Assessing the Evidence for Causal Associations Between Body Mass Index, C-Reactive Protein, Depression and Reported Trauma Using Mendelian Randomization

Supplement

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1. Phenotype definitions from the UK Biobank

a. Major depressive disorder phenotyping

Models on the MDD phenotype included individuals with probable lifetime MDD based on responses to questions in the World Health Organization World Mental Health Composite International Diagnostic Interview (WHO WMH-CIDI)(1) which were incorporated into the UK Biobank mental health questionnaire. Cases were defined as anyone who scored “Yes” for any of the three MDD questions (“Probable recurrent major depression (severe)”, “Probably recurrent major depression (moderate)” and “Single probably major depression episode”), collapsing them into a final binary “No MDD/Yes MDD” variable for the analyses, in line with a previous study design, which we are attempting to replicate (2, 3). Note, cases were excluded if they also self-reported a diagnosis of bipolar disorder. Controls were defined as anyone who fell into the “No MDD” category. See Table 1 for a full breakdown of MDD cases in our sample.

b. Inflammatory marker quantification

Circulating CRP concentrations were measured in serum using an immunoturbidimetric high sensitivity analysis methodology (AU5400, Beckman Coulter) and were available for each participant. CRP quantities (pg/mL) were log-transformed to achieve a normal distribution.

c. Genotyping and polygenic scores (PGS)

Genetic data came from a full release of the UK Biobank data (4). Genotype data from two overlapping arrays underwent quality control, imputation, and were limited to common variants (minor allele frequency > 0.01), which were either directly genotyped or imputed with high confidence (5, 6). Individuals who were related (KING r > 0.044) were removed using a greedy algorithm designed to retain as many individuals as possible, as were individuals with discordant data (X-chromosome homozygosity < 0.9 for males and > 0.5 for females).

Polygenic risk scores for MDD and BMI were calculated on the UK Biobank sample using PRSice v2.(7) Imputed variants for calculating PRS were limited to common variants (MAF > 0.01) with a call rate of > 98%, that were in approximate Hardy-Weinberg equilibrium (HWE test P > 10^-8). P-value thresholds for the inclusion of SNPs in the genetic scores for the analyses were based on those found to optimise predictive accuracy in the original publications of the datasets (MDD < 0.05, BMI < 0.2) (8, 9).
d. Trauma phenotyping

The trauma phenotype used in this study was based upon previous research, which this study was aiming to replicate (2). The trauma items taken from the UK Biobank were as follows:

Childhood trauma, consisting of six categories (“Prefer not to say” (-1), “Never true” (0), “Rarely true” (1) “Sometimes true” (2), “Often” (3), “Very often true” (4)):

- Felt loved as a child
- Physically abused by family as a child
- Felt hated by family member as a child
- Sexually molested as a child
- Someone to take to doctor when needed as a child

Adulthood trauma, consisting of six categories (“Prefer not to say” (-1), “Never true” (0), “Rarely true” (1) “Sometimes true” (2), “Often” (3), “Very often true” (4)):

- Physical violence by partner or ex-partner as an adult
- Belittlement by partner or ex-partner as an adult
- Sexual interference by partner or ex-partner without consent as an adult

Physical trauma, consisting of four categories (“Prefer not to say” (-1), “Never” (0), “Yes, but not in the past 12 months” (1), “Yes, within the past 12 months” (2)):

- Victim of physically violent crime
- Been in serious accident believed to be life-threatening

A mean score across all five questions was calculated for each individual, omitting “Prefer not to say”. The mean score was then collapsed into binary “No Trauma” and “Yes Trauma” scores, with “Yes Trauma” categorizing anyone who had a mean score of 0.5 and above and “No Trauma” categorizing anyone who had a mean score of less than 0.
2. Samples used for Mendelian randomization

a. MDD GWAS

For all analyses we used the latest and largest MDD GWAS from the Psychiatric Genomic Consortium. This GWA meta-analysis consisted of 135,458 cases and 344,901 controls of European ancestry (8). In total, this GWAS reported 44 significant genetic loci and could explain 8.7% of heritability in a lifetime depression diagnosis.

b. CRP GWAS

For all analyses we used the largest CRP GWAS from the CHARGE Inflammation Working Group, consisting of 204,402 individuals of European ancestry (10). This GWAS reported 58 significant genetic loci that could explain up to 7% of the variance in circulating CRP levels.

c. BMI GWAS

For all analyses, we used a meta-analysis of the largest BMI GWAS combining the UK Biobank and the GIANT consortia(9). This sample consisted of 694,649 individuals of European ancestry and identified 463 signals in 346 loci, and could explain 17.4% of heritability in BMI.

d. Childhood Trauma GWAS

For all analyses we used the latest and largest childhood trauma GWAS (11). The sample consisted of 185,414 individuals of European ancestry. This GWAS reported 14 genome-wide significant loci, and could explain 10% of heritability in childhood trauma.
3. Outline of the HEIDI outlier method used in GSMR

The basic idea of the HEIDI outlier test is to test where there is a significant difference between $b^{xy}$ estimated at an instrument $i$ (i.e., $b^{xy(i)}$) and $b^{xy}$ estimated at a target SNP that shows a strong association with the exposure. It performs a calculation to identify pleiotropic SNPs that have an effect on both the exposure and the outcome, taking into account the LD correlation between the two SNPs (estimated from a reference sample with individual-level genotypes) and tests the deviation of each SNP from the causal model using the $\chi^2$-statistic and removes the SNPs with P-values < 0.01
4. Output from phenotypic analyses - associations with CRP

