | 0.0051 | 4.61E-08 | -0.00215 | 0.011929 | 0.86 |
| rs34215985 | C | G | 0.24 | -0.0373 | 0.0063 | 3.13E-09 | -0.01158 | 0.013894 | 0.4 |
| rs4074723 | A | C | 0.41 | -0.027 | 0.0049 | 3.12E-08 | -0.00776 | 0.011339 | 0.49 |
| rs4143229 | A | C | 0.92 | -0.0509 | 0.0091 | 2.51E-08 | -0.01041 | 0.021772 | 0.63 |
| rs4261101 | A | G | 0.37 | -0.0285 | 0.005 | 1.04E-08 | -0.00062 | 0.01163 | 0.96 |
| rs4869056 | A | G | 0.63 | -0.0287 | 0.005 | 6.8E-09 | -0.03326 | 0.011455 | 0.0037 |
| rs4904738 | T | C | 0.57 | -0.0289 | 0.0049 | 2.57E-09 | -0.01675 | 0.011323 | 0.14 |
| rs5758265 | A | G | 0.28 | 0.031004 | 0.0054 | 7.55E-09 | -0.00885 | 0.012363 | 0.47 |
| rs5869436 | TA | T | 0.58 | -0.0323 | 0.005 | 7.87E-11 | 0.01275 | 0.011624 | 0.27 |
| rs61867293 | T | C | 0.2 | -0.0374 | 0.0061 | 6.97E-10 | -0.01933 | 0.014303 | 0.18 |
| rs7029033 | T | C | 0.07 | 0.051805 | 0.0093 | 2.74E-08 | 0.001856 | 0.022152 | 0.93 |
| rs7198928 | T | C | 0.62 | 0.028403 | 0.005 | 1E-08 | 0.01204 | 0.011619 | 0.3 |
| rs7200826 | T | C | 0.25 | 0.030704 | 0.0055 | 2.43E-08 | -0.00159 | 0.012771 | 0.9 |
| rs7430565 | A | G | 0.58 | -0.0288 | 0.0048 | 2.87E-09 | 0.005405 | 0.011278 | 0.63 |
| rs7856424 | T | C | 0.29 | -0.0306 | 0.0053 | 8.48E-09 | 0.001998 | 0.012335 | 0.87 |
| rs8025231 | A | C | 0.57 | -0.0339 | 0.0048 | 2.36E-12 | -0.01153 | 0.011181 | 0.3 |
| rs8063603 | A | G | 0.65 | -0.0308 | 0.0053 | 6.87E-09 | -0.008 | 0.01211 | 0.51 |
| rs915057 | A | G | 0.42 | -0.03 | 0.0049 | 7.61E-10 | 0.009391 | 0.011324 | 0.41 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | 0.026198 | 0.013068 | 0.045 |
| rs9427672 | A | G | 0.24 | -0.0321 | 0.0058 | 3.12E-08 | 0.028409 | 0.013051 | 0.029 |

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| Table S2d. Harmonized instruments used in the MR analyses investigating the potential causal effect of genetic predicted major depressive disorder (MDD) on non-alcoholic fatty liver disease (NAFLD) | | | | | | | | | |
| SNP | **A1** | **A2** | **EAF** | **beta.MDD** | **se.MDD** | **pval.MDD** | **beta.NAFLD** | **se.NAFLD** | **pval.NAFLD** |
| rs10149470 | A | G | 0.49 | -0.029 | 0.0049 | 3.05E-09 | 0.00521 | 0.017521 | 0.766207 |
| rs10950398 | A | G | 0.41 | 0.027498 | 0.0049 | 2.55E-08 | -0.00276 | 0.012485 | 0.825181 |
| rs10959913 | T | G | 0.76 | 0.033396 | 0.0057 | 5.06E-09 | 0.031118 | 0.028338 | 0.272162 |
| rs11135349 | A | C | 0.48 | -0.0294 | 0.0048 | 1.09E-09 | 0.012274 | 0.02241 | 0.583893 |
| rs115507122 | C | G | 0.18 | -0.0418 | 0.0063 | 3.3E-11 | -0.02821 | 0.02292 | 0.218368 |
| rs11643192 | A | C | 0.41 | 0.027002 | 0.0049 | 3.36E-08 | 0.001998 | 0.011447 | 0.861444 |
| rs11663393 | A | G | 0.45 | 0.0278 | 0.0049 | 1.65E-08 | 0.007541 | 0.024105 | 0.75439 |
| rs116755193 | T | C | 0.38 | -0.0292 | 0.005 | 7.01E-09 | 0.03053 | 0.017651 | 0.083685 |
| rs11682175 | T | C | 0.52 | -0.0281 | 0.0048 | 4.68E-09 | -0.01039 | 0.017071 | 0.542924 |
| rs12129573 | A | C | 0.37 | 0.034498 | 0.005 | 4.01E-12 | -0.01656 | 0.025418 | 0.514741 |
| rs1226412 | T | C | 0.79 | 0.033203 | 0.0059 | 2.38E-08 | -0.01881 | 0.023855 | 0.430507 |
| rs12552 | A | G | 0.44 | 0.042897 | 0.0048 | 6.07E-19 | 0.015035 | 0.021104 | 0.476197 |
| rs12666117 | A | G | 0.47 | 0.027401 | 0.0048 | 1.35E-08 | 0.003005 | 0.025235 | 0.905197 |
| rs12958048 | A | G | 0.33 | 0.033802 | 0.0051 | 3.61E-11 | 0.005943 | 0.030352 | 0.844772 |
| rs1354115 | A | C | 0.62 | 0.027596 | 0.0049 | 2.37E-08 | 0.029481 | 0.021736 | 0.175 |
| rs1432639 | A | C | 0.63 | 0.039 | 0.005 | 4.55E-15 | 0.036997 | 0.018967 | 0.051107 |
| rs159963 | A | C | 0.56 | -0.027 | 0.0049 | 3.19E-08 | -0.0273 | 0.01847 | 0.139463 |
| rs17727765 | T | C | 0.92 | -0.0508 | 0.0088 | 8.51E-09 | 0.001806 | 0.032166 | 0.955235 |
| rs1806153 | T | G | 0.22 | 0.0361 | 0.0059 | 1.18E-09 | 0.018743 | 0.031203 | 0.548042 |
| rs1833288 | A | G | 0.72 | 0.030199 | 0.0054 | 2.63E-08 | -0.00655 | 0.016699 | 0.69495 |
| rs200343480 | C | CAG | 0.49 | 0.028996 | 0.0049 | 3.77E-09 | 0.006386 | 0.042543 | 0.880675 |
| rs2389016 | T | C | 0.28 | 0.0305 | 0.0053 | 1.02E-08 | 0.056598 | 0.021825 | 0.009508 |
| rs34192913 | AT | A | 0.34 | 0.0278 | 0.0051 | 4.61E-08 | -0.00222 | 0.039319 | 0.954965 |
| rs34215985 | C | G | 0.24 | -0.0373 | 0.0063 | 3.13E-09 | -0.03327 | 0.027519 | 0.226707 |
| rs4074723 | A | C | 0.41 | -0.027 | 0.0049 | 3.12E-08 | -0.03497 | 0.019168 | 0.068077 |
| rs4143229 | A | C | 0.92 | -0.0509 | 0.0091 | 2.51E-08 | -0.04968 | 0.037294 | 0.182805 |
| rs4261101 | A | G | 0.37 | -0.0285 | 0.005 | 1.04E-08 | -0.01275 | 0.017359 | 0.462502 |
| rs4869056 | A | G | 0.63 | -0.0287 | 0.005 | 6.8E-09 | -0.01282 | 0.019662 | 0.514229 |
| rs4904738 | T | C | 0.57 | -0.0289 | 0.0049 | 2.57E-09 | -0.03152 | 0.02084 | 0.130441 |
| rs5758265 | A | G | 0.28 | 0.031004 | 0.0054 | 7.55E-09 | 0.033338 | 0.022105 | 0.131514 |
| rs5869436 | TA | T | 0.58 | -0.0323 | 0.005 | 7.87E-11 | 0.031431 | 0.020947 | 0.133486 |
| rs61867293 | T | C | 0.2 | -0.0374 | 0.0061 | 6.97E-10 | -0.03452 | 0.027257 | 0.205328 |
| rs7029033 | T | C | 0.07 | 0.051805 | 0.0093 | 2.74E-08 | 0.004898 | 0.018111 | 0.786818 |
| rs7198928 | T | C | 0.62 | 0.028403 | 0.005 | 1E-08 | -0.01774 | 0.022339 | 0.427087 |
| rs7200826 | T | C | 0.25 | 0.030704 | 0.0055 | 2.43E-08 | -0.00654 | 0.029935 | 0.826945 |
| rs7430565 | A | G | 0.58 | -0.0288 | 0.0048 | 2.87E-09 | -0.00399 | 0.035239 | 0.909875 |
| rs7856424 | T | C | 0.29 | -0.0306 | 0.0053 | 8.48E-09 | -0.01372 | 0.024628 | 0.577588 |
| rs8025231 | A | C | 0.57 | -0.0339 | 0.0048 | 2.36E-12 | -0.01268 | 0.025647 | 0.621047 |
| rs8063603 | A | G | 0.65 | -0.0308 | 0.0053 | 6.87E-09 | -0.03306 | 0.021498 | 0.124071 |
| rs915057 | A | G | 0.42 | -0.03 | 0.0049 | 7.61E-10 | 0.054699 | 0.020268 | 0.006958 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | 0.030064 | 0.023235 | 0.195694 |
| rs9427672 | A | G | 0.24 | -0.0321 | 0.0058 | 3.12E-08 | -0.00273 | 0.011605 | 0.814269 |

## Table S3. Harmonized instruments used in the univariable MR analyses for FinnGen outcome datasets

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| Table S3a. Harmonized instruments used in the MR analyses investigating the potential causal effect of genetic predicted major depressive disorder (MDD) on gastroesophageal reflux disease (GERD) | | | | | | | | | |
| SNP | **A1** | **A2** | **EAF** | **beta.MDD** | **se.MDD** | **pval.MDD** | **beta.GERD** | **se.GERD** | **pval.GERD** |
| rs10149470 | A | G | 0.49 | -0.029 | 0.0049 | 3.05E-09 | -0.0159 | 0.0135 | 0.2396 |
| rs10950398 | A | G | 0.41 | 0.027498 | 0.0049 | 2.55E-08 | 0.031 | 0.0139 | 0.02584 |
| rs10959913 | T | G | 0.76 | 0.033396 | 0.0057 | 5.06E-09 | -0.0033 | 0.0167 | 0.8448 |
| rs11135349 | A | C | 0.48 | -0.0294 | 0.0048 | 1.09E-09 | -0.0178 | 0.0138 | 0.1978 |
| rs11643192 | A | C | 0.41 | 0.027002 | 0.0049 | 3.36E-08 | -0.0101 | 0.0136 | 0.4551 |
| rs11663393 | A | G | 0.45 | 0.0278 | 0.0049 | 1.65E-08 | 0.0107 | 0.0134 | 0.427 |
| rs11682175 | T | C | 0.52 | -0.0281 | 0.0048 | 4.68E-09 | -0.0146 | 0.0137 | 0.2878 |
| rs12129573 | A | C | 0.37 | 0.034498 | 0.005 | 4.01E-12 | -0.0053 | 0.014 | 0.7069 |
| rs1226412 | T | C | 0.79 | 0.033203 | 0.0059 | 2.38E-08 | -0.002 | 0.0156 | 0.8983 |
| rs12552 | A | G | 0.44 | 0.042897 | 0.0048 | 6.07E-19 | 0.015 | 0.0136 | 0.2685 |
| rs12666117 | A | G | 0.47 | 0.027401 | 0.0048 | 1.35E-08 | 0.0211 | 0.0135 | 0.1177 |
| rs12958048 | A | G | 0.33 | 0.033802 | 0.0051 | 3.61E-11 | 0.0031 | 0.0155 | 0.8394 |
| rs1354115 | A | C | 0.62 | 0.027596 | 0.0049 | 2.37E-08 | -0.0089 | 0.0142 | 0.5307 |
| rs1432639 | A | C | 0.63 | 0.039 | 0.005 | 4.55E-15 | 0.0249 | 0.0141 | 0.076871 |
| rs159963 | A | C | 0.56 | -0.027 | 0.0049 | 3.19E-08 | 0.0201 | 0.0142 | 0.1554 |
| rs17727765 | T | C | 0.92 | -0.0508 | 0.0088 | 8.51E-09 | 0.0055 | 0.0218 | 0.8018 |
| rs1806153 | T | G | 0.22 | 0.0361 | 0.0059 | 1.18E-09 | 0.0242 | 0.0156 | 0.121 |
| rs1833288 | A | G | 0.72 | 0.030199 | 0.0054 | 2.63E-08 | 0.0189 | 0.0146 | 0.1953 |
| rs2389016 | T | C | 0.28 | 0.0305 | 0.0053 | 1.02E-08 | 0.0172 | 0.0169 | 0.3093 |
| rs34192913 | AT | A | 0.34 | 0.0278 | 0.0051 | 4.61E-08 | 0.0045 | 0.0142 | 0.7486 |
| rs34215985 | C | G | 0.24 | -0.0373 | 0.0063 | 3.13E-09 | -0.0184 | 0.0171 | 0.2809 |
| rs4074723 | A | C | 0.41 | -0.027 | 0.0049 | 3.12E-08 | -0.0029 | 0.0144 | 0.8428 |
| rs4143229 | A | C | 0.92 | -0.0509 | 0.0091 | 2.51E-08 | -0.0042 | 0.0219 | 0.8472 |
| rs4261101 | A | G | 0.37 | -0.0285 | 0.005 | 1.04E-08 | -0.0019 | 0.0148 | 0.8978 |
| rs4869056 | A | G | 0.63 | -0.0287 | 0.005 | 6.8E-09 | 0.0016 | 0.0142 | 0.9112 |
| rs4904738 | T | C | 0.57 | -0.0289 | 0.0049 | 2.57E-09 | -0.0226 | 0.0135 | 0.093659 |
| rs5758265 | A | G | 0.28 | 0.031004 | 0.0054 | 7.55E-09 | 0.0106 | 0.0146 | 0.4688 |
| rs5869436 | TA | T | 0.58 | -0.0323 | 0.005 | 7.87E-11 | 0.005 | 0.0137 | 0.715801 |
| rs61867293 | T | C | 0.2 | -0.0374 | 0.0061 | 6.97E-10 | -0.0141 | 0.016 | 0.3796 |
| rs62099069 | A | T | 0.42 | -0.0279 | 0.0049 | 1.31E-08 | 0.0086 | 0.0138 | 0.5343 |
| rs7029033 | T | C | 0.07 | 0.051805 | 0.0093 | 2.74E-08 | 0.0035 | 0.0219 | 0.8744 |
| rs7198928 | T | C | 0.62 | 0.028403 | 0.005 | 1E-08 | -0.0343 | 0.0144 | 0.01699 |
| rs7200826 | T | C | 0.25 | 0.030704 | 0.0055 | 2.43E-08 | 0.0063 | 0.0143 | 0.657301 |
| rs7430565 | A | G | 0.58 | -0.0288 | 0.0048 | 2.87E-09 | 0.0009 | 0.0135 | 0.9465 |
| rs7856424 | T | C | 0.29 | -0.0306 | 0.0053 | 8.48E-09 | -0.0158 | 0.0144 | 0.2727 |
| rs8025231 | A | C | 0.57 | -0.0339 | 0.0048 | 2.36E-12 | -0.0081 | 0.0135 | 0.5495 |
| rs8063603 | A | G | 0.65 | -0.0308 | 0.0053 | 6.87E-09 | 0.0043 | 0.014 | 0.7602 |
| rs915057 | A | G | 0.42 | -0.03 | 0.0049 | 7.61E-10 | -0.0111 | 0.0136 | 0.414 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | -0.0289 | 0.0259 | 0.2644 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | 0.0211 | 0.0186 | 0.2553 |
| rs9427672 | A | G | 0.24 | -0.0321 | 0.0058 | 3.12E-08 | -0.0081 | 0.0183 | 0.6579 |

