

# Causal Association of Trauma With Subsequent Psychiatric Disorder: A Mendelian Randomization Study

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## Research Article

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# Abstract

## Objective

Trauma has been proposed as a risk factor for the development of psychiatric disorder. This study aimed to determine the causal association between them.

## Methods

Two-sample Mendelian randomization analyses were performed to estimate the causal association between trauma and psychiatric disorder. We obtained summary-level data for genetic variants associated with trauma and the corresponding association with psychiatric disorder from previous genome-wide association studies, and inverse variance weighted was used as the main method in our Mendelian randomization analysis.

## Results

Genetically predisposed trauma was associated with an increased risk of psychiatric disorder (odds ratio [OR] = 1.02, 95% confidence interval [CI], 1.01–1.02), mood disorder (OR = 1.01, 95% CI, 1.00–1.01) and depression (OR = 1.02, 95% CI, 1.01–1.02) in UK Biobank, as well as increased risk of mood disorder (OR = 1.23, 95% CI, 1.03–1.48), depression (OR = 1.10, 95% CI, 1.04–1.17), bipolar disorder (OR = 1.24, 95% CI, 1.04–1.49) and schizophrenia (OR = 1.47, 95% CI, 1.21–1.78) in data source from MR Base. However, Mendelian randomization evidence did not support an association between trauma and risk of post-traumatic stress disorder, anxiety disorder, sleep disorder, and eating disorder.

## Conclusions

Findings from our Mendelian randomization analysis suggested that trauma might be causally associated with an increased risk of some common psychiatric disorder such as depression.

## Introduction

An estimated 89% of city dwellers have experienced traumatic events<sup>1</sup>. Experiencing traumatic events such as exposure to childhood physical, sexual, and emotional abuse; partner-based physical, sexual, and emotional abuse and other traumatic events, including exposure to sexual assault, violent crime, life-threatening accident, and witnessing violent death may contribute to psychiatric disorder<sup>2–7</sup>. However, whether their relationships are causality remains unclear since the results of observational studies are usually interfered by recall and reporting bias as they are susceptible to confounding factors<sup>8</sup>. Randomized clinical trials (RCTs) are arguably the gold standard to infer causality, however, such trials might be prohibitively costly, require the consideration of ethics, or be otherwise unfeasible.

A complement to traditional epidemiology is to conduct Mendelian randomization (MR) analysis. This approach utilizes genetic variants as a proxy for an exposure of interest to investigate its potential to have a causal association with a disorder<sup>9</sup>. As the inheritance of genetic variants is randomized at meiosis, the association between the alleles and the outcome are unlikely to be affected by reverse causality and confounding factors<sup>10</sup>. Importantly, the available studies have demonstrated that reported trauma exposure is heritable, with twin heritability estimates of 20–50%<sup>11,12</sup>, and single nucleotide polymorphisms (SNPs)-based heritability estimates of 30%<sup>13</sup>. Recently, a genome-wide association

study (GWAS) reported that SNPs were associated with trauma, making it possible to explore the causal relationship between trauma and psychiatric disorder using a two-sample Mendelian randomization analysis<sup>5</sup>.

In this study, we used a two-sample Mendelian randomization approach to comprehensively estimate genetically predisposed trauma and risk of psychiatric disorder using summary data from the Gene ATLAS and the MR-Base platform. We aim to shed light on whether trauma was a risk factor of psychiatric disorder.

## Materials And Methods

### Selection of genetic variants

Instrumental variables for trauma were derived from a recent GWAS including 35,269 European ancestry cases, and 63,451 European ancestry controls<sup>5</sup>. SNPs associated with trauma were selected at the  $P$ -value  $< 5 \times 10^{-6}$ , since only several SNPs arrived at a genome-wide significance level ( $P < 5 \times 10^{-8}$ ). After extracting the summary data for the SNPs, we pruned all SNPs in linkage disequilibrium (LD) using an  $r^2$  threshold  $< 0.1$ , and selected the SNPs with the lowest  $P$ -value as an independent instrument, resulting in a total of 73 independent SNPs associated with trauma. We calculated the proportion of variance ( $R^2$ ) explained in the risk factor by the SNP(s) and the strength of the instrument (F-statistic) using the formulae from Yarmolinsky et al.<sup>14</sup>. The variance explained by the independent variants was 1.79%, and the F-statistic was 25, satisfying the threshold of  $> 10^{15}$ . Detailed information of the SNPs used as instrumental variables was displayed in **Supplementary Table 1**.