Table S1. Output from linear models with CRP as the outcome of interest

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood Trauma</td>
<td>0.02 **</td>
<td>0.03 ***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.01, 0.03]</td>
<td>[0.02, 0.04]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adulthood Trauma</td>
<td></td>
<td></td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[-0.01, 0.04]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Trauma</td>
<td></td>
<td></td>
<td></td>
<td>0.00</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[-0.02, 0.02]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.00</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[-0.01, 0.01]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD PRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.07 ***</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[0.06, 0.08]</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>0.05 ***</td>
<td>0.05 ***</td>
<td>0.05 ***</td>
<td>0.04 ***</td>
<td>0.04 ***</td>
<td>0.07 ***</td>
</tr>
<tr>
<td></td>
<td>[0.04, 0.05]</td>
<td>[0.04, 0.05]</td>
<td>[0.04, 0.05]</td>
<td>[0.04, 0.05]</td>
<td>[0.04, 0.05]</td>
<td>[0.06, 0.08]</td>
</tr>
<tr>
<td>Age</td>
<td>0.05 ***</td>
<td>0.05 ***</td>
<td>0.05 ***</td>
<td>0.03 ***</td>
<td>0.03 ***</td>
<td>0.11 ***</td>
</tr>
<tr>
<td></td>
<td>[0.04, 0.06]</td>
<td>[0.04, 0.06]</td>
<td>[0.04, 0.06]</td>
<td>[0.05, 0.07]</td>
<td>[0.05, 0.07]</td>
<td>[0.10, 0.12]</td>
</tr>
<tr>
<td>BMI</td>
<td>0.44 ***</td>
<td>0.44 ***</td>
<td>0.44 ***</td>
<td>0.44 ***</td>
<td>0.45 ***</td>
<td>0.45 ***</td>
</tr>
<tr>
<td></td>
<td>[0.43, 0.45]</td>
<td>[0.43, 0.45]</td>
<td>[0.43, 0.45]</td>
<td>[0.43, 0.45]</td>
<td>[0.43, 0.45]</td>
<td>[0.43, 0.45]</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.17 ***</td>
<td>-0.17 ***</td>
<td>-0.17 ***</td>
<td>-0.20 ***</td>
<td>-0.20 ***</td>
<td>-0.00 ***</td>
</tr>
<tr>
<td></td>
<td>[-0.18, -0.16]</td>
<td>[-0.18, -0.16]</td>
<td>[-0.18, -0.16]</td>
<td>[-0.22, -0.18]</td>
<td>[-0.22, -0.18]</td>
<td>[-0.11, -0.07]</td>
</tr>
</tbody>
</table>

N  | 113481 | 113481 | 113481 | 30313 | 29870 | 29870 |
R2  | 0.23   | 0.23   | 0.23   | 0.23  | 0.23  | 0.04  |

Note: Each predictor was independently tested using a linear model. Each model was controlled for age, sex, six genomic principal components, 21 assessment centre covariates, 105 batch covariates, fasting time, smoking status and BMI (with the exception of when BMI was the predictor of interest). This table omits six genomic principal components, 21 assessment centre covariates and 105 batch covariates for ease of visualisation. Values displayed signify the beta and a 95% confidence interval. Significance is determined by the asterisk key at the bottom of the table. MDD = major depressive disorder; PRS = polygenic risk score; BMI = body mass index; N = number.
5. Output from phenotypic analyses - associations with MDD

**Table S2. Output from logistic models with MDD as the outcome of interest**

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood Trauma</td>
<td>0.69 ***</td>
<td></td>
<td>0.64 ***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.63, 0.75]</td>
<td></td>
<td>[0.62, 0.75]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adulthood Trauma</td>
<td></td>
<td>0.90 ***</td>
<td></td>
<td>0.84, 0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Trauma</td>
<td></td>
<td></td>
<td>0.51 ***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[0.31, 0.64]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI PRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.31, 0.35</td>
<td>0.32 ***</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>[0.27, 0.35]</td>
<td>[0.26, 0.34]</td>
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<tr>
<td>CRP</td>
<td>0.01</td>
<td></td>
<td>-0.02, 0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking Status</td>
<td>0.35 ***</td>
<td>0.27 ***</td>
<td>0.26 ***</td>
<td>0.30 ***</td>
<td>0.31 ***</td>
<td>0.32 ***</td>
</tr>
<tr>
<td></td>
<td>[0.27, 0.35]</td>
<td>[0.23, 0.31]</td>
<td>[0.21, 0.24]</td>
<td>[0.26, 0.34]</td>
<td>[0.27, 0.35]</td>
<td>[0.28, 0.36]</td>
</tr>
<tr>
<td>Age</td>
<td>-0.03 ***</td>
<td>-0.03 ***</td>
<td>-0.02 ***</td>
<td>-0.03 ***</td>
<td>-0.03 ***</td>
<td>-0.03 ***</td>
</tr>
<tr>
<td></td>
<td>[-0.03, -0.02]</td>
<td>[-0.03, -0.02]</td>
<td>[-0.03, -0.02]</td>
<td>[-0.03, -0.02]</td>
<td>[-0.03, -0.02]</td>
<td>[-0.03, -0.02]</td>
</tr>
<tr>
<td>BMI</td>
<td>0.95 ***</td>
<td>0.86 ***</td>
<td>0.92 ***</td>
<td>0.96 ***</td>
<td>0.97 ***</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[0.77, 1.13]</td>
<td>[0.76, 1.09]</td>
<td>[0.76, 1.09]</td>
<td>[0.80, 1.12]</td>
<td>[0.81, 1.13]</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>-0.65 ***</td>
<td>-0.67 ***</td>
<td>-0.65 ***</td>
<td>-0.71 ***</td>
<td>-0.62 ***</td>
<td>-0.64 ***</td>
</tr>
<tr>
<td></td>
<td>[-0.74, -0.53]</td>
<td>[-0.72, -0.61]</td>
<td>[-0.61, -0.58]</td>
<td>[-0.76, -0.65]</td>
<td>[-0.74, -0.63]</td>
<td>[-0.70, -0.59]</td>
</tr>
<tr>
<td>N</td>
<td>38137</td>
<td>38137</td>
<td>38137</td>
<td>38137</td>
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<td>38137</td>
</tr>
<tr>
<td>AIC</td>
<td>34479.79</td>
<td>33954.89</td>
<td>33722.89</td>
<td>34424.07</td>
<td>34477.76</td>
<td>34613.15</td>
</tr>
<tr>
<td>BIC</td>
<td>34484.29</td>
<td>34079.93</td>
<td>33847.59</td>
<td>34548.77</td>
<td>34598.35</td>
<td>34729.54</td>
</tr>
<tr>
<td>Pseudo R^2</td>
<td>0.85</td>
<td>0.88</td>
<td>0.89</td>
<td>0.86</td>
<td>0.85</td>
<td>0.85</td>
</tr>
</tbody>
</table>

* *** p < 0.001; ** p < 0.01; * p < 0.05.