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| Table S3b. Harmonized instruments used in the MR analyses investigating the potential causal effect of genetic predicted major depressive disorder (MDD) on irritable bowel syndrome (IBS) | | | | | | | | | |
| SNP | **A1** | **A2** | **EAF** | **beta.MDD** | **se.MDD** | **pval.MDD** | **beta.IBS** | **se.IBS** | **pval.IBS** |
| rs10149470 | A | G | 0.49 | -0.029 | 0.0049 | 3.05E-09 | 0.003 | 0.0217 | 0.8887 |
| rs10950398 | A | G | 0.41 | 0.027498 | 0.0049 | 2.55E-08 | 0.0385 | 0.0223 | 0.08418 |
| rs10959913 | T | G | 0.76 | 0.033396 | 0.0057 | 5.06E-09 | -0.011 | 0.0267 | 0.680899 |
| rs11135349 | A | C | 0.48 | -0.0294 | 0.0048 | 1.09E-09 | -0.0086 | 0.0221 | 0.697301 |
| rs11643192 | A | C | 0.41 | 0.027002 | 0.0049 | 3.36E-08 | 0.0138 | 0.0217 | 0.5259 |
| rs11663393 | A | G | 0.45 | 0.0278 | 0.0049 | 1.65E-08 | -0.0002 | 0.0215 | 0.9944 |
| rs11682175 | T | C | 0.52 | -0.0281 | 0.0048 | 4.68E-09 | -0.054 | 0.022 | 0.01414 |
| rs12129573 | A | C | 0.37 | 0.034498 | 0.005 | 4.01E-12 | -0.0319 | 0.0225 | 0.1562 |
| rs1226412 | T | C | 0.79 | 0.033203 | 0.0059 | 2.38E-08 | 0.0066 | 0.0251 | 0.793 |
| rs12552 | A | G | 0.44 | 0.042897 | 0.0048 | 6.07E-19 | 0.0444 | 0.0217 | 0.04091 |
| rs12666117 | A | G | 0.47 | 0.027401 | 0.0048 | 1.35E-08 | 0.0273 | 0.0217 | 0.2079 |
| rs12958048 | A | G | 0.33 | 0.033802 | 0.0051 | 3.61E-11 | 0.0364 | 0.0248 | 0.1428 |
| rs1354115 | A | C | 0.62 | 0.027596 | 0.0049 | 2.37E-08 | -0.0016 | 0.0228 | 0.9436 |
| rs1432639 | A | C | 0.63 | 0.039 | 0.005 | 4.55E-15 | 0.0461 | 0.0225 | 0.04061 |
| rs159963 | A | C | 0.56 | -0.027 | 0.0049 | 3.19E-08 | -0.0037 | 0.0227 | 0.8714 |
| rs17727765 | T | C | 0.92 | -0.0508 | 0.0088 | 8.51E-09 | -0.0189 | 0.035 | 0.5894 |
| rs1806153 | T | G | 0.22 | 0.0361 | 0.0059 | 1.18E-09 | -0.0201 | 0.025 | 0.4202 |
| rs1833288 | A | G | 0.72 | 0.030199 | 0.0054 | 2.63E-08 | -0.021 | 0.0234 | 0.3686 |
| rs2389016 | T | C | 0.28 | 0.0305 | 0.0053 | 1.02E-08 | 0.0188 | 0.0271 | 0.4885 |
| rs34192913 | AT | A | 0.34 | 0.0278 | 0.0051 | 4.61E-08 | 0.0178 | 0.0227 | 0.434 |
| rs34215985 | C | G | 0.24 | -0.0373 | 0.0063 | 3.13E-09 | -0.0257 | 0.0274 | 0.3485 |
| rs4074723 | A | C | 0.41 | -0.027 | 0.0049 | 3.12E-08 | -0.0293 | 0.0232 | 0.2053 |
| rs4143229 | A | C | 0.92 | -0.0509 | 0.0091 | 2.51E-08 | -0.0003 | 0.0349 | 0.9941 |
| rs4261101 | A | G | 0.37 | -0.0285 | 0.005 | 1.04E-08 | 0.0044 | 0.0237 | 0.8519 |
| rs4869056 | A | G | 0.63 | -0.0287 | 0.005 | 6.8E-09 | -0.0296 | 0.0227 | 0.1916 |
| rs4904738 | T | C | 0.57 | -0.0289 | 0.0049 | 2.57E-09 | 0.0002 | 0.0216 | 0.9913 |
| rs5758265 | A | G | 0.28 | 0.031004 | 0.0054 | 7.55E-09 | 0.0482 | 0.0234 | 0.03967 |
| rs5869436 | TA | T | 0.58 | -0.0323 | 0.005 | 7.87E-11 | -0.0091 | 0.022 | 0.679301 |
| rs61867293 | T | C | 0.2 | -0.0374 | 0.0061 | 6.97E-10 | -0.057 | 0.0257 | 0.0266 |
| rs62099069 | A | T | 0.42 | -0.0279 | 0.0049 | 1.31E-08 | -0.0081 | 0.0221 | 0.714399 |
| rs7029033 | T | C | 0.07 | 0.051805 | 0.0093 | 2.74E-08 | 0.0371 | 0.0351 | 0.2903 |
| rs7198928 | T | C | 0.62 | 0.028403 | 0.005 | 1E-08 | -0.0165 | 0.0231 | 0.4737 |
| rs7200826 | T | C | 0.25 | 0.030704 | 0.0055 | 2.43E-08 | 0.0215 | 0.0229 | 0.3472 |
| rs7430565 | A | G | 0.58 | -0.0288 | 0.0048 | 2.87E-09 | 0.0034 | 0.0216 | 0.8735 |
| rs7856424 | T | C | 0.29 | -0.0306 | 0.0053 | 8.48E-09 | -0.0088 | 0.0231 | 0.702901 |
| rs8025231 | A | C | 0.57 | -0.0339 | 0.0048 | 2.36E-12 | 0.0033 | 0.0216 | 0.8777 |
| rs8063603 | A | G | 0.65 | -0.0308 | 0.0053 | 6.87E-09 | -0.038 | 0.0225 | 0.090511 |
| rs915057 | A | G | 0.42 | -0.03 | 0.0049 | 7.61E-10 | -0.0132 | 0.0218 | 0.5464 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | -0.0153 | 0.0416 | 0.7127 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | 0.056 | 0.0297 | 0.05887 |
| rs9427672 | A | G | 0.24 | -0.0321 | 0.0058 | 3.12E-08 | -0.0308 | 0.0294 | 0.2941 |

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| Table S3c. Harmonized instruments used in the MR analyses investigating the potential causal effect of genetic predicted major depressive disorder (MDD) on peptic ulcer disease (PUD) | | | | | | | | | |
| SNP | **A1** | **A2** | **EAF** | **beta.MDD** | **se.MDD** | **pval.MDD** | **beta.PUD** | **se.PUD** | **pval.PUD** |
| rs10149470 | A | G | 0.49 | -0.029 | 0.0049 | 3.05E-09 | -0.0063 | 0.0222 | 0.777301 |
| rs10950398 | A | G | 0.41 | 0.027498 | 0.0049 | 2.55E-08 | 0.0042 | 0.0229 | 0.8546 |
| rs10959913 | T | G | 0.76 | 0.033396 | 0.0057 | 5.06E-09 | 0.0308 | 0.0274 | 0.2618 |
| rs11135349 | A | C | 0.48 | -0.0294 | 0.0048 | 1.09E-09 | -0.0104 | 0.0227 | 0.647201 |
| rs11643192 | A | C | 0.41 | 0.027002 | 0.0049 | 3.36E-08 | -0.0286 | 0.0222 | 0.198 |
| rs11663393 | A | G | 0.45 | 0.0278 | 0.0049 | 1.65E-08 | 0.0244 | 0.022 | 0.2673 |
| rs11682175 | T | C | 0.52 | -0.0281 | 0.0048 | 4.68E-09 | 0.0058 | 0.0226 | 0.7971 |
| rs12129573 | A | C | 0.37 | 0.034498 | 0.005 | 4.01E-12 | -0.0104 | 0.023 | 0.649901 |
| rs1226412 | T | C | 0.79 | 0.033203 | 0.0059 | 2.38E-08 | -0.0016 | 0.0256 | 0.951 |
| rs12552 | A | G | 0.44 | 0.042897 | 0.0048 | 6.07E-19 | -0.0018 | 0.0223 | 0.934 |
| rs12666117 | A | G | 0.47 | 0.027401 | 0.0048 | 1.35E-08 | 0.0159 | 0.0221 | 0.4729 |
| rs12958048 | A | G | 0.33 | 0.033802 | 0.0051 | 3.61E-11 | 0.0062 | 0.0255 | 0.8074 |
| rs1354115 | A | C | 0.62 | 0.027596 | 0.0049 | 2.37E-08 | 0.0016 | 0.0233 | 0.9435 |
| rs1432639 | A | C | 0.63 | 0.039 | 0.005 | 4.55E-15 | 0.0171 | 0.0231 | 0.4583 |
| rs159963 | A | C | 0.56 | -0.027 | 0.0049 | 3.19E-08 | 0.0141 | 0.0233 | 0.5439 |
| rs17727765 | T | C | 0.92 | -0.0508 | 0.0088 | 8.51E-09 | 0.0068 | 0.0359 | 0.8486 |
| rs1806153 | T | G | 0.22 | 0.0361 | 0.0059 | 1.18E-09 | -0.0165 | 0.0256 | 0.5196 |
| rs1833288 | A | G | 0.72 | 0.030199 | 0.0054 | 2.63E-08 | -0.0116 | 0.0239 | 0.6262 |
| rs2389016 | T | C | 0.28 | 0.0305 | 0.0053 | 1.02E-08 | 0.0261 | 0.0278 | 0.3472 |
| rs34192913 | AT | A | 0.34 | 0.0278 | 0.0051 | 4.61E-08 | -0.0149 | 0.0233 | 0.522001 |
| rs34215985 | C | G | 0.24 | -0.0373 | 0.0063 | 3.13E-09 | -0.0249 | 0.028 | 0.3737 |
| rs4074723 | A | C | 0.41 | -0.027 | 0.0049 | 3.12E-08 | -0.0009 | 0.0237 | 0.9684 |
| rs4143229 | A | C | 0.92 | -0.0509 | 0.0091 | 2.51E-08 | -0.0142 | 0.0357 | 0.690501 |
| rs4261101 | A | G | 0.37 | -0.0285 | 0.005 | 1.04E-08 | -0.0403 | 0.0243 | 0.09675 |
| rs4869056 | A | G | 0.63 | -0.0287 | 0.005 | 6.8E-09 | -0.0248 | 0.0232 | 0.2852 |
| rs4904738 | T | C | 0.57 | -0.0289 | 0.0049 | 2.57E-09 | 0.0212 | 0.022 | 0.3363 |
| rs5758265 | A | G | 0.28 | 0.031004 | 0.0054 | 7.55E-09 | -0.0272 | 0.024 | 0.2573 |
| rs5869436 | TA | T | 0.58 | -0.0323 | 0.005 | 7.87E-11 | -0.0027 | 0.0225 | 0.9047 |
| rs61867293 | T | C | 0.2 | -0.0374 | 0.0061 | 6.97E-10 | -0.0168 | 0.0262 | 0.5221 |
| rs62099069 | A | T | 0.42 | -0.0279 | 0.0049 | 1.31E-08 | -0.0525 | 0.0226 | 0.02023 |
| rs7029033 | T | C | 0.07 | 0.051805 | 0.0093 | 2.74E-08 | -0.0133 | 0.036 | 0.710799 |
| rs7198928 | T | C | 0.62 | 0.028403 | 0.005 | 1E-08 | 0.0008 | 0.0237 | 0.972 |
| rs7200826 | T | C | 0.25 | 0.030704 | 0.0055 | 2.43E-08 | 0.0225 | 0.0234 | 0.3348 |
| rs7430565 | A | G | 0.58 | -0.0288 | 0.0048 | 2.87E-09 | 0.0157 | 0.0221 | 0.478 |
| rs7856424 | T | C | 0.29 | -0.0306 | 0.0053 | 8.48E-09 | -0.0035 | 0.0236 | 0.8828 |
| rs8025231 | A | C | 0.57 | -0.0339 | 0.0048 | 2.36E-12 | -0.0058 | 0.0221 | 0.7934 |
| rs8063603 | A | G | 0.65 | -0.0308 | 0.0053 | 6.87E-09 | -0.0323 | 0.023 | 0.161 |
| rs915057 | A | G | 0.42 | -0.03 | 0.0049 | 7.61E-10 | -0.0305 | 0.0223 | 0.1725 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | -0.02 | 0.0425 | 0.638 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | -0.0015 | 0.0305 | 0.9602 |
| rs9427672 | A | G | 0.24 | -0.0321 | 0.0058 | 3.12E-08 | 0.0454 | 0.0301 | 0.1313 |