### Outcome source

Summary statistics for the genetic association estimates of each SNP used as instrumental variables with psychiatric disorder were obtained from the Gene ATLAS ([geneatlas.roslin.ed.ac.uk](http://geneatlas.roslin.ed.ac.uk)) and MR-Base platform ([www.mrbase.org](http://www.mrbase.org)). Gene ATLAS is a large database of associations between hundreds of traits and millions of variants using the UK Biobank cohort, and MR Base database holds a collection of the summary statistics from a large number of GWASs.

### Mendelian randomization analysis

The inverse variance weighted (IVW) method was used to estimate the effect of the exposure on the outcome from the slope of the relationship between bXG (SNP-exposure association) and bYG (SNP-outcome association). Several sensitivity analyses including simple mode, weighted mode, MR-Egger, and weighted median method were used to evaluate the robustness of our main analyses. To further assess the potential presence of horizontal pleiotropy, we used Cochran's Q for heterogeneity and the intercept from the MR-Egger method<sup>16,17</sup>. Leave-one-out analyse was employed to test the sensitivity of our results to single SNP effects.

### Statistical analysis

All analyses were conducted using the package TwoSampleMR (version 0.5.6) in R (version 3.6.3), and the TwoSampleMR R package curated by MR-Base. All tests were two-sided, and  $P$  value of less than 0.05 was considered statistically significant unless stated otherwise.

## Results

Genetically predisposed trauma was associated with overall psychiatric disorder risk in the UK Biobank (odds ratio [OR] = 1.02, 95% confidence interval [CI], 1.01–1.02,  $P = 2.32E-07$ ). Although the Egger intercept did not indicate the presence of horizontal pleiotropy, significant heterogeneity (Cochran's Q  $P = 0.01$ ) was observed for the inverse-variance weighted

estimate. We had consistent findings using two other Mendelian randomization analysis methods (weighted median and weighted mode). However, using summary statistics from MR Base, we showed no association between genetically predisposed trauma and overall psychiatric disorder risk. See Table 1, **Supplementary Table S2, and Supplementary Table S3.**

Table 1

Mendelian randomization analyses of the causality between genetically predisposed trauma and psychiatric disorder risk.

Outcome	Outcome source	Consortium	Sample size	SNPs (N)	OR (95% CI)	P value	Heterogeneity Q tests P value	MR-Egger intercept test P value
Psychiatric disorder	Gene ATLAS	UK Biobank	452,264	66	1.02 (1.01–1.02)	2.32E-07	0.01	0.05
	MR Base	NA	94,402	49	0.81 (0.49–1.32)	0.3907	0.2565	0.863
Mood disorder	Gene ATLAS	UK Biobank	452,264	65	1.01 (1.00–1.01)	6.11E-06	0.58	0.2
	MR Base	NA	96,499	49	1.23 (1.03–1.48)	0.02368	0.965	0.349
Depression	Gene ATLAS	UK Biobank	452,264	66	1.02 (1.01–1.02)	5.29E-08	0.02	0.07
	MR Base	NA	180,866	49	1.10 (1.04–1.17)	5.97E-04	7.54E-06	0.142
Bipolar disorder	Gene ATLAS	UK Biobank	452,264	66	1.00 (1.00–1.00)	0.19	0.13	0.66
	MR Base	Bipolar Disorder Working Group of the Psychiatric Genomics Consortium	51,710	66	1.24 (1.04–1.49)	0.02	7.97E-05	0.122
Anxiety disorder	MR Base	NA	93,291	49	1.18 (0.92–1.53)	0.1951	0.7287	0.677
PTSD	MR Base	NA	89,058	49	0.77 (0.33–1.80)	0.5392	0.9251	0.228
Sleep disorder	Gene ATLAS	UK Biobank	452,264	66	1.00 (1.00–1.00)	0.28	0.05	0.78
	MR Base	NA	95,720	49	0.99 (0.78–1.26)	0.9221	0.1047	0.906