Note: Each predictor was independently tested using a logistic model. Each model was controlled for age, sex, six genomic principal components, 21 assessment centre covariates, 105 batch covariates, fasting time, smoking status and BMI (with the exception of when BMI was the predictor of interest). This table omits six genomic principal components, 21 assessment centre covariates and 105 batch covariates for ease of visualisation. Values displayed signify the beta and a 95% confidence interval. Significance is determined by the asterisk key at the bottom of the table. MDD = major depressive disorder; PRS = polygenic risk score; BMI = body mass index; N = number.
6. All GSMR analyses in table form

Table S3. GSMR output table

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Beta xy</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>P</th>
<th>N SNPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>CRP</td>
<td>0.3676</td>
<td>0.3487</td>
<td>0.3864</td>
<td>&gt;0.0000</td>
<td>1175</td>
</tr>
<tr>
<td>CRP</td>
<td>BMI</td>
<td>-0.0016</td>
<td>-0.0108</td>
<td>0.0076</td>
<td>0.7325</td>
<td>55</td>
</tr>
<tr>
<td>BMI</td>
<td>MDD</td>
<td>0.1532</td>
<td>0.1308</td>
<td>0.1756</td>
<td>&gt;0.0000</td>
<td>1111</td>
</tr>
<tr>
<td>MDD</td>
<td>BMI</td>
<td>0.1664</td>
<td>0.1406</td>
<td>0.1921</td>
<td>&gt;0.0000</td>
<td>24</td>
</tr>
<tr>
<td>BMI</td>
<td>Childhood trauma</td>
<td>0.0882</td>
<td>0.0729</td>
<td>0.1035</td>
<td>&gt;0.0000</td>
<td>1184</td>
</tr>
<tr>
<td>Childhood trauma</td>
<td>BMI</td>
<td>0.1006</td>
<td>0.0480</td>
<td>0.1532</td>
<td>0.0002</td>
<td>10</td>
</tr>
<tr>
<td>CRP</td>
<td>MDD</td>
<td>0.0201</td>
<td>-0.0034</td>
<td>0.0436</td>
<td>0.0930</td>
<td>88</td>
</tr>
<tr>
<td>MDD</td>
<td>CRP</td>
<td>0.0596</td>
<td>0.0169</td>
<td>0.1023</td>
<td>0.0062</td>
<td>43</td>
</tr>
<tr>
<td>MDD</td>
<td>Childhood trauma</td>
<td>0.1843</td>
<td>0.1480</td>
<td>0.2206</td>
<td>&gt;0.0000</td>
<td>42</td>
</tr>
<tr>
<td>Childhood trauma</td>
<td>MDD</td>
<td>0.5108</td>
<td>0.3595</td>
<td>0.6622</td>
<td>&gt;0.0000</td>
<td>11</td>
</tr>
<tr>
<td>CRP</td>
<td>Childhood trauma</td>
<td>0.0117</td>
<td>-0.0008</td>
<td>0.0241</td>
<td>0.0658</td>
<td>130</td>
</tr>
<tr>
<td>Childhood trauma</td>
<td>CRP</td>
<td>0.1031</td>
<td>-0.0165</td>
<td>0.2227</td>
<td>0.0912</td>
<td>11</td>
</tr>
</tbody>
</table>

Note: Each row represents one Mendelian randomization test between the exposure and the outcome. MDD = major depressive disorder; BMI = body mass index; Beta xy = beta of the exposure (x) on the outcome (y); Lower CI = lower 95% confidence interval; Upper CI = upper 95% confidence interval; P = p-value; nSNP = number of SNPs used in the analyses.
7. Figures from all GSMR analyses
   a. MDD on CRP

43 index SNPs were obtained from the clumping analysis with p < 5.0e-08 and LD r2 < 0.05. 43 index SNPs were retained after HEIDI-outlier analysis.

![Figure S1. GSMR chart with MDD as exposure and CRP as the outcome](image)

**Figure S1. GSMR chart with MDD as exposure and CRP as the outcome**

This figure illustrates the MR relationship between MDD and CRP. SNP effects associated with MDD are displayed on the x-axis and SNP effects associated with CRP are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
b. CRP on MDD

94 index SNPs were obtained from the clumping analysis with \( p < 5.0 \times 10^{-8} \) and LD \( r^2 < 0.05 \). 6 pleiotropic SNPs were filtered by HEIDI-outlier analysis. 88 index SNPs were retained after HEIDI-outlier analysis.

Figure S2. GSMR chart with CRP as exposure and MDD as the outcome

This figure illustrates the MR relationship between CRP and MDD. SNP effects associated with CRP are displayed on the x-axis and SNP effects associated with MDD are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
c. BMI on CRP

1224 index SNPs were obtained from the clumping analysis with $p < 5.0 \times 10^{-8}$ and LD $r^2 < 0.05$. 49 pleiotropic SNPs were filtered by HEIDI-outlier analysis. 1175 index SNPs were retained after HEIDI-outlier analysis.

Figure S3. GSMR chart with BMI as exposure and CRP as the outcome

This figure illustrates the MR relationship between BMI and CRP. SNP effects associated with BMI are displayed on the x-axis and SNP effects associated with CRP are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
d. CRP on BMI

88 index SNPs are obtained from the clumping analysis with \( p < 5.0\times10^{-8} \) and LD \( r^2 < 0.05 \). 33 pleiotropic SNPs are filtered by HEIDI-outlier analysis. 55 index SNPs are retained after HEIDI-outlier analysis.

Figure S4. GSMR chart with CRP as exposure and BMI as the outcome

This figure illustrates the MR relationship between CRP and BMI. SNP effects associated with CRP are displayed on the x-axis and SNP effects associated with BMI are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
e. BMI on MDD

1199 index SNPs are obtained from the clumping analysis with $p < 5.0 \times 10^{-8}$ and LD $r^2 < 0.05$. 88 pleiotropic SNPs are filtered by HEIDI-outlier analysis. 1111 index SNPs are retained after HEIDI-outlier analysis.

Figure S5. GSMR chart with BMI as exposure and MDD as the outcome

This figure illustrates the MR relationship between BMI and MDD. SNP effects associated with BMI are displayed on the x-axis and SNP effects associated with MDD are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
f. MDD on BMI

35 index SNPs are obtained from the clumping analysis with p < 5.0e-08 and LD r2 < 0.05. 11 pleiotropic SNPs are filtered by HEIDI-outlier analysis. 24 index SNPs are retained after HEIDI-outlier analysis.

Figure S6. GSMR chart with MDD as exposure and BMI as the outcome

This figure illustrates the MR relationship between MDD and BMI. SNP effects associated with MDD are displayed on the x-axis and SNP effects associated with BMI are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
g. Childhood trauma on CRP

11 index SNPs are obtained from the clumping analysis with $p < 5.0e-08$ and LD $r^2 < 0.05$. 11 index SNPs are retained after HEIDI-outlier analysis.

Figure S7. GSMR chart with childhood trauma as exposure and CRP as the outcome

This figure illustrates the MR relationship between childhood trauma and CRP. SNP effects associated with childhood trauma are displayed on the x-axis and SNP effects associated with CRP are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
h. CRP on childhood trauma

133 index SNPs are obtained from the clumping analysis with $p < 5.0e^{-08}$ and LD $r^2 < 0.05$. 3 pleiotropic SNPs are filtered by HEIDI-outlier analysis. 130 index SNPs are retained after HEIDI-outlier analysis.