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| Table S3d. Harmonized instruments used in the MR analyses investigating the potential causal effect of genetic predicted major depressive disorder (MDD) on non-alcoholic fatty liver disease (NAFLD) | | | | | | | | | |
| SNP | **A1** | **A2** | **EAF** | **beta.MDD** | **se.MDD** | **pval.MDD** | **beta.NAFLD** | **se.NAFLD** | **pval.NAFLD** |
| rs10149470 | A | G | 0.49 | -0.029 | 0.0049 | 3.05E-09 | -0.0166 | 0.0483 | 0.730601 |
| rs10950398 | A | G | 0.41 | 0.027498 | 0.0049 | 2.55E-08 | -0.028 | 0.0496 | 0.5729 |
| rs10959913 | T | G | 0.76 | 0.033396 | 0.0057 | 5.06E-09 | 0.0431 | 0.0593 | 0.468 |
| rs11135349 | A | C | 0.48 | -0.0294 | 0.0048 | 1.09E-09 | 0.0194 | 0.0491 | 0.6934 |
| rs11643192 | A | C | 0.41 | 0.027002 | 0.0049 | 3.36E-08 | -0.0355 | 0.0483 | 0.4619 |
| rs11663393 | A | G | 0.45 | 0.0278 | 0.0049 | 1.65E-08 | 0.0325 | 0.0479 | 0.4982 |
| rs11682175 | T | C | 0.52 | -0.0281 | 0.0048 | 4.68E-09 | 0.0378 | 0.049 | 0.4403 |
| rs12129573 | A | C | 0.37 | 0.034498 | 0.005 | 4.01E-12 | -0.0266 | 0.0499 | 0.5936 |
| rs1226412 | T | C | 0.79 | 0.033203 | 0.0059 | 2.38E-08 | -0.0238 | 0.0557 | 0.6692 |
| rs12552 | A | G | 0.44 | 0.042897 | 0.0048 | 6.07E-19 | -0.0003 | 0.0482 | 0.9948 |
| rs12666117 | A | G | 0.47 | 0.027401 | 0.0048 | 1.35E-08 | 0.0318 | 0.0481 | 0.5086 |
| rs12958048 | A | G | 0.33 | 0.033802 | 0.0051 | 3.61E-11 | 0.0506 | 0.0553 | 0.3606 |
| rs1354115 | A | C | 0.62 | 0.027596 | 0.0049 | 2.37E-08 | -0.0364 | 0.0505 | 0.4712 |
| rs1432639 | A | C | 0.63 | 0.039 | 0.005 | 4.55E-15 | 0.0591 | 0.05 | 0.2372 |
| rs159963 | A | C | 0.56 | -0.027 | 0.0049 | 3.19E-08 | -0.0838 | 0.0505 | 0.09717 |
| rs17727765 | T | C | 0.92 | -0.0508 | 0.0088 | 8.51E-09 | -0.0039 | 0.0776 | 0.9604 |
| rs1806153 | T | G | 0.22 | 0.0361 | 0.0059 | 1.18E-09 | 0.13 | 0.0555 | 0.01909 |
| rs1833288 | A | G | 0.72 | 0.030199 | 0.0054 | 2.63E-08 | 0.0719 | 0.052 | 0.1664 |
| rs2389016 | T | C | 0.28 | 0.0305 | 0.0053 | 1.02E-08 | -0.0428 | 0.0601 | 0.4762 |
| rs34192913 | AT | A | 0.34 | 0.0278 | 0.0051 | 4.61E-08 | 0.0746 | 0.0505 | 0.1392 |
| rs34215985 | C | G | 0.24 | -0.0373 | 0.0063 | 3.13E-09 | -0.0396 | 0.0609 | 0.5161 |
| rs4074723 | A | C | 0.41 | -0.027 | 0.0049 | 3.12E-08 | 0.0019 | 0.0515 | 0.9702 |
| rs4143229 | A | C | 0.92 | -0.0509 | 0.0091 | 2.51E-08 | -0.1574 | 0.0777 | 0.04276 |
| rs4261101 | A | G | 0.37 | -0.0285 | 0.005 | 1.04E-08 | 0.0004 | 0.0527 | 0.9946 |
| rs4869056 | A | G | 0.63 | -0.0287 | 0.005 | 6.8E-09 | 0.005 | 0.0504 | 0.9205 |
| rs4904738 | T | C | 0.57 | -0.0289 | 0.0049 | 2.57E-09 | 0.0249 | 0.048 | 0.6034 |
| rs5758265 | A | G | 0.28 | 0.031004 | 0.0054 | 7.55E-09 | 0.0569 | 0.052 | 0.2731 |
| rs5869436 | TA | T | 0.58 | -0.0323 | 0.005 | 7.87E-11 | -0.0007 | 0.0488 | 0.9891 |
| rs61867293 | T | C | 0.2 | -0.0374 | 0.0061 | 6.97E-10 | -0.024 | 0.0571 | 0.6743 |
| rs62099069 | A | T | 0.42 | -0.0279 | 0.0049 | 1.31E-08 | 0.0086 | 0.0491 | 0.8613 |
| rs7029033 | T | C | 0.07 | 0.051805 | 0.0093 | 2.74E-08 | -0.0924 | 0.0783 | 0.238 |
| rs7198928 | T | C | 0.62 | 0.028403 | 0.005 | 1E-08 | -0.0466 | 0.0513 | 0.3638 |
| rs7200826 | T | C | 0.25 | 0.030704 | 0.0055 | 2.43E-08 | 0.0034 | 0.0507 | 0.9459 |
| rs7430565 | A | G | 0.58 | -0.0288 | 0.0048 | 2.87E-09 | -0.0838 | 0.048 | 0.080599 |
| rs7856424 | T | C | 0.29 | -0.0306 | 0.0053 | 8.48E-09 | 0.0113 | 0.0512 | 0.8256 |
| rs8025231 | A | C | 0.57 | -0.0339 | 0.0048 | 2.36E-12 | -0.0435 | 0.048 | 0.3649 |
| rs8063603 | A | G | 0.65 | -0.0308 | 0.0053 | 6.87E-09 | 0.039 | 0.05 | 0.4353 |
| rs915057 | A | G | 0.42 | -0.03 | 0.0049 | 7.61E-10 | -0.0545 | 0.0485 | 0.2607 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | -0.0039 | 0.0919 | 0.9664 |
| rs9402472 | A | G | 0.24 | 0.032699 | 0.0059 | 2.78E-08 | -0.0587 | 0.0661 | 0.3743 |
| rs9427672 | A | G | 0.24 | -0.0321 | 0.0058 | 3.12E-08 | 0.0686 | 0.0652 | 0.2931 |

## Table S4. Power calculations

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Table S4. Power Calculations | | | | | | |
| Gastroesophgeal reflux disease (GERD) |  |  |  |  |  |  |
| Exposure - Outcome | R-squared | N total | Ncases | Ncontrols | Proportion of cases:controls | OR we can detect at 80% power |
| MDD - GERD (UKB, QSkin) | 0.0184 | 332601 | 71522 | 261079 | 0.273947732 | 1.1 |
| MDD - GERD (FinnGen) | 0.0184 | 202836 | 13141 | 189695 | 0.069274361 | 1.21 |
| MDD - GERD (Meta-analysis) | 0.0184 | 535437 | 84663 | 450774 | 0.187816955 | 1.09 |
| Irritable bowel disease (IBS) |  |  |  |  |  |  |
| Exposure - Outcome | R-squared | N total | Ncases | Ncontrols | Proportion of cases:controls | OR we can detect at 80% power |
| MDD - IBS (UKB, Bellygenes) | 0.0184 | 486601 | 53400 | 433201 | 0.123268414 | 1.1 |
| MDD - IBS (FinnGen) | 0.0184 | 187028 | 4605 | 182423 | 0.025243527 | 1.37 |
| MDD - IBS (Meta-analysis) | 0.0184 | 673629 | 58005 | 615624 | 0.094221473 | 1.1 |
| Peptic ulcer disease (PUD) |  |  |  |  |  |  |
| Exposure - Outcome | R-squared | N total | Ncases | Ncontrols | Proportion of cases:controls | OR we can detect at 80% power |
| MDD - PUD (UKB) | 0.0184 | 456327 | 16666 | 439661 | 0.037906478 | 1.18 |
| MDD - PUD (FinnGen) | 0.0184 | 194205 | 4510 | 189695 | 0.023775007 | 1.37 |
| MDD - PUD (Meta-analysis) | 0.0184 | 650532 | 21176 | 629356 | 0.033647093 | 1.16 |
| Non-alcoholic fatty liver disease (NAFLD) |  |  |  |  |  |  |
| Exposure - Outcome | R-squared | N total | Ncases | Ncontrols | Proportion of cases:controls | OR we can detect at 80% power |
| MDD - NAFLD (UKB) | 0.0184 | 377988 | 4761 | 373227 | 0.012756312 | 1.36 |
| MDD - NAFLD (FinnGen) | 0.0184 | 218792 | 894 | 217898 | 0.004102837 | 2 |
| MDD - NAFLD (Meta-analysis) | 0.0184 | 596780 | 5655 | 591125 | 0.009566505 | 1.32 |

## Table S5. List of SNPs with genome-wide significance for potential confounding traits in searched from GWAS catalog and PhenoScanner

|  |  |  |
| --- | --- | --- |
| Phenotypes IVs | SNP | Confounders |
| MDD | rs10149470 | intelligence, self reported educational attainment, anorexia nervosa, obsessive-compulsive disorder, attention deficit hyperactivity disorder, Tourette syndrome, schizophrenia, autism spectrum disorder, bipolar disorder |
| rs11682175 | schizophrenia, autism spectrum disorder, sleep duration, irritability measurement, attention deficit hyperactivity disorder, |
| rs12129573 | anorexia nervosa, obsessive-compulsive disorder, attention deficit hyperactivity disorder, Tourette syndrome, schizophrenia, autism spectrum disorder, bipolar disorder |
| rs1226412 | anorexia nervosa, obsessive-compulsive disorder, attention deficit hyperactivity disorder, Tourette syndrome, schizophrenia, autism spectrum disorder, bipolar disorder |
| rs12552 | self reported educational attainment |
| rs12958048 | neuroticism measurement |
| rs159963 | eosinophil count, neutrophil percentage of granulocytes, eosinophil percentage of granulocytes, respiratory system disease, lymphocyte count |
| rs1806153 | neuroticism measurement, wellbeing measurement, autism spectrum disorder |
| rs5758265 | schizophrenia, neuroticism measurement, anorexia nervosa, obsessive-compulsive disorder, attention deficit hyperactivity disorder, Tourette syndrome, schizophrenia, autism spectrum disorder, bipolar disorder |
| rs61867293 | anorexia nervosa, obsessive-compulsive disorder, attention deficit hyperactivity disorder, Tourette syndrome, schizophrenia, autism spectrum disorder, bipolar disorder |
| rs7200826 | wellbeing measurement, anorexia nervosa, obsessive-compulsive disorder, attention deficit hyperactivity disorder, Tourette syndrome, schizophrenia, autism spectrum disorder, bipolar disorder |
| rs915057 | anorexia nervosa, obsessive-compulsive disorder, attention deficit hyperactivity disorder, Tourette syndrome, schizophrenia, autism spectrum disorder, bipolar disorder |
| rs9427672 | neuroticism measurement |

MDD: major depressive disorder.