CI: Confidence interval; NA: Not available; OR: Odds ratio; PTSD: Post-traumatic stress disorder; SNP: Single nucleotide polymorphism

Outcome	Outcome source	Consortium	Sample size	SNPs (N)	OR (95% CI)	P value	Heterogeneity Q tests P value	MR-Egger intercept test P value
Eating disorder	MR Base	NA	96,499	49	1.19 (0.62–2.29)	0.5919	0.2046	0.424
Schizophrenia	Gene ATLAS	UK Biobank	452,264	66	1.00 (1.00–1.00)	0.10	0.01	0.93
	MR Base	Schizophrenia Working Group of the Psychiatric Genomics Consortium	77,096	66	1.47 (1.21–1.78)	1.04E-04	3.98E-16	0.0455
CI: Confidence interval; NA: Not available; OR: Odds ratio; PTSD: Post-traumatic stress disorder; SNP: Single nucleotide polymorphism								

In particular, a positive association was observed between genetically predisposed trauma and the risk of mood disorder and depression in UK Biobank (OR = 1.01, 95% CI, 1.00-1.01,  $P = 6.11E-06$ ; OR = 1.02, 95% CI, 1.01–1.02,  $P = 5.29E-08$ ; respectively), as well as in data source from MR Base (OR = 1.23, 95% CI, 1.03–1.48,  $P = 0.02$ ; OR = 1.10, 95% CI, 1.04–1.17,  $P = 5.97E-04$ ; respectively). Egger intercept did not indicate the presence of horizontal pleiotropy, whereas significant heterogeneity (Cochran's Q  $P < 0.05$ ) was observed for trauma and depression. However, other Mendelian randomization analysis methods were not support these findings, except for weighted median. Further investigations are thus warranted to elucidate these suggestive findings.

Besides, summary statistics from MR Base showed that genetically predisposed trauma increased risk of bipolar disorder (OR = 1.24, 95% CI, 1.04–1.49,  $P = 0.02$ ) and schizophrenia (OR = 1.47, 95% CI, 1.21–1.78,  $P = 1.04E-04$ ). However, no association was observed between genetically predisposed trauma and risk of post-traumatic stress disorder, anxiety disorder, sleep disorder, and eating disorder, with no evidence of effect heterogeneity or horizontal pleiotropy.

Leave-one-out analysis suggested that no single instrument was strongly driving the overall effect of trauma on psychiatric disorder, indicating that these results were not sensitive to SNP selection. Funnel plots, scatter plots and leave-one-out plots were shown in Fig. 1, and **Supplementary Fig. S1-6 online**.

Furthermore, we evaluated whether the correlation between trauma and psychiatric disorder was influenced by obesity, smoking status, alcohol consumption, diabetes mellitus, vitamin D use, or physical activity. The results demonstrated that genetically predisposed trauma was not causally associated with these potential confounders and mediators except obesity class 1 [body mass index(BMI):35-39.9 kg/m<sup>2</sup>] (OR = 1.24, 95% CI 1.07–1.43,  $P = 0.004$ ). See Table 2.

Table 2  
Causal effects between genetically predisposed trauma and potential confounders.

Trait	First author	Consortium	Sample size	OR (95% CI)	Pvalue
Obesity class 1 (BMI: 30-34.9 kg/m <sup>2</sup> )	Berndt SI	GIANT	98,697	1.24 (1.07–1.43)	0.004
Obesity class 2 (BMI: 35-39.9 kg/m <sup>2</sup> )	Berndt SI	GIANT	72,546	1.18 (0.92–1.50)	0.20
Obesity class 3 (BMI: ≥40 kg/m <sup>2</sup> )	Berndt SI	GIANT	50,364	1.31 (0.87–1.97)	0.20
Alcohol consumption	Clarke	UK Biobank	112,117	0.99 (0.97–1.02)	0.52
Smoking status (ever vs never)	Neale	Neale Lab	336,024	1.02 (1.00–1.04)	0.07
Physical activity	Ben Elsworth	MRC-IEU	440,512	1.03 (0.97–1.09)	0.30
Vitamin D use	Ben Elsworth	MRC-IEU	64,949	0.99 (0.98–1.01)	0.29
Diabetes mellitus	NA	NA	96,499	1.17 (0.99–1.38)	0.06
BMI: Body mass index; CI: Confidence interval; NA: Not available; OR: Odds ratio.					