![Figure S8. GSMR chart with CRP as exposure and childhood trauma as the outcome](image)

Figure S8. GSMR chart with CRP as exposure and childhood trauma as the outcome

This figure illustrates the MR relationship between CRP and childhood trauma. SNP effects associated with CRP are displayed on the x-axis and SNP effects associated with childhood trauma are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
i. Childhood trauma on MDD

11 index SNPs are obtained from the clumping analysis with $p < 5.0e^{-08}$ and LD $r^2 < 0.05$. 11 index SNPs are retained after HEIDI-outlier analysis.

**Figure S9. GSMR chart with childhood trauma as exposure and MDD as the outcome**

This figure illustrates the MR relationship between childhood trauma and MDD. SNP effects associated with childhood trauma are displayed on the x-axis and SNP effects associated with MDD are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
j. MDD on childhood trauma

43 index SNPs are obtained from the clumping analysis with $p < 5.0 \times 10^{-8}$ and LD $r^2 < 0.05$. 1 pleiotropic SNP was filtered by HEIDI-outlier analysis. 42 index SNPs are retained after HEIDI-outlier analysis.

Figure S10. GSMR chart with MDD as exposure and childhood trauma as the outcome

This figure illustrates the MR relationship between MDD and childhood trauma. SNP effects associated with MDD are displayed on the x-axis and SNP effects associated with childhood trauma are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
k. BMI on childhood trauma

1223 index SNPs are obtained from the clumping analysis with \( p < 5.0e-08 \) and LD \( r^2 < 0.05 \). 39 pleiotropic SNPs are filtered by HEIDI-outlier analysis. 1184 index SNPs are retained after HEIDI-outlier analysis.

Figure S11. GSMR chart with BMI as exposure and childhood trauma as the outcome

This figure illustrates the MR relationship between BMI and childhood trauma. SNP effects associated with BMI are displayed on the x-axis and SNP effects associated with childhood trauma are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
1. Childhood trauma on BMI

10 index SNPs are obtained from the clumping analysis with $p < 5.0e-08$ and LD $r^2 < 0.05$. 10 index SNPs are retained after HEIDI-outlier analysis.

**Figure S12. GSMR chart with childhood trauma as exposure and BMI as the outcome**

This figure illustrates the MR relationship between childhood trauma and BMI. SNP effects associated with childhood trauma are displayed on the x-axis and SNP effects associated with BMI are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. The dotted line represents the regression line between these two traits.
8. Sensitivity analyses using other MR methods

a. MDD on CRP

Table S4. Sensitivity analyses of MDD (exposure) on CRP (outcome)

<table>
<thead>
<tr>
<th>exposure</th>
<th>outcome</th>
<th>method</th>
<th>nsnp</th>
<th>b</th>
<th>lo_ci</th>
<th>up_ci</th>
<th>pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>CRP</td>
<td>MR Egger</td>
<td>39</td>
<td>0.31822744</td>
<td>-0.06834157</td>
<td>0.7047965</td>
<td>0.11513552</td>
</tr>
<tr>
<td>MDD</td>
<td>CRP</td>
<td>Weighted median</td>
<td>39</td>
<td>0.06212780</td>
<td>-0.01016365</td>
<td>0.1344192</td>
<td>0.09209699</td>
</tr>
<tr>
<td>MDD</td>
<td>CRP</td>
<td>Inverse variance weighted</td>
<td>39</td>
<td>0.05143699</td>
<td>-0.01479167</td>
<td>0.1176657</td>
<td>0.12794674</td>
</tr>
<tr>
<td>MDD</td>
<td>CRP</td>
<td>Simple mode</td>
<td>39</td>
<td>0.06243798</td>
<td>-0.11697313</td>
<td>0.2418491</td>
<td>0.49930515</td>
</tr>
<tr>
<td>MDD</td>
<td>CRP</td>
<td>Weighted mode</td>
<td>39</td>
<td>0.08048370</td>
<td>-0.08203682</td>
<td>0.2430042</td>
<td>0.33786824</td>
</tr>
</tbody>
</table>

Number of SNPS = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S13. MR sensitivity analyses chart with MDD as exposure and CRP as the outcome

This figure illustrates the MR relationship between MDD and CRP. SNP effects associated with MDD are displayed on the x-axis and SNP effects associated with CRP are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
b. CRP on MDD

**Table S5. Sensitivity analyses of CRP (exposure) on MDD (outcome)**

<table>
<thead>
<tr>
<th>exposure</th>
<th>outcome</th>
<th>method</th>
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<th>b</th>
<th>lo_ci</th>
<th>up_ci</th>
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</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>MDD</td>
<td>MR Egger</td>
<td>84</td>
<td>-0.02744912</td>
<td>-0.08381248</td>
<td>0.02891424</td>
<td>0.3426231</td>
</tr>
<tr>
<td>CRP</td>
<td>MDD</td>
<td>Weighted median</td>
<td>84</td>
<td>-0.01723914</td>
<td>-0.05750394</td>
<td>0.02302567</td>
<td>0.4013782</td>
</tr>
<tr>
<td>CRP</td>
<td>MDD</td>
<td>Inverse variance weighted</td>
<td>84</td>
<td>0.00261655</td>
<td>-0.02833948</td>
<td>0.03357258</td>
<td>0.8684178</td>
</tr>
<tr>
<td>CRP</td>
<td>MDD</td>
<td>Simple mode</td>
<td>84</td>
<td>-0.04855294</td>
<td>-0.12173694</td>
<td>0.02463106</td>
<td>0.1970851</td>
</tr>
<tr>
<td>CRP</td>
<td>MDD</td>
<td>Weighted mode</td>
<td>84</td>
<td>-0.01048489</td>
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<td>0.02954343</td>
<td>0.6090383</td>
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Number of SNPS = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

**Figure S14. MR sensitivity analyses with CRP as exposure and MDD as the outcome**

This figure illustrates the MR relationship between CRP and MDD. SNP effects associated with CRP are displayed on the x-axis and SNP effects associated with MDD are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
c. BMI on CRP

Table S6. Sensitivity analyses of BMI (exposure) on CRP (outcome)

<table>
<thead>
<tr>
<th>exposure</th>
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<th>method</th>
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<th>b</th>
<th>lo_ci</th>
<th>up_ci</th>
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</tr>
</thead>
<tbody>
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<td>BMI</td>
<td>CRP</td>
<td>MR Egger</td>
<td>1207</td>
<td>0.4355467</td>
<td>0.3434297</td>
<td>0.5276636</td>
<td>8.521059e-20</td>
</tr>
<tr>
<td>BMI</td>
<td>CRP</td>
<td>Weighted median</td>
<td>1207</td>
<td>0.3587296</td>
<td>0.3261866</td>
<td>0.3912725</td>
<td>1.591675e-103</td>
</tr>
<tr>
<td>BMI</td>
<td>CRP</td>
<td>Inverse variance weighted</td>
<td>1207</td>
<td>0.3588448</td>
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<td>0.3885391</td>
<td>5.040997e-124</td>
</tr>
<tr>
<td>BMI</td>
<td>CRP</td>
<td>Simple mode</td>
<td>1207</td>
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<td>3.688743e-09</td>
</tr>
<tr>
<td>BMI</td>
<td>CRP</td>
<td>Weighted mode</td>
<td>1207</td>
<td>0.3787394</td>
<td>0.2900788</td>
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<td>1.544415e-16</td>
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</tbody>
</table>