## Table S6. MR for genetically predicted major depressive disorder (MDD) and gastrointestinal disorders (GIS) (UKB and several international consortia)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table S6. MR for genetically predicted major depressive disorder (MDD) and gastrointestinal disorders(GIS) (UKB and several international consortia) | | | | | | | | | | | | |
| Exposure | **Outcome** | **N\_snp** | **Method** | **OR** | **95% CI** | **SE** | **P value** | **Cochran’s Q** | **Cochran’s Q P valuea** | **I squareb** | **Egger Intercept** | **Egger Intercept P valuec** |
| MDD | GERD | 40 | IVW raw | 1.318 | (1.214,1.431) | 0.042 | 4.97E-11 | 66.11 | 0.0043 | 0.41 | -0.0027 | 0.767 |
| 40 | Simple median | 1.3 | (1.179,1.433) | 0.05 | 1.44E-07 |  |  |  |  |  |
| 40 | Weighted median | 1.315 | (1.191,1.453) | 0.051 | 6.79E-08 |  |  |  |  |  |
| 40 | Weighted mode | 1.147 | (0.932,1.411) | 0.106 | 0.1962 |  |  |  |  |  |
| 40 | MR-Egger | 1.433 | (0.822,2.499) | 0.284 | 0.2046 |  |  |  |  |  |
| 40 | MR-RAPS | 1.328 | (1.22,1.44) | 0.042 | 1.89E-11 |  |  |  |  |  |
| 40 | MR-PRESSO:raw | 1.32 | (1.21,1.43) | 0.042 | 8.34E-08 |  |  |  |  |  |
| **†** | MR-PRESSO:Outlier-corrected | **†** | **†** | **†** | **†** |  |  |  |  |  |
| MDD | IBS | 42 | IVW raw | 1.464 | (1.329,1.612) | 0.049 | 8.43E-15 | 73.45 | 0.0014 | 0.442 | -0.0064 | 0.53 |
| 42 | Simple median | 1.366 | (1.219,1.531) | 0.058 | 8.03E-08 |  |  |  |  |  |
| 42 | Weighted median | 1.388 | (1.238,1.557) | 0.059 | 2.10E-08 |  |  |  |  |  |
| 42 | Weighted mode | 1.231 | (0.953,1.59) | 0.131 | 0.1122 |  |  |  |  |  |
| 42 | MR-Egger | 1.785 | (0.96,3.319) | 0.317 | 0.0673 |  |  |  |  |  |
| 42 | MR-RAPS | 1.483 | (1.35,1.64) | 0.05 | 2.66E-15 |  |  |  |  |  |
| 42 | MR-PRESSO:raw | 1.46 | (1.33,1.61) | 0.049 | 1.42E-09 |  |  |  |  |  |
| **†** | MR-PRESSO:Outlier-corrected | **†** | **†** | **†** | **†** |  |  |  |  |  |
| MDD | PUD | 42 | IVW raw | 1.237 | (1.093,1.401) | 0.063 | 0.0008 | 46.26 | 0.264 | 0.114 | -0.0043 | 0.747 |
| 42 | Simple median | 1.315 | (1.109,1.559) | 0.087 | 0.0017 |  |  |  |  |  |
| 42 | Weighted median | 1.324 | (1.115,1.571) | 0.088 | 0.0014 |  |  |  |  |  |
| 42 | Weighted mode | 1.4 | (0.978,2.004) | 0.183 | 0.0664 |  |  |  |  |  |
| 42 | MR-Egger | 1.413 | (0.628,3.179) | 0.414 | 0.4033 |  |  |  |  |  |
| 42 | MR-RAPS | 1.245 | (1.1,1.41) | 0.065 | 0.0007 |  |  |  |  |  |
| 42 | MR-PRESSO:raw | 1.24 | (1.09,1.4) | 0.063 | 0.0017 |  |  |  |  |  |
| **†** | MR-PRESSO:Outlier-corrected | **†** | **†** | **†** | **†** |  |  |  |  |  |
| MDD | NAFLD | 42 | IVW raw | 1.284 | (1.047,1.576) | 0.104 | 0.0166 | 45.61 | 0.2863 | 0.101 | -0.0112 | 0.551 |
| 42 | Simple median | 1.365 | (1.015,1.835) | 0.151 | 0.0396 |  |  |  |  |  |
| 42 | Weighted median | 1.115 | (0.834,1.49) | 0.148 | 0.4629 |  |  |  |  |  |
| 42 | Weighted mode | 1.126 | (0.725,1.749) | 0.225 | 0.5978 |  |  |  |  |  |
| 42 | MR-Egger | 1.81 | (0.58,5.648) | 0.581 | 0.3069 |  |  |  |  |  |
| 42 | MR-RAPS | 1.297 | (1.06,1.59) | 0.104 | 0.0122 |  |  |  |  |  |
| 42 | MR-PRESSO:raw | 1.28 | (1.05,1.58) | 0.104 | 0.0212 |  |  |  |  |  |
| **†** | MR-PRESSO:Outlier-corrected | **†** | **†** | **†** | **†** |  |  |  |  |  |

**a:** Cochran’s Q was calculated to quantify heterogeneity, with a P-value < 0.05 indicating the presence of heterogeneity.

**b:** I square was used to assess effect heterogeneity. a value of I square between 0 and 0.25 is considered low heterogeneity; between 0.25 and 0.5 is considered moderate heterogeneity, and above 0.5 is considered high heterogeneity.

**c:** Egger Intercept means the estimate of intercept in MR-Egger regression, and was used to evaluate the directional pleiotropy of IVs, with a P-value < 0.05 indicating the presence of horizontal pleiotropy.

**†:** means MR-PRESSO global test can’t reach significance for our specified significance threshold (MR-PRESSO parameter setting: NbDistribution = 2000, SignifThreshold = 0.05), therefore no outlier can be detected and the outlier-corrected analysis does not make sense, hence the NAs.

Abbreviations: IVW = inverse variance weighted; N\_snp = number of instrumental variables; OR = odds ratio; SE = standard error; SNP = single nucleotide polymorphism;

## Table S7. MR for genetically predicted major depressive disorder (MDD) and gastrointestinal disorders (GIS) (FinnGen)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table S7. MR for genetically predicted major depressive disorder (MDD) and gastrointestinal disorders(GIS) (FinnGen) | | | | | | | | | | | | |
| Exposure | **Outcome** | **N\_snp** | **Method** | **OR** | **95% CI** | **SE** | **P value** | **Cochran’s Q** | **Cochran’s Q P valuea** | **I squareb** | **Egger Intercept** | **Egger Intercept P valuec** |
| MDD | GERD | 41 | IVW raw | 1.221 | (1.059,1.408) | 0.073 | 0.006 | 34.35 | 0.722 | 0 | -0.005 | 0.7283 |
| 41 | Simple median | 1.228 | (1.004,1.501) | 0.102 | 0.0452 |  |  |  |  |  |
| 41 | Weighted median | 1.269 | (1.039,1.548) | 0.102 | 0.0194 |  |  |  |  |  |
| 41 | Weighted mode | 1.371 | (0.917,2.05) | 0.205 | 0.1243 |  |  |  |  |  |
| 41 | MR-Egger | 1.421 | (0.592,3.41) | 0.447 | 0.4316 |  |  |  |  |  |
| 41 | MR-RAPS | 1.227 | (1.06,1.42) | 0.075 | 0.0067 |  |  |  |  |  |
| 41 | MR-PRESSO:raw | 1.22 | (1.07,1.39) | 0.067 | 0.0051 |  |  |  |  |  |
| 41 | MR-PRESSO:Outlier-corrected | | (NA,NA) |  |  |  |  |  |  |  |
| MDD | IBS | 41 | IVW raw | 1.605 | (1.277,2.018) | 0.117 | 4.93E-05 | 34.73 | 0.706 | 0 | -0.0089 | 0.6982 |
| 41 | Simple median | 1.451 | (1.041,2.021) | 0.169 | 0.0278 |  |  |  |  |  |
| 41 | Weighted median | 1.498 | (1.081,2.077) | 0.167 | 0.0153 |  |  |  |  |  |
| 41 | Weighted mode | 1.203 | (0.563,2.572) | 0.388 | 0.6337 |  |  |  |  |  |
| 41 | MR-Egger | 2.11 | (0.52,8.565) | 0.715 | 0.2963 |  |  |  |  |  |
| 41 | MR-RAPS | 1.624 | (1.28,2.06) | 0.121 | 6.19E-05 |  |  |  |  |  |
| 41 | MR-PRESSO:raw | 1.61 | (1.3,1.99) | 0.109 | 8.97E-05 |  |  |  |  |  |
| **†** | MR-PRESSO:Outlier-corrected | **†** | **†** | **†** | **†** |  |  |  |  |  |
| MDD | PUD | 41 | IVW raw | 1.152 | (0.911,1.455) | 0.119 | 0.2372 | 27.71 | 0.929 | 0 | 0.0093 | 0.6947 |
| 41 | Simple median | 1.087 | (0.784,1.507) | 0.167 | 0.6157 |  |  |  |  |  |
| 41 | Weighted median | 1.102 | (0.798,1.522) | 0.165 | 0.5534 |  |  |  |  |  |
| 41 | Weighted mode | 1.053 | (0.564,1.963) | 0.318 | 0.8717 |  |  |  |  |  |
| 41 | MR-Egger | 0.864 | (0.205,3.63) | 0.733 | 0.8414 |  |  |  |  |  |
| 41 | MR-RAPS | 1.155 | (0.91,1.47) | 0.123 | 0.2442 |  |  |  |  |  |
| 41 | MR-PRESSO:raw | 1.15 | (0.95,1.4) | 0.099 | 0.1633 |  |  |  |  |  |
| **†** | MR-PRESSO:Outlier-corrected | **†** | **†** | **†** | **†** |  |  |  |  |  |
| MDD | NAFLD | 41 | IVW raw | 1.483 | (0.892,2.464) | 0.259 | 0.1285 | 33.03 | 0.775 | 0 | -0.0299 | 0.5598 |
| 41 | Simple median | 0.993 | (0.481,2.05) | 0.37 | 0.9849 |  |  |  |  |  |
| 41 | Weighted median | 1.031 | (0.501,2.119) | 0.368 | 0.9344 |  |  |  |  |  |
| 41 | Weighted mode | 0.754 | (0.166,3.426) | 0.773 | 0.7143 |  |  |  |  |  |
| 41 | MR-Egger | 3.725 | (0.165,83.956) | 1.589 | 0.408 |  |  |  |  |  |
| 41 | MR-RAPS | 1.497 | (0.89,2.53) | 0.267 | 0.1315 |  |  |  |  |  |
| 41 | MR-PRESSO:raw | 1.48 | (0.93,2.35) | 0.235 | 0.1022 |  |  |  |  |  |
| **†** | MR-PRESSO:Outlier-corrected | **†** | **†** | **†** | **†** |  |  |  |  |  |

**a:** Cochran’s Q was calculated to quantify heterogeneity, with a P-value < 0.05 indicating the presence of heterogeneity.

**b:** I square was used to assess effect heterogeneity. a value of I square between 0 and 0.25 is considered low heterogeneity; between 0.25 and 0.5 is considered moderate heterogeneity, and above 0.5 is considered high heterogeneity.

**c:** Egger Intercept means the estimate of intercept in MR-Egger regression, and was used to evaluate the directional pleiotropy of IVs, with a P-value < 0.05 indicating the presence of horizontal pleiotropy.

**†:** means MR-PRESSO global test can’t reach significance for our specified significance threshold (MR-PRESSO parameter setting: NbDistribution = 2000, SignifThreshold = 0.05), therefore no outlier can be detected and the outlier-corrected analysis does not make sense, hence the NAs.