## Discussion

In this study, we performed a comprehensive two-sample MR analysis using trauma-associated SNPs as genetic instruments to determine the causal role of trauma in risk of psychiatric disorder. Our study suggested that trauma exposure was causally associated with an increased risk of psychiatric disorder, which highlights the critical role of trauma exposure in shaping risk for psychopathology throughout the life course.

Mendelian randomization rests on three main assumptions<sup>18</sup>. Assumption one is that the instrumental variables must be associated with the phenotype. To satisfy the first assumption, we selected SNPs with a genome-wide significant association with trauma<sup>5</sup>. Assumption two is that the instrumental variables should not be associated with confounders. Assumption three is that the instrumental variables should affect the outcome only through the phenotype. We carried out statistical tests and sensitivity analyses to evaluate the potential violation of the second and third assumptions. Besides, we evaluated horizontal pleiotropy by MR-Egger regression method, and the results also did not show any evidence for the presence of horizontal pleiotropy for any of the reported associations.

Furthermore, potential confounders such as obesity, smoking status, alcohol consumption, diabetes mellitus, vitamin D use, and physical activity were checked in our study. The results demonstrated that genetically predisposed trauma was not causally associated with these potential confounders except obesity class 1 (BMI: 30-34.9 kg/m<sup>2</sup>), the risk of which increased by 24%. Given that the results of epidemiological studies concerning the effects of obesity on psychiatric disorder risk were conflicting<sup>19–21</sup>, this confounder was unlikely to influence the trauma-psychiatric disorder relation from our study. Nevertheless, caution is required in interpreting the outcomes.

Although trauma has been shown to play a meaningful role in the etiology of some common psychiatric disorders, the relationship between them is complex and poorly understood. Previous studies have provided evidence for underlying mechanisms through which trauma may influence mental health. Specifically, trauma exposure has been linked with HPA axis dysregulation and emotion dysregulation, which could increase risk of psychiatric disorders and transitions between disorders<sup>22,23</sup>. In addition, trauma appears to be an important correlate of a cascade of psychiatric disorders, between which both gene-environment correlations and gene-environment interactions have been observed<sup>5,24</sup>. Further studies are needed to illustrate the possible mechanisms. Interestingly, our results do not support a positive association

between trauma and PTSD, which were inconsistent with previous observational studies<sup>25–27</sup>. Therefore, we speculate that there is only a simple epidemiological correlation, instead of a causal association between them.

Our study has several limitations. First, although the F-statistic satisfied the threshold, the selected SNPs for trauma exposure could only explain 1.79% of the phenotypic variation, other unknown trauma-related SNPs could also play an important role in the development of psychiatric disorder. Second, although sensitivity analyses have been conducted, we cannot assure that each SNP meets the three MR assumptions as instrumental variables. We checked several confounding factors such as obesity, smoking status, alcohol consumption, diabetes mellitus, vitamin D use, and physical activity. However, unknown possible confounders may inevitably affect causal inference. Third, statistical heterogeneity was observed in some estimates, which may require further investigation. Finally, the summary statistics used in our study were from participants of European ancestry, which limits the inference of findings in other populations, further studies in non-European populations are required.

## Conclusions

In summary, our study suggested a causal effect of trauma on psychiatric disorder, especially mood disorder (mainly bipolar and depressive disorders). However, Mendelian randomization evidence did not support an association between trauma and risk of post-traumatic stress disorder, anxiety disorder, sleep disorder, and eating disorder. Better designed cohort studies and MR analysis are necessary to examine our findings, and deepen our understanding of their associations.