Number of SNPs = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S15. MR sensitivity analyses with BMI as exposure and CRP as the outcome

This figure illustrates the MR relationship between BMI and CRP. SNP effects associated with BMI are displayed on the x-axis and SNP effects associated with CRP are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
d. CRP on BMI

Table S7. Sensitivity analyses of CRP (exposure) on BMI (outcome)

<table>
<thead>
<tr>
<th>exposure</th>
<th>outcome</th>
<th>method</th>
<th>nsnp</th>
<th>b</th>
<th>lo_ci</th>
<th>up_ci</th>
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</thead>
<tbody>
<tr>
<td>CRP</td>
<td>BMI</td>
<td>MR Egger</td>
<td>36</td>
<td>0.01672391</td>
<td>-0.050116781</td>
<td>0.08356461</td>
<td>0.625998883</td>
</tr>
<tr>
<td>CRP</td>
<td>BMI</td>
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<td>36</td>
<td>0.03757493</td>
<td>0.005704457</td>
<td>0.06944541</td>
<td>0.020842910</td>
</tr>
<tr>
<td>CRP</td>
<td>BMI</td>
<td>Inverse variance weighted</td>
<td>36</td>
<td>0.06574389</td>
<td>0.024611739</td>
<td>0.10687604</td>
<td>0.001731585</td>
</tr>
<tr>
<td>CRP</td>
<td>BMI</td>
<td>Simple mode</td>
<td>36</td>
<td>0.02943334</td>
<td>-0.016234530</td>
<td>0.07510121</td>
<td>0.214854490</td>
</tr>
<tr>
<td>CRP</td>
<td>BMI</td>
<td>Weighted mode</td>
<td>36</td>
<td>0.02943334</td>
<td>-0.028976265</td>
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<td>0.330093944</td>
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Number of SNPS = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S16. MR sensitivity analyses with CRP as exposure and BMI as the outcome

This figure illustrates the MR relationship between CRP and BMI. SNP effects associated with CRP are displayed on the x-axis and SNP effects associated with BMI are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
e. BMI on MDD

Table S8. Sensitivity analyses of BMI (exposure) on MDD (outcome)

<table>
<thead>
<tr>
<th>exposure</th>
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<th>b</th>
<th>lo_ci</th>
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</thead>
<tbody>
<tr>
<td>BMI</td>
<td>MDD</td>
<td>MR Egger</td>
<td>1178</td>
<td>0.05198342</td>
<td>-0.057009727</td>
<td>0.1609766</td>
<td>3.500799e-01</td>
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<td>BMI</td>
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<td>Weighted median</td>
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<td>0.11348985</td>
<td>0.075417559</td>
<td>0.1515622</td>
<td>5.140108e-09</td>
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<td>BMI</td>
<td>MDD</td>
<td>Inverse variance weighted</td>
<td>1178</td>
<td>0.13039944</td>
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<td>4.025125e-14</td>
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<td>BMI</td>
<td>MDD</td>
<td>Simple mode</td>
<td>1178</td>
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<td>0.3065828</td>
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Number of SNPS = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S17. MR sensitivity analyses with BMI as exposure and MDD as the outcome

This figure illustrates the MR relationship between BMI and MDD. SNP effects associated with BMI are displayed on the x-axis and SNP effects associated with MDD are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
f. MDD on BMI

Table S9. Sensitivity analyses of MDD (exposure) on BMI (outcome)

<table>
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<tbody>
<tr>
<td>MDD</td>
<td>BMI</td>
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<td>14</td>
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<td>BMI</td>
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<tr>
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<td>BMI</td>
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Number of SNPS = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S18. MR sensitivity analyses with MDD as exposure and BMI as the outcome

This figure illustrates the MR relationship between MDD and BMI. SNP effects associated with MDD are displayed on the x-axis and SNP effects associated with BMI are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
g. Childhood trauma on CRP

Table S10. Sensitivity analyses of childhood trauma (exposure) on CRP (outcome)

<table>
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<tr>
<th>exposure</th>
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<th>nsnp</th>
<th>b</th>
<th>lo_ci</th>
<th>up_ci</th>
<th>pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAUMA</td>
<td>CRP</td>
<td>MR Egger</td>
<td>9</td>
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<td>-2.78004916</td>
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</tr>
<tr>
<td>TRAUMA</td>
<td>CRP</td>
<td>Weighted median</td>
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<td>CRP</td>
<td>Inverse variance weighted</td>
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<td>TRAUMA</td>
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<td>Simple mode</td>
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<td>CRP</td>
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Number of SNPS = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S19. MR sensitivity analyses with childhood trauma as exposure and CRP as the outcome

This figure illustrates the MR relationship between childhood trauma and CRP. SNP effects associated with childhood trauma are displayed on the x-axis and SNP effects associated with CRP are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
h. CRP on childhood trauma

Table S11. Sensitivity analyses of CRP (exposure) on reported trauma (outcome)

<table>
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<tr>
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<th>b</th>
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<th>pval</th>
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</thead>
<tbody>
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<tr>
<td>CRP</td>
<td>TRAUMA</td>
<td>Weighted median</td>
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<td>0.035165745</td>
<td>0.35694151</td>
</tr>
<tr>
<td>CRP</td>
<td>TRAUMA</td>
<td>Inverse variance weighted</td>
<td>122</td>
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<td>0.027791138</td>
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<tr>
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Number of SNPs = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S20. MR sensitivity analyses with CRP as exposure and childhood trauma as the outcome

This figure illustrates the MR relationship between CRP and childhood trauma. SNP effects associated with CRP are displayed on the x-axis and SNP effects associated with childhood trauma are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
i. Childhood trauma on MDD

Table S12. Sensitivity analyses of childhood trauma (exposure) on MDD (outcome)

<table>
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<tr>
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<th>b</th>
<th>lo_ci</th>
<th>up_ci</th>
<th>pval</th>
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<tbody>
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<td>TRAUMA</td>
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<td>MR Egger</td>
<td>9</td>
<td>-1.2459949</td>
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<td>Weighted median</td>
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</tr>
<tr>
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</tr>
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<td>Simple mode</td>
<td>9</td>
<td>0.5957979</td>
<td>0.2007060</td>
<td>0.9908898</td>
<td>1.826650e-02</td>
</tr>
<tr>
<td>TRAUMA</td>
<td>MDD</td>
<td>Weighted mode</td>
<td>9</td>
<td>0.5703777</td>
<td>0.1622967</td>
<td>0.9734588</td>
<td>2.546869e-02</td>
</tr>
</tbody>
</table>