Abbreviations: IVW = inverse variance weighted; N\_snp = number of instrumental variables; OR = odds ratio; SE = standard error; SNP = single nucleotide polymorphism;

## Table S8. Fixed effect meta-analysis of MR for genetically predicted major depressive disorder (MDD) and gastrointestinal disorders (GIS) (UK Biobank, FinnGen, and several international genetic consortium)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| method | outcome | OR | se | pval | exposure | p.bon |
| IVW raw | GERD | 1.293173 | 0.036405 | 1.64E-12 | MDD | 6.55E-12 |
| IVW raw | IBS | 1.483981 | 0.045196 | 2.47E-18 | MDD | 9.87E-18 |
| IVW raw | NAFLD | 1.309957 | 0.09651 | 0.005149 | MDD | 0.0206 |
| IVW raw | PUD | 1.218034 | 0.055679 | 0.000396 | MDD | 0.0016 |
| MR-Egger | GERD | 1.429624 | 0.23971 | 0.135957 | MDD |  |
| MR-Egger | IBS | 1.834181 | 0.289795 | 0.036332 | MDD |  |
| MR-Egger | NAFLD | 1.970215 | 0.545668 | 0.213951 | MDD |  |
| MR-Egger | PUD | 1.254538 | 0.360477 | 0.529299 | MDD |  |
| MR-PRESSO:raw | GERD | 1.289894 | 0.035586 | 8.47E-13 | MDD |  |
| MR-PRESSO:raw | IBS | 1.486563 | 0.044692 | 7.24E-19 | MDD |  |
| MR-PRESSO:raw | NAFLD | 1.314668 | 0.095103 | 0.004018 | MDD |  |
| MR-PRESSO:raw | PUD | 1.21197 | 0.053151 | 0.000298 | MDD |  |
| MR-RAPS | GERD | 1.303302 | 0.036645 | 4.87E-13 | MDD |  |
| MR-RAPS | IBS | 1.502713 | 0.04621 | 1.21E-18 | MDD |  |
| MR-RAPS | NAFLD | 1.321593 | 0.096908 | 0.00401 | MDD |  |
| MR-RAPS | PUD | 1.224616 | 0.057469 | 0.000422 | MDD |  |
| Simple median | GERD | 1.285255 | 0.044896 | 2.27E-08 | MDD |  |
| Simple median | IBS | 1.374819 | 0.054859 | 6.53E-09 | MDD |  |
| Simple median | NAFLD | 1.304211 | 0.139806 | 0.057464 | MDD |  |
| Simple median | PUD | 1.262939 | 0.077158 | 0.002482 | MDD |  |
| Weighted median | GERD | 1.305779 | 0.045616 | 4.95E-09 | MDD |  |
| Weighted median | IBS | 1.399946 | 0.05563 | 1.47E-09 | MDD |  |
| Weighted median | NAFLD | 1.102964 | 0.137311 | 0.475403 | MDD |  |
| Weighted median | PUD | 1.270862 | 0.077647 | 0.002022 | MDD |  |
| Weighted mode | GERD | 1.190963 | 0.094158 | 0.063445 | MDD |  |
| Weighted mode | IBS | 1.228319 | 0.124117 | 0.097544 | MDD |  |
| Weighted mode | NAFLD | 1.091553 | 0.216034 | 0.685113 | MDD |  |
| Weighted mode | PUD | 1.303558 | 0.158612 | 0.09465 | MDD |  |

## Table S9. Univariable Mendelian randomization between major depressive disorder (MDD) and gastrointestinal disorders (GIS based on UKB sample) after removing SNPs associated with potential confounding diseases or traits.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Univariable Mendelian randomization between major depressive disorder (MDD) and gastrointestinal disorders (GIS) after removing SNPs associated with potential confounding diseases or traits. | | | | | | | | | | | | |
| Exposure | **Outcome** | **N\_snp** | **Method** | **OR** | **95% CI** | **SE** | **P value** | **Cochran’s Q** | **Cochran’s Q P valuea** | **I squareb** | **Egger Intercept** | **Egger Intercept P valuec** |
| MDD | GERD | 27 | IVW raw | 1.321 | (1.196,1.459) | 0.051 | 3.95E-08 | 41.42 | 0.028 | 0.372 | 0.0004 | 0.972 |
| 27 | Simple median | 1.331 | (1.176,1.507) | 0.063 | 6.05E-06 |  |  |  |  |  |
| 27 | Weighted median | 1.333 | (1.18,1.506) | 0.062 | 3.94E-06 |  |  |  |  |  |
| 27 | Weighted mode | 1.221 | (0.956,1.56) | 0.125 | 0.1104 |  |  |  |  |  |
| 27 | MR-Egger | 1.305 | (0.678,2.515) | 0.335 | 0.4258 |  |  |  |  |  |
| 27 | MR-RAPS | 1.331 | (1.21,1.47) | 0.05 | 1.15E-08 |  |  |  |  |  |
| 27 | MR-PRESSO:raw | 1.32 | (1.2,1.46) | 0.051 | 9.19E-06 |  |  |  |  |  |
| **†** | **MR-PRESSO:Outlier-corrected** | **†** | **†** | **†** |  |  |  |  |  |  |
| MDD | IBS | 29 | IVW raw | 1.447 | (1.305,1.605) | 0.053 | 2.50E-12 | 38.08 | 0.097 | 0.265 | -0.0106 | 0.299 |
| 29 | Simple median | 1.312 | (1.145,1.503) | 0.069 | 9.05E-05 |  |  |  |  |  |
| 29 | Weighted median | 1.311 | (1.147,1.498) | 0.068 | 7.01E-05 |  |  |  |  |  |
| 29 | Weighted mode | 1.232 | (0.968,1.568) | 0.123 | 0.0893 |  |  |  |  |  |
| 29 | MR-Egger | 2.019 | (1.081,3.769) | 0.319 | 0.0275 |  |  |  |  |  |
| 29 | MR-RAPS | 1.466 | (1.32,1.63) | 0.053 | 7.86E-13 |  |  |  |  |  |
| 29 | MR-PRESSO:raw | 1.45 | (1.3,1.6) | 0.053 | 1.29E-07 |  |  |  |  |  |
|  |  | **†** | **MR-PRESSO:Outlier-corrected** | **†** | **†** | **†** |  |  |  |  |  |  |
| MDD | PUD | 29 | IVW raw | 1.217 | (1.055,1.405) | 0.073 | 0.0072 | 26.68 | 0.536 | -0.05 | 0.0038 | 0.792 |
| 29 | Simple median | 1.297 | (1.053,1.597) | 0.106 | 0.0146 |  |  |  |  |  |
| 29 | Weighted median | 1.317 | (1.074,1.616) | 0.104 | 0.0083 |  |  |  |  |  |
| 29 | Weighted mode | 1.387 | (0.916,2.099) | 0.212 | 0.1222 |  |  |  |  |  |
| 29 | MR-Egger | 1.082 | (0.448,2.609) | 0.449 | 0.8613 |  |  |  |  |  |
| 29 | MR-RAPS | 1.224 | (1.06,1.42) | 0.076 | 0.0076 |  |  |  |  |  |
| 29 | MR-PRESSO:raw | 1.22 | (1.06,1.4) | 0.071 | 0.0102 |  |  |  |  |  |
|  |  | **†** | **MR-PRESSO:Outlier-corrected** | **†** | **†** | **†** |  |  |  |  |  |  |
| MDD | NAFLD | 29 | IVW raw | 1.378 | (1.084,1.751) | 0.122 | 0.0088 | 29.02 | 0.411 | 0.035 | -0.0093 | 0.641 |
| 29 | Simple median | 1.454 | (1.002,2.108) | 0.19 | 0.0487 |  |  |  |  |  |
| 29 | Weighted median | 1.141 | (0.801,1.625) | 0.18 | 0.4650 |  |  |  |  |  |
| 29 | Weighted mode | 1.117 | (0.66,1.892) | 0.269 | 0.68 |  |  |  |  |  |
| 29 | MR-Egger | 1.829 | (0.551,6.076) | 0.613 | 0.3243 |  |  |  |  |  |
| 29 | MR-RAPS | 1.397 | (1.09,1.79) | 0.126 | 0.0082 |  |  |  |  |  |
| 29 | MR-PRESSO:raw | 1.38 | (1.08,1.75) | 0.122 | 0.0140 |  |  |  |  |  |
|  |  | **†** | **MR-PRESSO:Outlier-corrected** | **†** | **†** | **†** |  |  |  |  |  |  |

**a:** Cochran’s Q was calculated to quantify heterogeneity, with a P-value < 0.05 indicating the presence of heterogeneity.

**b:** I square was used to assess effect heterogeneity. a value of I square between 0 and 0.25 is considered low heterogeneity; between 0.25 and 0.5 is considered moderate heterogeneity, and above 0.5 is considered high heterogeneity.

**c:** Egger Intercept means the estimate of intercept in MR-Egger regression, and was used to evaluate the directional pleiotropy of IVs, with a P-value < 0.05 indicating the presence of horizontal pleiotropy.

**†:** means MR-PRESSO global test can’t reach significance for our specified significance threshold (MR-PRESSO parameter setting: NbDistribution = 2000, SignifThreshold = 0.05), therefore no outlier can be detected and the outlier-corrected analysis does not make sense, hence the NAs.

Abbreviations: IVW = inverse variance weighted; N\_snp = number of instrumental variables; OR = odds ratio; SE = standard error; SNP = single nucleotide polymorphism;

## Table S10. Mendelian randomization analyses for the genetically predicted effects of MDD on negative control outcomes

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table S9. Mendelian randomization analyses for the genetically predicted effects of MDD on negative control outcomes | | | | | | | | | | | | |
| Exposure | **Outcome** | **N\_snp** | **Method** | **OR** | **95% CI** | **SE** | **P value** | **Cochran**’**s Q** | **Cochran’s Q P value**a | **I square**b | **Egger Intercept** | **Egger Intercept P value**c |
| MDD | Skin colour | 36 | IVW raw | 0.996 | (0.974,1.02) | 0.012 | 0.753 | 103.61 | 1.04E-08 | 0.662 | -0.0019 | 0.451 |
| 36 | Simple median | 0.992 | (0.97,1.015) | 0.012 | 0.479 |  |  |  |  |  |
| 36 | Weighted median | 0.992 | (0.97,1.015) | 0.012 | 0.482 |  |  |  |  |  |
| 36 | Weighted mode | 0.993 | (0.942,1.047) | 0.027 | 0.799 |  |  |  |  |  |
| 36 | MR-Egger | 1.055 | (0.909,1.226) | 0.076 | 0.481 |  |  |  |  |  |
| 36 | MR-RAPS | 0.998 | (0.98,1.02) | 0.012 | 0.887 |  |  |  |  |  |
| 36 | MR-PRESSO:raw | 1 | (0.97,1.02) | 0.012 | 0.755 |  |  |  |  |  |
| 33 | MR-PRESSO:Outlier-corrected | 1 | (0.98,1.02) | 0.01 | 0.852 |  |  |  |  |  |
| MDD | Ease of  skin tanning | 36 | IVW raw | 0.981 | (0.938,1.025) | 0.023 | 0.389 | 135.04 | 1.12E-13 | 0.741 | -0.004 | 0.402 |
| 36 | Simple median | 0.969 | (0.93,1.009) | 0.021 | 0.125 |  |  |  |  |  |
| 36 | Weighted median | 0.967 | (0.928,1.007) | 0.021 | 0.108 |  |  |  |  |  |
| 36 | Weighted mode | 0.952 | (0.876,1.035) | 0.043 | 0.247 |  |  |  |  |  |
| 36 | MR-Egger | 1.108 | (0.833,1.475) | 0.146 | 0.48 |  |  |  |  |  |
| 36 | MR-RAPS | 0.984 | (0.94,1.03) | 0.022 | 0.476 |  |  |  |  |  |
| 36 | MR-PRESSO:raw | 0.98 | (0.94,1.03) | 0.023 | 0.395 |  |  |  |  |  |
| 32 | MR-PRESSO:Outlier-corrected | 0.99 | (0.95,1.03) | 0.021 | 0.653 |  |  |  |  |  |

**a:** Cochran’s Q was calculated to quantify heterogeneity, with a P-value < 0.05 indicating the presence of heterogeneity.

**b:** I square was used to assess effect heterogeneity. a value of I square between 0 and 0.25 is considered low heterogeneity; between 0.25 and 0.5 is considered moderate heterogeneity, and above 0.5 is considered high heterogeneity.

**c:** Egger Intercept means the estimate of intercept in MR-Egger regression, and was used to evaluate the directional pleiotropy of IVs, with a P-value < 0.05 indicating the presence of horizontal pleiotropy.

## Table S11. Mendelian randomization analyses for the genetically predicted effects of major depressive disorder (MDD) on potential confounders of the association between major depressive disorder (MDD) and gastrointestinal disorders (GIS).