## Declarations

### Availability of data and materials

Summary statistics of trauma were obtained from GWAS catalog ([www.ebi.ac.uk/gwas](http://www.ebi.ac.uk/gwas)). Summary statistics of outcome were obtained from the Gene ATLAS ([GeneATLAS | The University of Edinburgh](http://GeneATLAS | The University of Edinburgh)) and MR-Base platform ([www.mrbase.org](http://www.mrbase.org)).

### Competing interests

The authors declare that they have no competing interests

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### Authors' contributions

G.L. and D.G. contributed to conception and design of the study; D.G. and S.O. did the literature search, data extraction and quality assessment; G.L. and D.G. did statistical analysis; D.G. wrote the first draft of the original manuscript with significant contributions from S.O. and G.L.. All authors read and approved the final manuscript.

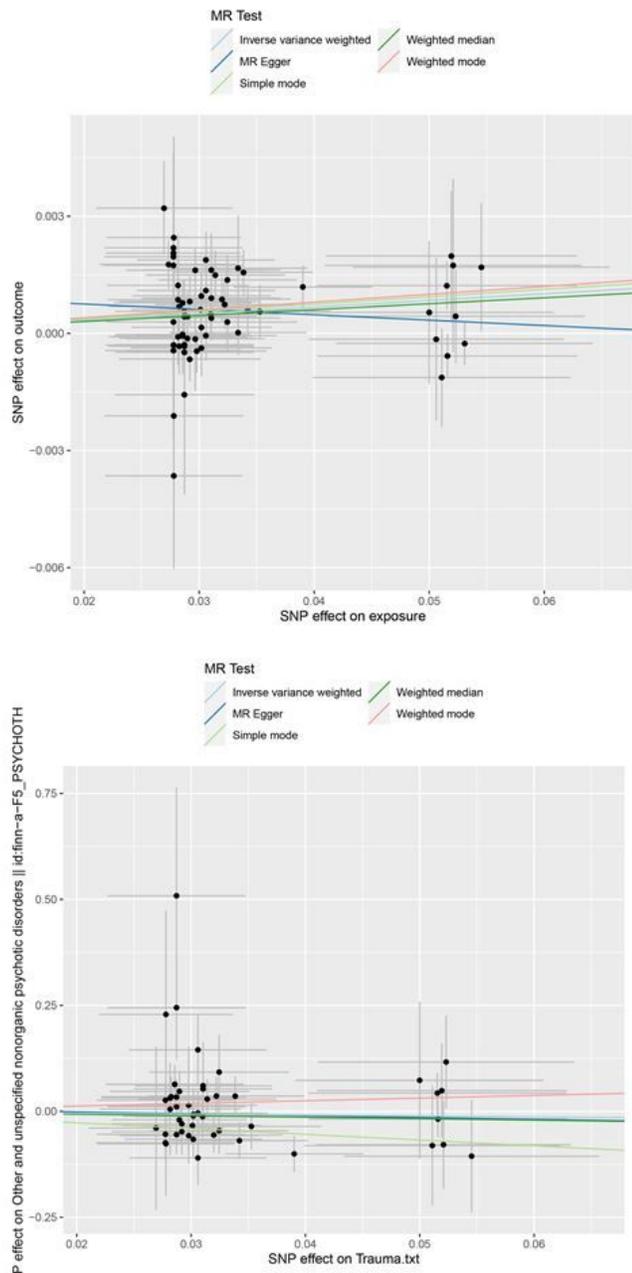
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## Figures



**Figure 1**

Scatter plots of the genetic causal associations between trauma and psychiatric disorder using different MR methods. (A) Trauma and psychiatric disorder in UK Biobank; (B) trauma and psychiatric disorder in MR Base. The slopes of the line represent the causal association for different methods. The light green line represents the simple mode estimate, the dark green line represents the weighted median estimate, the pink line represents the weighted mode estimate, the light blue line represents the inverse variance weighted estimate, and the dark blue line represents the MR Egger.

## Supplementary Files

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