Number of SNPS = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S21. MR sensitivity analyses with childhood trauma as exposure and MDD as the outcome

This figure illustrates the MR relationship between childhood trauma and MDD. SNP effects associated with childhood trauma are displayed on the x-axis and SNP effects associated with MDD are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
j. MDD on childhood trauma

Table S13. Sensitivity analyses of MDD (exposure) on childhood trauma (outcome)

<table>
<thead>
<tr>
<th>exposure</th>
<th>outcome</th>
<th>method</th>
<th>nsnp</th>
<th>b</th>
<th>lo_ci</th>
<th>up_ci</th>
<th>pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>TRAUMA</td>
<td>MR Egger</td>
<td>39</td>
<td>0.1671215</td>
<td>-0.19221832</td>
<td>0.5264613</td>
<td>3.679039e-01</td>
</tr>
<tr>
<td>MDD</td>
<td>TRAUMA</td>
<td>Weighted median</td>
<td>39</td>
<td>0.1490930</td>
<td>0.08848384</td>
<td>0.2097022</td>
<td>1.425400e-06</td>
</tr>
<tr>
<td>MDD</td>
<td>TRAUMA</td>
<td>Inverse variance weighted</td>
<td>39</td>
<td>0.1584021</td>
<td>0.10877681</td>
<td>0.2280274</td>
<td>3.099751e-08</td>
</tr>
<tr>
<td>MDD</td>
<td>TRAUMA</td>
<td>Simple mode</td>
<td>39</td>
<td>0.1522308</td>
<td>0.03004396</td>
<td>0.2744177</td>
<td>1.937338e-02</td>
</tr>
<tr>
<td>MDD</td>
<td>TRAUMA</td>
<td>Weighted mode</td>
<td>39</td>
<td>0.1601247</td>
<td>0.05074481</td>
<td>0.2695047</td>
<td>6.683095e-03</td>
</tr>
</tbody>
</table>

Number of SNPS = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S22. MR sensitivity analyses with MDD as exposure and childhood trauma as the outcome

This figure illustrates the MR relationship between MDD and childhood trauma. SNP effects associated with MDD are displayed on the x-axis and SNP effects associated with childhood trauma are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
k. BMI on childhood trauma

Table S14. Sensitivity analyses of BMI (exposure) on childhood trauma (outcome)

<table>
<thead>
<tr>
<th>exposure</th>
<th>outcome</th>
<th>method</th>
<th>nsnp</th>
<th>b</th>
<th>lo_ci</th>
<th>up_ci</th>
<th>pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>TRAUMA</td>
<td>MR Egger</td>
<td>1210</td>
<td>0.07901132</td>
<td>0.01840696</td>
<td>0.1396157</td>
<td>1.073136e-02</td>
</tr>
<tr>
<td>BMI</td>
<td>TRAUMA</td>
<td>Weighted median</td>
<td>1210</td>
<td>0.08349578</td>
<td>0.0675121</td>
<td>0.1102404</td>
<td>9.412651e-10</td>
</tr>
<tr>
<td>BMI</td>
<td>TRAUMA</td>
<td>Inverse variance weighted</td>
<td>1210</td>
<td>0.09356167</td>
<td>0.07400228</td>
<td>0.1131211</td>
<td>6.878888e-21</td>
</tr>
<tr>
<td>BMI</td>
<td>TRAUMA</td>
<td>Simple mode</td>
<td>1210</td>
<td>0.06555600</td>
<td>-0.05154276</td>
<td>0.1826548</td>
<td>2.727389e-01</td>
</tr>
<tr>
<td>BMI</td>
<td>TRAUMA</td>
<td>Weighted mode</td>
<td>1210</td>
<td>0.07166605</td>
<td>-0.01817549</td>
<td>0.1615076</td>
<td>1.182014e-01</td>
</tr>
</tbody>
</table>

Number of SNPS = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S23. MR sensitivity analyses with BMI as exposure and childhood trauma as the outcome

This figure illustrates the MR relationship between BMI and childhood trauma. SNP effects associated with BMI are displayed on the x-axis and SNP effects associated with childhood trauma are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
1. Childhood trauma on BMI

Table S15. Sensitivity analyses of childhood trauma (exposure) on BMI (outcome)

<table>
<thead>
<tr>
<th>exposure</th>
<th>outcome</th>
<th>method</th>
<th>nsnp</th>
<th>b</th>
<th>lo_ci</th>
<th>up_ci</th>
<th>pval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAUMA</td>
<td>BMI</td>
<td>MR Egger</td>
<td>3</td>
<td>-0.6942578</td>
<td>-2.12378733</td>
<td>0.7352518</td>
<td>0.515683610</td>
</tr>
<tr>
<td>TRAUMA</td>
<td>BMI</td>
<td>Weighted median</td>
<td>3</td>
<td>0.1853717</td>
<td>0.05111271</td>
<td>0.3196307</td>
<td>0.006806283</td>
</tr>
<tr>
<td>TRAUMA</td>
<td>BMI</td>
<td>Inverse variance weighted</td>
<td>3</td>
<td>0.2130452</td>
<td>0.03552759</td>
<td>0.3905627</td>
<td>0.018659434</td>
</tr>
<tr>
<td>TRAUMA</td>
<td>BMI</td>
<td>Simple mode</td>
<td>3</td>
<td>0.1868267</td>
<td>-0.01289239</td>
<td>0.3865457</td>
<td>0.208179557</td>
</tr>
<tr>
<td>TRAUMA</td>
<td>BMI</td>
<td>Weighted mode</td>
<td>3</td>
<td>0.1824019</td>
<td>0.02295570</td>
<td>0.3418481</td>
<td>0.154187208</td>
</tr>
</tbody>
</table>

Number of SNPs = nsnp / Beta = b / Lower 95% confidence interval = lo_ci / Upper 95% confidence interval = up_ci / P-value = pval

Figure S24. MR sensitivity analyses with childhood trauma as exposure and BMI as the outcome

This figure illustrates the MR relationship between childhood trauma and BMI. SNP effects associated with childhood trauma are displayed on the x-axis and SNP effects associated with BMI are displayed on the y-axis. Each point represents the beta coefficient of these two traits. The horizontal line on each point represents the standard error associated with the exposure and the vertical line on each point represents the standard error associated with the outcome. Each coloured line represents a regression line using the MR test outlined in the legend key.
9. **mtCOJO sensitivity analyses results**

Given that BMI is known to be a strong confounding factor in this model, we conditioned the other three traits (MDD, CRP and childhood trauma) on BMI and performed the same MR analyses using GSMR. Our results show that when conditioned on BMI, childhood trauma is genetically predicting an increased risk of MDD (OR: 1.89, 95% CI: 1.62 – 2.20, p = < 0.001) whereby childhood trauma is associated with a 89% higher odds of MDD; MDD is genetically predicting childhood trauma (OR: 1.22, 95% CI: 1.16 – 1.27, p = < 0.001); and MDD is associated with a decrease in BMI (β: -0.11, 95% CI: -0.09 to -0.14, p = < 0.001) whereby MDD results in a 0.11 kg/m² decrease in BMI. These results remain significant after Bonferroni correction (pBonferroni = 0.004).