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Exposure | Outcome | N\_snp | Method | OR | 95% CI | SE | P value | Cochran’s Q | Cochran’s Q P valuea | I squareb | Egger Intercept | Egger Intercept P valuec |
| MDD | Years of schooling | 36 | IVW raw | 1.024 | (0.963,1.09) | 0.032 | 0.4465 | 174.35 | 2.06E-20 | 0.799 | -0.00002 | 0.998 |
| 36 | Simple median | 0.99 | (0.937,1.046) | 0.028 | 0.7305 |  |  |  |  |  |
| 36 | Weighted median | 0.998 | (0.945,1.055) | 0.028 | 0.9538 |  |  |  |  |  |
| 36 | Weighted mode | 0.944 | (0.835,1.067) | 0.062 | 0.3556 |  |  |  |  |  |
| 36 | MR-Egger | 1.025 | (0.691,1.519) | 0.201 | 0.9027 |  |  |  |  |  |
| 36 | DIVW | 1.025 | (0.958,1.096) | 0.034 | 0.4724 |  |  |  |  |  |
| 36 | MR-RAPS | 1.007 | (0.95,1.07) | 0.031 | 0.8205 |  |  |  |  |  |
| 36 | MR-PRESSO:raw | 1.02 | (0.96,1.09) | 0.032 | 0.4516 |  |  |  |  |  |
| 28 | MR-PRESSO:Outlier-corrected | 0.98 | (0.94,1.03) | 0.024 | 0.4827 |  |  |  |  |  |
| MDD | Pack years of smoking | 35 | IVW raw | 1.052 | (0.994,1.113) | 0.029 | 0.0786 | 69.02 | 0.0004 | 0.507 | 0.0001 | 0.985 |
| 35 | Simple median | 1.052 | (0.986,1.121) | 0.033 | 0.1247 |  |  |  |  |  |
| 35 | Weighted median | 1.071 | (1.005,1.141) | 0.032 | 0.0345 |  |  |  |  |  |
| 35 | Weighted mode | 1.072 | (0.946,1.215) | 0.064 | 0.2741 |  |  |  |  |  |
| 35 | MR-Egger | 1.048 | (0.73,1.506) | 0.185 | 0.799 |  |  |  |  |  |
| 35 | DIVW | 1.053 | (0.995,1.115) | 0.029 | 0.0757 |  |  |  |  |  |
| 35 | MR-RAPS | 1.049 | (0.99,1.11) | 0.029 | 0.1015 |  |  |  |  |  |
| 35 | MR-PRESSO:raw | 1.05 | (0.99,1.11) | 0.029 | 0.0876 |  |  |  |  |  |
| 34 | MR-PRESSO:Outlier-corrected | | (NA,NA) |  |  |  |  |  |  |  |
| MDD | Alcohol intake frequency | 37 | IVW raw | 1.071 | (0.989,1.159) | 0.04 | 0.0903 | 200.07 | 1.22E-24 | 0.82 | -0.006 | 0.472 |
| 37 | Simple median | 1.099 | (1.035,1.166) | 0.03 | 0.0019 |  |  |  |  |  |
| 37 | Weighted median | 1.096 | (1.034,1.161) | 0.03 | 0.0019 |  |  |  |  |  |
| 37 | Weighted mode | 1.065 | (0.967,1.174) | 0.049 | 0.1998 |  |  |  |  |  |
| 37 | MR-Egger | 1.292 | (0.774,2.156) | 0.261 | 0.327 |  |  |  |  |  |
| 37 | DIVW | 1.073 | (0.99,1.163) | 0.041 | 0.0881 |  |  |  |  |  |
| 37 | MR-RAPS | 1.074 | (1,1.16) | 0.038 | 0.0625 |  |  |  |  |  |
| 37 | MR-PRESSO:raw | 1.07 | (0.99,1.16) | 0.04 | 0.099 |  |  |  |  |  |
| 28 | MR-PRESSO:Outlier-corrected | 1.1 | (1.05,1.15) | 0.024 | 0.0004 |  |  |  |  |  |
| MDD | Body mass index | 32 | IVW raw | 0.976 | (0.897,1.062) | 0.043 | 0.5711 | 102.3 | 1.51E-09 | 0.697 | -0.014 | 0.126 |
| 32 | Simple median | 1.018 | (0.939,1.104) | 0.041 | 0.6696 |  |  |  |  |  |
| 32 | Weighted median | 1.04 | (0.96,1.125) | 0.04 | 0.3365 |  |  |  |  |  |
| 32 | Weighted mode | 1.127 | (0.991,1.283) | 0.066 | 0.0694 |  |  |  |  |  |
| 32 | MR-Egger | 1.53 | (0.874,2.679) | 0.286 | 0.1365 |  |  |  |  |  |
| 32 | DIVW | 0.975 | (0.894,1.064) | 0.044 | 0.572 |  |  |  |  |  |
| 32 | MR-RAPS | 0.984 | (0.9,1.08) | 0.046 | 0.7263 |  |  |  |  |  |
| 32 | MR-PRESSO:raw | 0.98 | (0.9,1.06) | 0.043 | 0.5752 |  |  |  |  |  |
| 29 | MR-PRESSO:Outlier-corrected | 1.02 | (0.95,1.1) | 0.038 | 0.5998 |  |  |  |  |  |
| MDD | Waist circumference | 32 | IVW raw | 0.991 | (0.906,1.083) | 0.045 | 0.8393 | 87.06 | 3.17E-07 | 0.644 | -0.013 | 0.189 |
| 32 | Simple median | 1.021 | (0.932,1.117) | 0.046 | 0.6606 |  |  |  |  |  |
| 32 | Weighted median | 1.019 | (0.931,1.117) | 0.047 | 0.679 |  |  |  |  |  |
| 32 | Weighted mode | 1.176 | (0.995,1.391) | 0.085 | 0.0577 |  |  |  |  |  |
| 32 | MR-Egger | 1.497 | (0.824,2.721) | 0.305 | 0.1856 |  |  |  |  |  |
| 32 | DIVW | 0.991 | (0.904,1.086) | 0.047 | 0.8392 |  |  |  |  |  |
| 32 | MR-RAPS | 1.003 | (0.91,1.1) | 0.048 | 0.9454 |  |  |  |  |  |
| 32 | MR-PRESSO:raw | 0.99 | (0.91,1.08) | 0.045 | 0.8406 |  |  |  |  |  |
| 31 | MR-PRESSO:Outlier-corrected | | (NA,NA) |  |  |  |  |  |  |  |
| MDD | Time spent doing vigorous physical activity | 36 | IVW raw | 0.927 | (0.85,1.01) | 0.044 | 0.084 | 31.77 | 0.6248 | -0.102 | 0.005 | 0.563 |
| 36 | Simple median | 0.886 | (0.784,1.002) | 0.063 | 0.0531 |  |  |  |  |  |
| 36 | Weighted median | 0.887 | (0.785,1.003) | 0.063 | 0.0555 |  |  |  |  |  |
| 36 | Weighted mode | 0.908 | (0.689,1.195) | 0.14 | 0.4901 |  |  |  |  |  |
| 36 | MR-Egger | 0.787 | (0.451,1.372) | 0.284 | 0.3976 |  |  |  |  |  |
| 36 | DIVW | 0.925 | (0.851,1.005) | 0.043 | 0.0655 |  |  |  |  |  |
| 36 | MR-RAPS | 0.925 | (0.85,1.01) | 0.045 | 0.0857 |  |  |  |  |  |
| 36 | MR-PRESSO:raw | 0.93 | (0.85,1.01) | 0.042 | 0.0783 |  |  |  |  |  |
| 36 | MR-PRESSO:Outlier-corrected | | (NA,NA) |  |  |  |  |  |  |  |
| MDD | C-Reactive protein level | 32 | IVW raw | 1.067 | (0.996,1.143) | 0.035 | 0.0669 | 78.8 | 4.89E-06 | 0.607 | -0.0117 | 0.109 |
| 32 | Simple median | 1.084 | (1.011,1.163) | 0.036 | 0.0239 |  |  |  |  |  |
| 32 | Weighted median | 1.102 | (1.028,1.182) | 0.036 | 0.0064 |  |  |  |  |  |
| 32 | Weighted mode | 1.141 | (0.989,1.317) | 0.073 | 0.0704 |  |  |  |  |  |
| 32 | MR-Egger | 1.544 | (0.998,2.388) | 0.223 | 0.0509 |  |  |  |  |  |
| 32 | DIVW | 1.069 | (0.996,1.147) | 0.036 | 0.0658 |  |  |  |  |  |
| 32 | MR-RAPS | 1.071 | (1,1.15) | 0.037 | 0.0606 |  |  |  |  |  |
| 32 | MR-PRESSO:raw | 1.07 | (1,1.14) | 0.035 | 0.0765 |  |  |  |  |  |
| 29 | MR-PRESSO:Outlier-corrected | 1.08 | (1.03,1.15) | 0.029 | 0.0085 |  |  |  |  |  |
| MDD | Household income | 37 | IVW raw | 0.959 | (0.9,1.022) | 0.032 | 0.2009 | 168.99 | 4.04E-19 | 0.787 | -0.0020908699076701 | 0.758 |
| 37 | Simple median | 0.952 | (0.9,1.008) | 0.029 | 0.091 |  |  |  |  |  |
| 37 | Weighted median | 0.953 | (0.902,1.008) | 0.028 | 0.0926 |  |  |  |  |  |
| 37 | Weighted mode | 0.925 | (0.785,1.09) | 0.084 | 0.3524 |  |  |  |  |  |
| 37 | MR-Egger | 1.024 | (0.677,1.548) | 0.211 | 0.9121 |  |  |  |  |  |
| 37 | DIVW | 0.958 | (0.898,1.022) | 0.033 | 0.1977 |  |  |  |  |  |
| 37 | MR-RAPS | 0.956 | (0.9,1.02) | 0.032 | 0.1572 |  |  |  |  |  |
| 37 | MR-PRESSO:raw | 0.96 | (0.9,1.02) | 0.032 | 0.2091 |  |  |  |  |  |
| 32 | MR-PRESSO:Outlier-corrected | 0.97 | (0.92,1.03) | 0.028 | 0.2973 |  |  |  |  |  |
| MDD | Townsend deprivation index | 37 | IVW raw | 1.052 | (1.011,1.094) | 0.02 | 0.0116 | 110.91 | 1.47E-09 | 0.675 | 0.000626532242157887 | 0.882 |
| 37 | Simple median | 1.056 | (1.016,1.099) | 0.02 | 0.0064 |  |  |  |  |  |
| 37 | Weighted median | 1.053 | (1.013,1.095) | 0.02 | 0.0089 |  |  |  |  |  |
| 37 | Weighted mode | 1.062 | (0.97,1.162) | 0.046 | 0.1919 |  |  |  |  |  |
| 37 | MR-Egger | 1.032 | (0.798,1.334) | 0.131 | 0.8106 |  |  |  |  |  |
| 37 | DIVW | 1.054 | (1.012,1.097) | 0.021 | 0.0109 |  |  |  |  |  |
| 37 | MR-RAPS | 1.049 | (1.01,1.09) | 0.021 | 0.021 |  |  |  |  |  |
| 37 | MR-PRESSO:raw | 1.05 | (1.01,1.09) | 0.02 | 0.0161 |  |  |  |  |  |
| 34 | MR-PRESSO:Outlier-corrected | 1.06 | (1.02,1.1) | 0.018 | 0.0036 |  |  |  |  |  |

**a:** Cochran’s Q was calculated to quantify heterogeneity, with a P-value < 0.05 indicating the presence of heterogeneity.

**b:** I square was used to assess effect heterogeneity. a value of I square between 0 and 0.25 is considered low heterogeneity; between 0.25 and 0.5 is considered moderate heterogeneity, and above 0.5 is considered high heterogeneity.

**c:** Egger Intercept means the estimate of intercept in MR-Egger regression, and was used to evaluate the directional pleiotropy of IVs, with a P-value < 0.05 indicating the presence of horizontal pleiotropy.

**†:** means MR-PRESSO global test can’t reach significance for our specified significance threshold (MR-PRESSO parameter setting: NbDistribution = 2000, SignifThreshold = 0.05), therefore no outlier can be detected and the outlier-corrected analysis does not make sense, hence the NAs.