![Graphs showing the results of mtCOJO sensitivity analyses](image-url)

**Figure S25.** All generalised-summary mendelian randomization (GSMR) results conditioned on BMI using mtCOJO.
This figure represents a summary of three bi-directional GSMR analyses involving four traits (12 analyses in total). The charts are split by the exposure of interest. Dots represent effect sizes (as measured by odds ratios, ORs) on the liability scale of the disorders of risk factors on traits (childhood trauma and MDD) and effect sizes (as measured by $\beta$, $b_y$) on the liability scale of the disorders of risk factors on traits (BMI and CRP). Each outcome is labelled on the y-axis and the strength of each exposure on the outcome displayed on the x-axis (as an odds ratio or a beta, plotted on a linear scale). Error bars represent 95% confidence intervals. Childhood trauma was associated with increased odds of MDD, and MDD was associated with a decrease in BMI and an increased odds of childhood trauma, after multiple testing correction ($p_{Bonferroni} = 0.004$).
10. cis-CRP SNP effects on MDD and childhood trauma

Our findings are mixed, suggesting that cis-CRP genetic variants mildly genetically predict higher odds of MDD at $R^2 < 0.8$ (OR: 1.03, 95% CI: 1.00 – 1.05, $p = 0.02$), although they do not at the advised threshold of $R^2 < 0.05$ (OR: 1.02, 95% CI: 0.97 – 1.06, $p = 0.5$). They also show that cis-CRP genetic variants predict lower odds of childhood trauma at $R^2 < 0.2$ (OR: 0.97, 95% CI: 0.95 – 1.00, $p = 0.04$), $R^2 < 0.4$ (OR: 0.97, 95% CI: 0.95 – 0.99, $p = 0.01$), $R^2 < 0.6$ (OR: 0.97, 95% CI: 0.95 – 0.99, $p = 0.01$) and $R^2 < 0.8$ (OR: 0.97, 95% CI: 0.95 – 0.99, $p < 0.01$), although they do not at the advised $R^2 < 0.05$ (OR: 0.97, 95% CI: 0.94 – 1.00, $p = 0.06$).

Table S16. GSMR output with cis-CRP SNPs only, at different clumping thresholds

<table>
<thead>
<tr>
<th>R2</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Beta xy</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>P</th>
<th>N SNPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 0.05$</td>
<td>CRP</td>
<td>MDD</td>
<td>0.015</td>
<td>-0.02812</td>
<td>0.05812</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>$&lt; 0.2$</td>
<td>CRP</td>
<td>MDD</td>
<td>0.023</td>
<td>-0.01424</td>
<td>0.06024</td>
<td>0.219</td>
<td>7</td>
</tr>
<tr>
<td>$&lt; 0.4$</td>
<td>CRP</td>
<td>MDD</td>
<td>0.023</td>
<td>-0.00836</td>
<td>0.05436</td>
<td>0.144</td>
<td>12</td>
</tr>
<tr>
<td>$&lt; 0.6$</td>
<td>CRP</td>
<td>MDD</td>
<td>0.024</td>
<td>-0.0054</td>
<td>0.0534</td>
<td>0.117</td>
<td>12</td>
</tr>
<tr>
<td>$&lt; 0.8$</td>
<td>CRP</td>
<td>MDD</td>
<td>0.029</td>
<td>0.00548</td>
<td>0.05252</td>
<td>0.019</td>
<td>17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R2</th>
<th>Exposure</th>
<th>Outcome</th>
<th>Beta xy</th>
<th>Lower CI</th>
<th>Lower CI</th>
<th>P</th>
<th>N SNPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 0.05$</td>
<td>CRP</td>
<td>Trauma</td>
<td>-0.031</td>
<td>-0.06236</td>
<td>0.00036</td>
<td>0.057</td>
<td>3</td>
</tr>
<tr>
<td>$&lt; 0.2$</td>
<td>CRP</td>
<td>Trauma</td>
<td>-0.028</td>
<td>-0.05348</td>
<td>-0.00252</td>
<td>0.036</td>
<td>7</td>
</tr>
<tr>
<td>$&lt; 0.4$</td>
<td>CRP</td>
<td>Trauma</td>
<td>-0.027</td>
<td>-0.04856</td>
<td>-0.00544</td>
<td>0.014</td>
<td>12</td>
</tr>
<tr>
<td>$&lt; 0.6$</td>
<td>CRP</td>
<td>Trauma</td>
<td>-0.029</td>
<td>-0.05056</td>
<td>-0.00744</td>
<td>0.009</td>
<td>12</td>
</tr>
<tr>
<td>$&lt; 0.8$</td>
<td>CRP</td>
<td>Trauma</td>
<td>-0.032</td>
<td>-0.04964</td>
<td>-0.01436</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

Note: Each row represents one Mendelian randomization test between the exposure and the outcome. MDD = major depressive disorder; CRP = C-reactive protein; $R^2$ = the clumping threshold for SNPs; Beta xy = beta of the exposure (x) on the outcome (y); Lower CI = lower 95% confidence interval; Upper CI = upper 95% confidence interval; $P = p$-value; nSNP = number of SNPs used in the analyses.
11. Multivariable MR analyses of all traits on MDD

Table S17. Multivariable MR output with BMI, CRP and reported trauma as joint exposures, and MDD as the outcome

This table displays the results from Multivariable MR analyses, which model the joint effects of exposures (reported trauma, CRP and BMI) on a single outcome (MDD). Therefore, outcomes for each exposure display the direct effects on MDD, whilst accounting for the other two exposures.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Beta</th>
<th>SE</th>
<th>T-value</th>
<th>P</th>
<th>OR</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported Trauma</td>
<td>0.45</td>
<td>0.00</td>
<td>99.20</td>
<td>0.00E+00</td>
<td>1.57</td>
<td>1.56</td>
<td>1.58</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.02</td>
<td>0.00</td>
<td>-6.67</td>
<td>2.61E-11</td>
<td>0.98</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>BMI</td>
<td>0.10</td>
<td>0.00</td>
<td>43.37</td>
<td>0.00E+00</td>
<td>1.11</td>
<td>1.10</td>
<td>1.12</td>
</tr>
</tbody>
</table>

Note: these results represent the joint exposure effects of BMI, CRP and reported trauma on MDD (outcome). CRP = C-reactive protein; BMI = body mass index; SE = standard error; P = p-value; OR = odds ratio; CI = confidence interval.
12. Testing the strength of our genetic instruments

Table S18. F-statistic and I-squared statistic tests of our genetic instruments

This table displays results of F-statistic tests, as a measure of instrument strength; and the adapted I-squared statistic measure as an indicator of the strength of the NOME violation for MR Egger (12). Results from the F-statistic test indicates relative strength of all genetic instruments (> 30). However, the I-squared statistic is below the acceptable threshold for reported trauma and MDD, indicating that MR egger estimates when these two traits are the exposures of interest should be interpreted with caution.

<table>
<thead>
<tr>
<th></th>
<th>Trauma</th>
<th>CRP</th>
<th>BMI</th>
<th>MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-statistic</td>
<td>34.02</td>
<td>104.22</td>
<td>57.03</td>
<td>34.89</td>
</tr>
<tr>
<td>I-squared</td>
<td>0.00</td>
<td>0.97</td>
<td>0.85</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Note: these results represent the F-statistic and I-squared statistic test results, for each of our genetic instruments. CRP = C-reactive protein; BMI = body mass index; MDD = major depressive disorder.
13. Testing for shared or causal effects between CRP, reported trauma, BMI and MDD using MR-CAUSE

a) CRP on MDD

Table S19. The effects of CRP on MDD using MR-CAUSE

In this case we see that neither model is significant.

Note: \( \text{delta}_\text{elpd} = \text{delta expected log pointwise posterior density (the estimator)} \) – if the \( \text{delta}_\text{elpd} \) is negative, model 2 is a better fit; \( \text{se}_{\text{delta}_\text{elpd}} = \text{standard error of the estimator; } z = \text{z-score that can be compared to a normal distribution to test if the difference in model fit it significant; } p = \text{corresponding one-sided p-value.} \)

b) MDD on CRP

In this case we see that neither model is significant.

Note: \( \text{delta}_\text{elpd} = \text{delta expected log pointwise posterior density (the estimator)} \) – if the \( \text{delta}_\text{elpd} \) is negative, model 2 is a better fit; \( \text{se}_{\text{delta}_\text{elpd}} = \text{standard error of the estimator; } z = \text{z-score that can be compared to a normal distribution to test if the difference in model fit it significant; } p = \text{corresponding one-sided p-value.} \)

c) Reported trauma on MDD

In this case we see that the sharing model, with the lowest \( \text{delta}_\text{elpd} \) and the smallest standard error is the best fit.

Note: \( \text{delta}_\text{elpd} = \text{delta expected log pointwise posterior density (the estimator)} \) – if the \( \text{delta}_\text{elpd} \) is negative, model 2 is a better fit; \( \text{se}_{\text{delta}_\text{elpd}} = \text{standard error of the estimator; } z = \text{z-score that can be compared to a normal distribution to test if the difference in model fit it significant; } p = \text{corresponding one-sided p-value.} \)
d) MDD on Reported trauma

In this case we see that the causal model with the lowest delta_elpd and the lowest standard error is the best fit.

<table>
<thead>
<tr>
<th>model1</th>
<th>model2</th>
<th>delta_elpd</th>
<th>se_delta_elpd</th>
<th>z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>null</td>
<td>sharing</td>
<td>-5.5</td>
<td>2.6</td>
<td>-2.1</td>
</tr>
<tr>
<td>2</td>
<td>null</td>
<td>causal</td>
<td>-9.2</td>
<td>4.2</td>
<td>-2.2</td>
</tr>
<tr>
<td>3</td>
<td>sharing</td>
<td>causal</td>
<td>-3.7</td>
<td>1.7</td>
<td>-2.2</td>
</tr>
</tbody>
</table>

Note: $\Delta_{elpd} = \Delta$ expected log pointwise posterior density (the estimator) – if the $\Delta_{elpd}$ is negative, model 2 is a better fit; $se_{\Delta_{elpd}} = \text{standard error of the estimator}; z = \text{z-score that can be compared to a normal distribution to test if the difference in model fit is significant}; p = \text{corresponding one-sided p-value}$.

e) BMI on MDD

In this case we see that the sharing model with the lowest delta_elpd and the lowest standard error is the best fit.

<table>
<thead>
<tr>
<th>model1</th>
<th>model2</th>
<th>delta_elpd</th>
<th>se_delta_elpd</th>
<th>z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>null</td>
<td>sharing</td>
<td>-2.4</td>
<td>1.4</td>
<td>-1.7</td>
</tr>
<tr>
<td>2</td>
<td>null</td>
<td>causal</td>
<td>-6.3</td>
<td>3.3</td>
<td>-1.9</td>
</tr>
<tr>
<td>3</td>
<td>sharing</td>
<td>causal</td>
<td>-3.9</td>
<td>2.0</td>
<td>-2.0</td>
</tr>
</tbody>
</table>

Note: $\Delta_{elpd} = \Delta$ expected log pointwise posterior density (the estimator) – if the $\Delta_{elpd}$ is negative, model 2 is a better fit; $se_{\Delta_{elpd}} = \text{standard error of the estimator}; z = \text{z-score that can be compared to a normal distribution to test if the difference in model fit is significant}; p = \text{corresponding one-sided p-value}$.

f) MDD on BMI

In this case we see that the causal model with the lowest delta_elpd and the lowest standard error is the best fit.

<table>
<thead>
<tr>
<th>model1</th>
<th>model2</th>
<th>delta_elpd</th>
<th>se_delta_elpd</th>
<th>z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>null</td>
<td>sharing</td>
<td>-5.2</td>
<td>2.5</td>
<td>-2.1</td>
</tr>
<tr>
<td>2</td>
<td>null</td>
<td>causal</td>
<td>-9.2</td>
<td>4.2</td>
<td>-2.2</td>
</tr>
<tr>
<td>3</td>
<td>sharing</td>
<td>causal</td>
<td>-3.9</td>
<td>1.8</td>
<td>-2.2</td>
</tr>
</tbody>
</table>

Note: $\Delta_{elpd} = \Delta$ expected log pointwise posterior density (the estimator) – if the $\Delta_{elpd}$ is negative, model 2 is a better fit; $se_{\Delta_{elpd}} = \text{standard error of the estimator}; z = \text{z-score that can be compared to a normal distribution to test if the difference in model fit is significant}; p = \text{corresponding one-sided p-value}$.
14. Supplementary References