Abbreviations: IVW = inverse variance weighted; N\_snp = number of instrumental variables; OR = odds ratio; SE = standard error; SNP = single nucleotide polymorphism;

## Table S12. Reversed MR for genetically predicted gastrointestinal disorders (GIS, based on UKB sample) on major depressive disorder (MDD)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Exposure | Outcome | N\_snp | Method | OR | 95% CI | SE | P value | Cochran’s Q | Cochran’s Q P valuea | I squareb | Egger Intercept | Egger Intercept P valuec |
| GERD | MDD | 8 | IVW raw | 1.398 | (1.114,1.754) | 0.116 | **0.0038** | 12.21 | 0.094 | 0.427 | -0.0277 | 0.529 |
| IBS | MDD | 3 | IVW raw | 1.301 | (1.003,1.688) | 0.133 | **0.0474** | 1.08 | 0.583 | -0.853 | 0.0739 | 0.501 |
| PUD | MDD | 5 | IVW raw | 0.969 | (0.845,1.111) | 0.07 | 0.6494 | 8.95 | 0.062 | 0.553 | -0.0071 | 0.867 |
| NAFLD | MDD | 2 | IVW raw | 0.987 | (0.942,1.035) | 0.024 | 0.5938 | 0.3 | 0.582 | -2.304 | NA | NA |

## Table S13. Bias and Type 1 error rate for Mendelian randomization with sample overlap

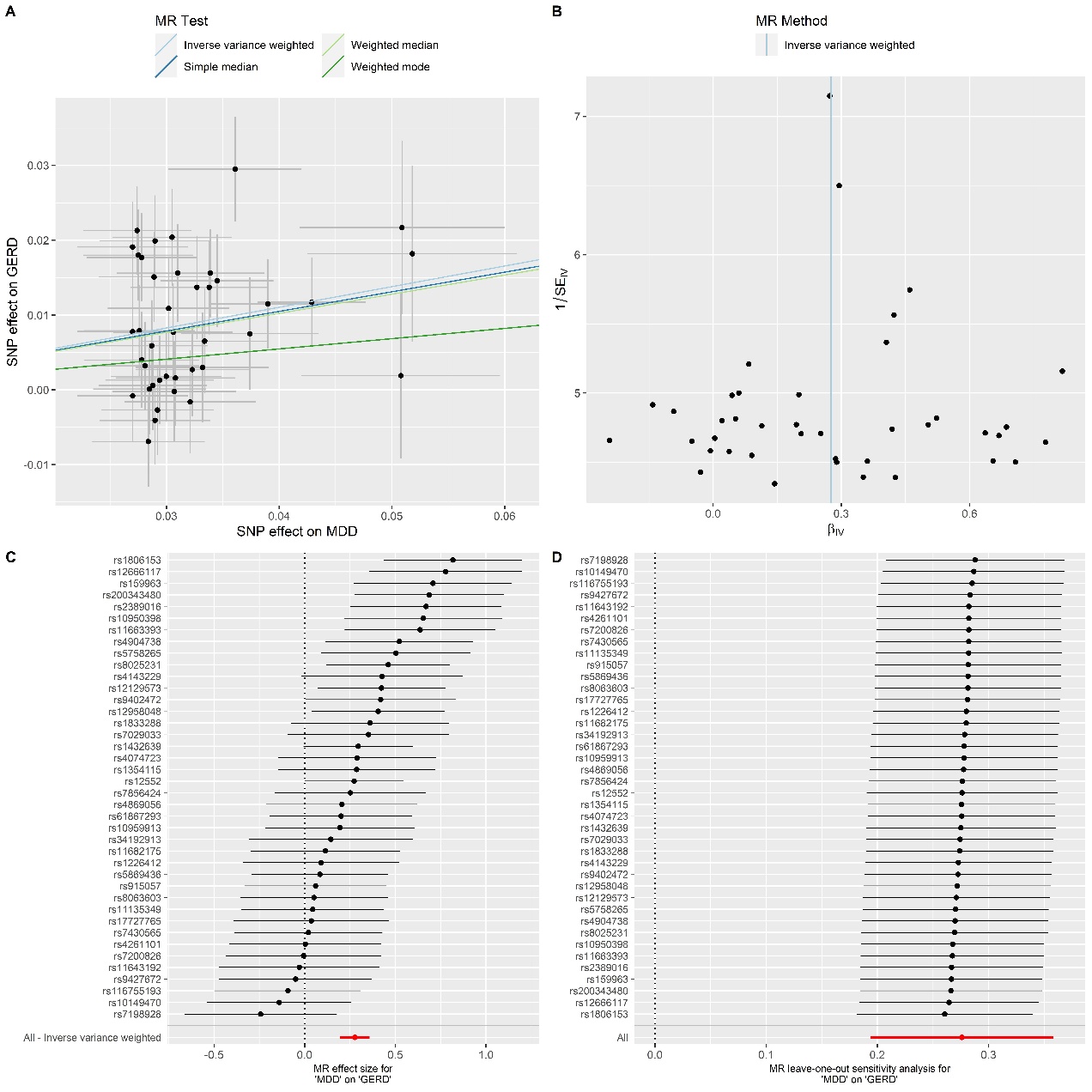
|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Lactate → NAFLD\_UKB |  |  |  |  |  |  |
| Parameters | **R2** | **N exposure** | **N outcome** | **Number of instruments** | **Bias of the observational estimate (Beta)** | **Proportion of cases** |
|  | 0.0184 | 480359 | 332601 | 40 | 0.256 | 0.215 |
| Results |  |  |  |  |  |  |
|  | Using specified value of concentration parameter | | | Using conservative value of concentration parameter | | |
|  | Overlap proportion | Bias | Type 1 error rate | Overlap proportion | Bias | Type 1 error rate |
|  | 0 | 0 | 0.05 | 0 | 0 | 0.05 |
|  | 0.1 | 0 | 0.05 | 0.1 | 0 | 0.05 |
|  | 0.2 | 0 | 0.05 | 0.2 | 0 | 0.05 |
|  | 0.3 | 0 | 0.05 | 0.3 | 0 | 0.05 |
|  | 0.4 | 0 | 0.05 | 0.4 | 0 | 0.05 |
|  | 0.5 | 0.001 | 0.05 | 0.5 | 0.001 | 0.05 |
|  | 0.6 | 0.001 | 0.05 | 0.6 | 0.001 | 0.05 |
|  | 0.7 | 0.001 | 0.05 | 0.7 | 0.001 | 0.05 |
|  | 0.8 | 0.001 | 0.05 | 0.8 | 0.001 | 0.05 |
|  | 0.9 | 0.001 | 0.05 | 0.9 | 0.001 | 0.05 |
|  | 1 | 0.001 | 0.05 | 1 | 0.001 | 0.05 |
| MDD → IBS |  |  |  |  |  |  |
| Parameters | **R2** | **N exposure** | **N outcome** | **Number of instruments** | **Bias of the observational estimate (Beta)** | **Proportion of cases** |
|  | 0.0184 | 480359 | 486601 | 42 | 0.3947 | 0.11 |
| Results |  |  |  |  |  |  |
|  | Using specified value of concentration parameter | | | Using conservative value of concentration parameter | | |
|  | Overlap proportion | Bias | Type 1 error rate | Overlap proportion | Bias | Type 1 error rate |
|  | 0 | 0 | 0.05 | 0 | 0 | 0.05 |
|  | 0.1 | 0 | 0.05 | 0.1 | 0 | 0.05 |
|  | 0.2 | 0 | 0.05 | 0.2 | 0 | 0.05 |
|  | 0.3 | 0.001 | 0.05 | 0.3 | 0.001 | 0.05 |
|  | 0.4 | 0.001 | 0.05 | 0.4 | 0.001 | 0.05 |
|  | 0.5 | 0.001 | 0.05 | 0.5 | 0.001 | 0.05 |
|  | 0.6 | 0.001 | 0.05 | 0.6 | 0.001 | 0.05 |
|  | 0.7 | 0.001 | 0.05 | 0.7 | 0.001 | 0.05 |
|  | 0.8 | 0.001 | 0.05 | 0.8 | 0.001 | 0.05 |
|  | 0.9 | 0.002 | 0.05 | 0.9 | 0.002 | 0.05 |
|  | 1 | 0.002 | 0.05 | 1 | 0.002 | 0.05 |
| MDD → PUD |  |  |  |  |  |  |
| Parameters | **R2** | **N exposure** | **N outcome** | **Number of instruments** | **Bias of the observational estimate (Beta)** | **Proportion of cases** |
|  | 0.0184 | 480359 | 456327 | 42 | 0.197 | 0.0365 |
| Results |  |  |  |  |  |  |
|  | Using specified value of concentration parameter | | | Using conservative value of concentration parameter | | |
|  | Overlap proportion | Bias | Type 1 error rate | Overlap proportion | Bias | Type 1 error rate |
|  | 0 | 0 | 0.05 | 0 | 0 | 0.05 |
|  | 0.1 | 0 | 0.05 | 0.1 | 0 | 0.05 |
|  | 0.2 | 0 | 0.05 | 0.2 | 0 | 0.05 |
|  | 0.3 | 0 | 0.05 | 0.3 | 0 | 0.05 |
|  | 0.4 | 0 | 0.05 | 0.4 | 0 | 0.05 |
|  | 0.5 | 0 | 0.05 | 0.5 | 0 | 0.05 |
|  | 0.6 | 0.001 | 0.05 | 0.6 | 0.001 | 0.05 |
|  | 0.7 | 0.001 | 0.05 | 0.7 | 0.001 | 0.05 |
|  | 0.8 | 0.001 | 0.05 | 0.8 | 0.001 | 0.05 |
|  | 0.9 | 0.001 | 0.05 | 0.9 | 0.001 | 0.05 |
|  | 1 | 0.001 | 0.05 | 1 | 0.001 | 0.05 |
| MDD → NAFLD |  |  |  |  |  |  |
| Parameters | **R2** | **Sample size for exposure** | **Sample size for outcome** | **Number of instruments** | **Bias of the observational estimate (OLS estimate)** | **Proportion of cases** |
|  | 0.0184 | 480359 | 377988 | 42 | 0.27 | 0.0126 |
| Results |  |  |  |  |  |  |
|  | Using specified value of concentration parameter | | | Using conservative value of concentration parameter | | |
|  | Overlap proportion | Bias | Type 1 error rate | Overlap proportion | Bias | Type 1 error rate |
|  | 0 | 0 | 0.05 | 0 | 0 | 0.05 |
|  | 0.1 | 0 | 0.05 | 0.1 | 0 | 0.05 |
|  | 0.2 | 0 | 0.05 | 0.2 | 0 | 0.05 |
|  | 0.3 | 0 | 0.05 | 0.3 | 0 | 0.05 |
|  | 0.4 | 0.001 | 0.05 | 0.4 | 0.001 | 0.05 |
|  | 0.5 | 0.001 | 0.05 | 0.5 | 0.001 | 0.05 |
|  | 0.6 | 0.001 | 0.05 | 0.6 | 0.001 | 0.05 |
|  | 0.7 | 0.001 | 0.05 | 0.7 | 0.001 | 0.05 |
|  | 0.8 | 0.001 | 0.05 | 0.8 | 0.001 | 0.05 |
|  | 0.9 | 0.001 | 0.05 | 0.9 | 0.001 | 0.05 |
|  | 1 | 0.001 | 0.05 | 1 | 0.001 | 0.05 |

## Table S14. The observed residual sum of square and the corresponding P value for the studies associations in the MR-PRESSO global test.

|  |  |  |  |
| --- | --- | --- | --- |
| Exposure | Outcome for Main Consortium | Observed residual sum of square | Global Test P value |
| MDD | GERD | 69.39 | 0.0075 |
|  | IBS | 77.17 | 0.0023 |
|  | PUD | 48.57 | 0.2707 |
|  | NAFLD | 47.79 | 0.2913 |
| Exposure | Outcome for FinnGen | Observed residual sum of square | Global Test P value |
| MDD | GERD | 35.95 | 0.7267 |
|  | IBS | 36.63 | 0.7087 |
|  | PUD | 28.99 | 0.9273 |
|  | NAFLD | 34.71 | 0.7677 |

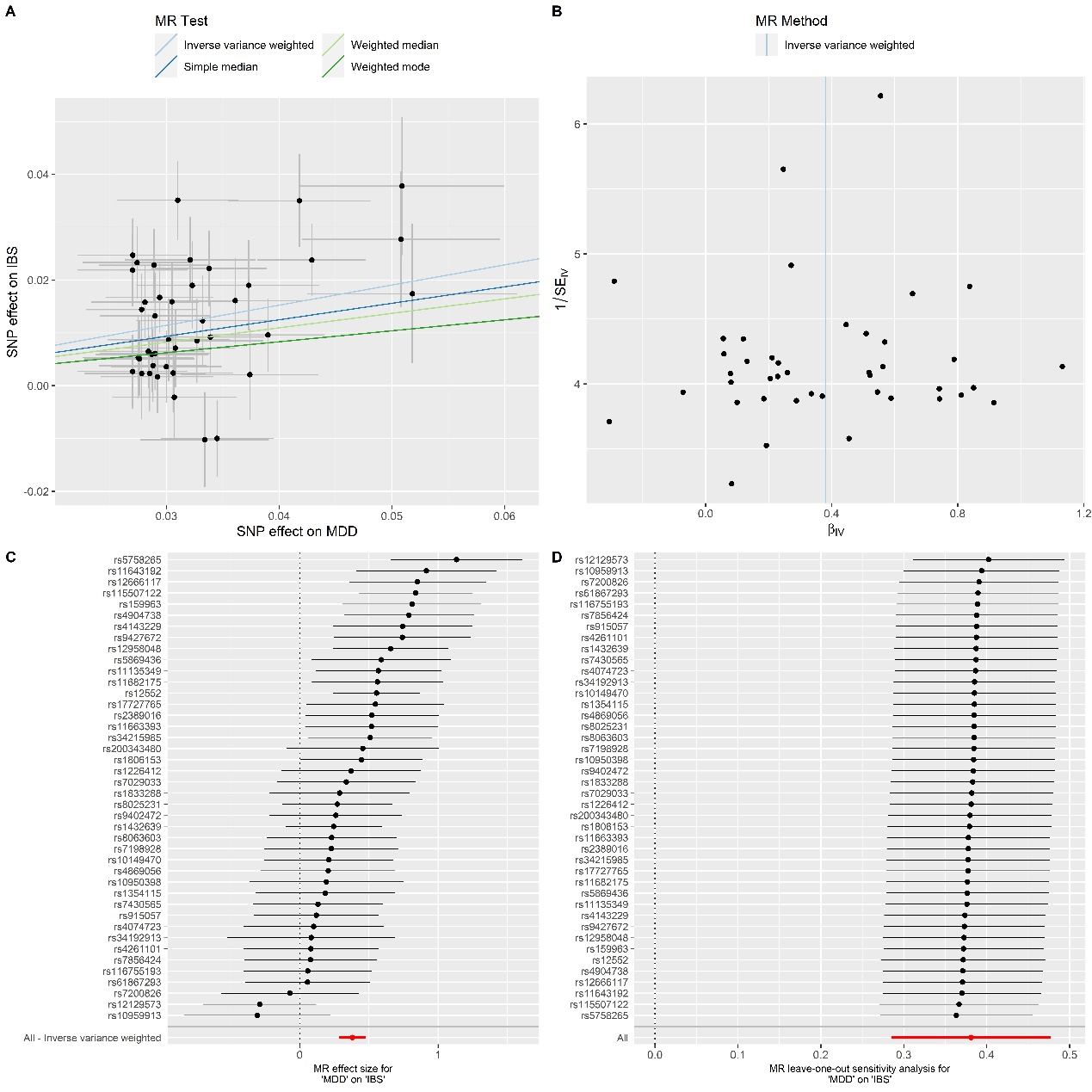
# Supplementary Figure

## Figure S1. Graphical diagnosis for univariable MR analysis of genetic predicted major depressive disorder (MDD) on gastroesophageal reflux disease (GERD, based on UKB sample).



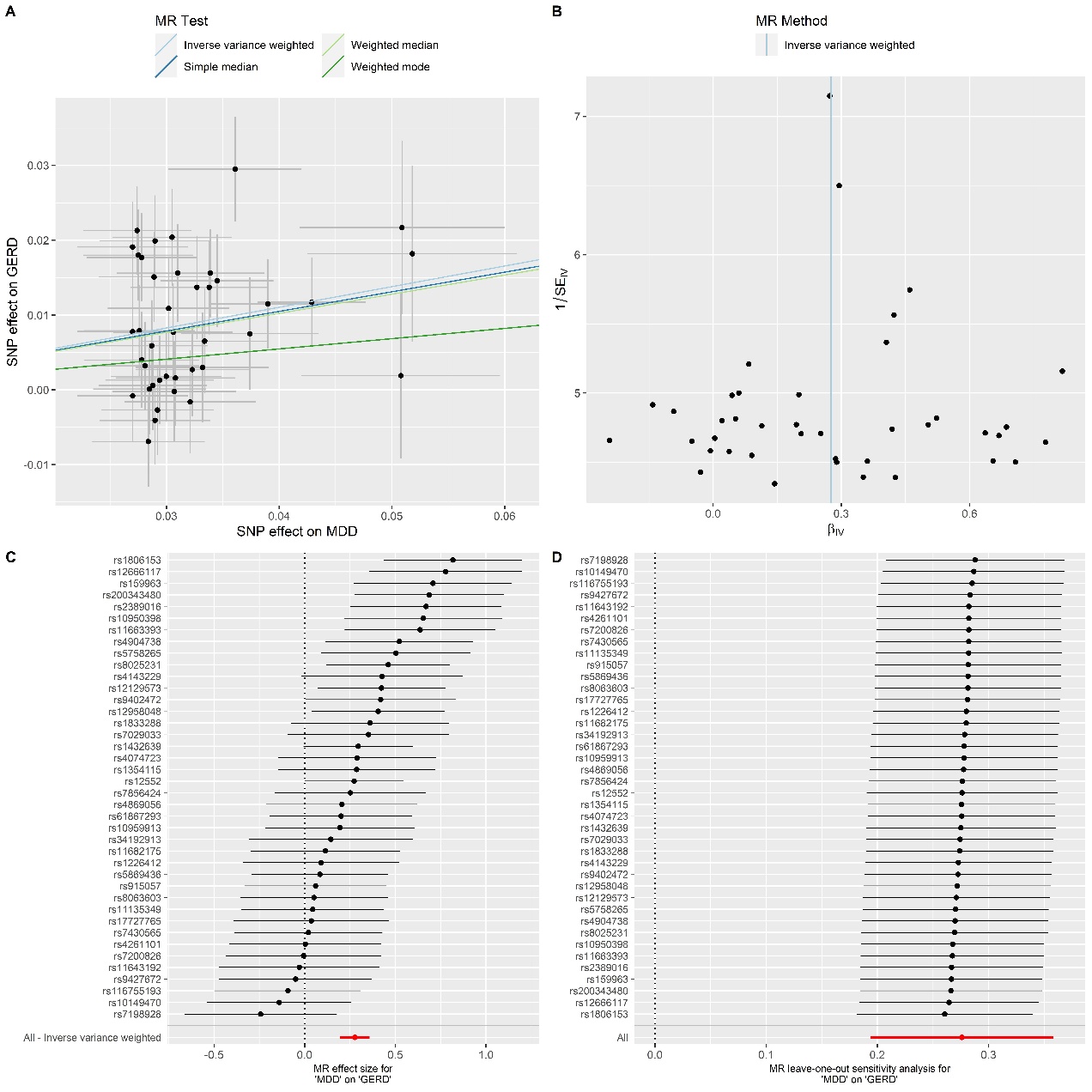
**A.** Scatter plot displays the relationship between the effect size estimates on MDD (*x*-axis) and the effect size estimates on GERD (*y*-axis) for all SNPs that served as instrumental variables for MDD in the European population. Here, a total of 40 MDD instrumental variables were employed. The 95% confidence intervals for the estimated SNP effect sizes on GERD are shown as vertical gray lines, while the 95% confidence intervals for the estimated SNP effect sizes on MDD are shown as horizontal gray lines. The slope of fitted lines represents the estimated causal effect of MDD on GERD obtained using different MR methods. **B.** Funnel plot displays individual causal effect estimates (using IVW) for MDD on GERD in the European population. The dots represent the estimated causal effect for each instrumental variable. The vertical light blue solid line represents the estimated causal effect obtained using all instrumental variables. **C.** Forest plot for individual causal effect estimate (using IVW). **D.** Leave-one-out plot sensitivity analysis for the causal effect estimate (using IVW) excluding that particular SNP.

## Figure S2. Graphical diagnosis for univariable MR analysis of genetic predicted major depressive disorder (MDD) on irritable bowel syndrome (IBS, based on UKB sample).



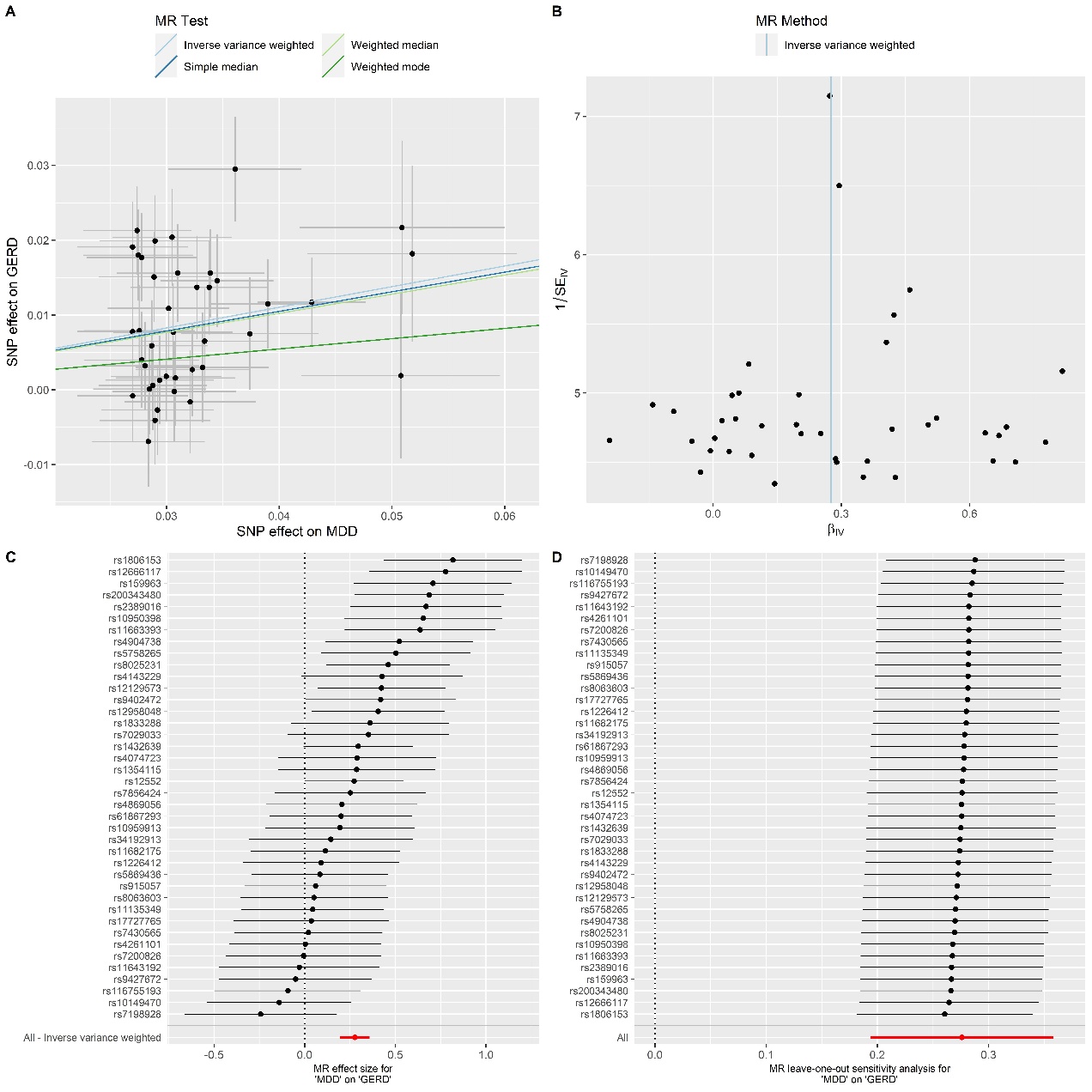
**A.** Scatter plot displays the relationship between the effect size estimates on MDD (*x*-axis) and the effect size estimates on IBS (*y*-axis) for all SNPs that served as instrumental variables for MDD in the European population. Here, a total of 42 MDD instrumental variables were employed. The 95% confidence intervals for the estimated SNP effect sizes on IBS are shown as vertical gray lines, while the 95% confidence intervals for the estimated SNP effect sizes on MDD are shown as horizontal gray lines. The slope of fitted lines represents the estimated causal effect of MDD on IBS obtained using different MR methods. **B.** Funnel plot displays individual causal effect estimates (using IVW) for MDD on IBS in the European population. The dots represent the estimated causal effect for each instrumental variable. The vertical light blue solid line represents the estimated causal effect obtained using all instrumental variables. **C.** Forest plot for individual causal effect estimate (using IVW). **D.** Leave-one-out plot sensitivity analysis for the causal effect estimate (using IVW) excluding that particular SNP.

## Figure S3. Graphical diagnosis for univariable MR analysis of genetic predicted major depressive disorder (MDD) on peptic ulcer disease (PUD, based on UKB sample).



**A.** Scatter plot displays the relationship between the effect size estimates on MDD (*x*-axis) and the effect size estimates on PUD (*y*-axis) for all SNPs that served as instrumental variables for MDD in the European population. Here, a total of 42 MDD instrumental variables were employed. The 95% confidence intervals for the estimated SNP effect sizes on PUD are shown as vertical gray lines, while the 95% confidence intervals for the estimated SNP effect sizes on MDD are shown as horizontal gray lines. The slope of fitted lines represents the estimated causal effect of MDD on PUD obtained using different MR methods. **B.** Funnel plot displays individual causal effect estimates (using IVW) for MDD on PUD in the European population. The dots represent the estimated causal effect for each instrumental variable. The vertical light blue solid line represents the estimated causal effect obtained using all instrumental variables. **C.** Forest plot for individual causal effect estimate (using IVW). **D.** Leave-one-out plot sensitivity analysis for the causal effect estimate (using IVW) excluding that particular SNP.

## Figure S4. Graphical diagnosis for univariable MR analysis of genetic predicted major depressive disorder (MDD) on non-alcoholic fatty liver disease (NAFLD, based on UKB sample).



**A.** Scatter plot displays the relationship between the effect size estimates on MDD (*x*-axis) and the effect size estimates on NAFLD (*y*-axis) for all SNPs that served as instrumental variables for MDD in the European population. Here, a total of 40 MDD instrumental variables were employed. The 95% confidence intervals for the estimated SNP effect sizes on NAFLD are shown as vertical gray lines, while the 95% confidence intervals for the estimated SNP effect sizes on MDD are shown as horizontal gray lines. The slope of fitted lines represents the estimated causal effect of MDD on NAFLD obtained using different MR methods. **B.** Funnel plot displays individual causal effect estimates (using IVW) for MDD on NAFLD in the European population. The dots represent the estimated causal effect for each instrumental variable. The vertical light blue solid line represents the estimated causal effect obtained using all instrumental variables. **C.** Forest plot for individual causal effect estimate (using IVW). **D.** Leave-one-out plot sensitivity analysis for the causal effect estimate (using IVW) excluding that particular SNP.