Diabetology & Metabolic Syndrome

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Causal associations between posttraumatic stress disorder and type 2 diabetes

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Abstract

Posttraumatic stress disorder (PTSD) patients have a high comorbidity with type 2 diabetes (T2D). Whether PTSD influences the risk of diabetes is still not known. We used GWAS data from European ancestry of PTSD (23,121 cases and 151,447 controls) and T2D (80,154 cases and 853,816 controls) to investigate the bidirectional associations between PTSD and T2D by the Mendelian randomization (MR) analysis. We showed that PTSD was causally associated with higher odds of T2D (OR = 1.04, 95% CI: 1.01–1.06, $P = 0.0086$), but not vice versa. Our study suggests that PTSD may increase the risk of T2D. PTSD sufferers should be screened for T2D and its precursor known as metabolic syndrome.

Keywords Posttraumatic stress disorder, Diabetes, Mendelian randomization

Introduction

Patients with posttraumatic stress disorder (PTSD) suffer from prolonged severe psychological distress. According to mind-body interaction theory, the human body undergoes physiological changes when subjected to long-term negative emotional influence [1]. Some researchers suggest that PTSD may be more than a brain disorder; instead, it should be analyzed as a systemic dysfunction that affects neuroendocrine, metabolic, and inflammatory circuits [2]. Possibly, PTSD phenotypes are orchestrated by changes in the hypothalamic-pituitary-adrenal axis (HPA) [3]. From this perspective, common PTSD comorbidities, such as arthritis [4], cardiovascular disease [5], and inflammatory disorders [6], may not be independent entities but rather manifestations of PTSD itself.

Type 2 diabetes mellitus (T2D) and PTSD frequently co-occur in the same individual and are significantly associated with each other [7]. Approximately 30–46% of the variance in PTSD [8], and 25–72% of the variance in T2D can be accounted for by inherited DNA variants. The sets of genetic variants that predispose to T2D and PTSD may overlap.

Previous studies have explored the association between PTSD and T2D from biological, psychological, and behavioral perspectives. Observational studies of the relationship between PTSD and T2D may not be free of confounding factors. However, in a 22-year follow-up study, the incidence of T2D was still associated with PTSD symptoms in a dose-response manner even after adjusting for BMI (Body Mass Index) and other risk factors [9]. After accounting for commonly co-occurring

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depression, asylum seekers with PTSD still had a higher incidence of T2D compared to appropriate population controls [8]. Among servicewomen, both the military trauma itself and the severity of PTSD have been shown to increase the risks of gestational diabetes [10].

Mendelian randomization (MR) utilizes genetic instrumental variables (IVs) to assess the relationship between an exposure and an outcome, thus reducing the influence of confounding factors [11]. MR has been widely employed in recent studies to investigate risk factors for mental disorders and somatic diseases [12–16]. Previous research has identified causal associations between mental disorders and T2D, including major depressive disorder (MDD), Alzheimer's disease, and attention-deficit/hyperactivity disorder (ADHD) [17–21]. Notably, PTSD is closely associated with other mental disorders, particularly MDD and ADHD [22]. PTSD shares significant genetic overlap with MDD and has even been proposed as a subtype of MDD [23]. Furthermore, ADHD has been reported to exert a causal effect on PTSD [24]. In the current study, we employed MR methods to investigate the bidirectional causal associations between PTSD on T2D.

Materials and methods

Study design and data sources

Genetic association data on PTSD were obtained from a genome-wide association study (GWAS) involving 23,212 cases and 151,447 controls [25]. Summary data of T2D included 80,154 T2D cases and 853,816 controls from published GWASs [26]. All participants were of European ancestry.

MR analyses

We identified single-nucleotide polymorphisms (SNPs) showing genome-wide significance ($P < 5 \times 10^{-8}$) in the T2D datasets as IVs. For PTSD, a lenient P value threshold ($P < 1 \times 10^{-5}$) was used to select IVs due to the inadequate number of genome-wide significant SNPs in the dataset. These SNPs were further refined by applying a clumping r2 cutoff of 0.001 within a 10 Mb window. The causal relationship between PTSD and T2D was assessed using the inverse-variance weighted (IVW) regression method in Mendelian randomization (MR) analysis. Sensitivity analyses were carried out using the weighted median (WM) and MR−Egger methods. Heterogeneity in the MR analyses was assessed using Cochran's Q test and I2 statistics, with significance set at $P < 0.05$ and $I2 > 0.25$.

Results

MR analyses

A total of 23 SNPs were selected as IVs to predict PTSD, and 232 SNPs to predict T2D. The F statistics of these IVs were all larger than 10. In the MR analysis performed using IWM with T2D as the outcome, we found that the genetic component of PTSD increases the risk of T2D, with approximately 4% increase in the odds of T2D per standard deviation (SD) increase in PTSD (OR:1.04, 95%CI: 1.01–1.06, $P = 0.0086$) (Table 1; Fig. 1). The directions of the causal effect of PTSD on T2D estimates across the three methods, namely, IWM, WM and MR−Egger, were largely consistent. Both WM and MR−Egger intercepts did not yield statistically significant results (OR = 1.02, 95% CI: 0.99–1.04, $P = 0.132$ and OR = 0.99, 95% CI: 0.93–1.05, $P = 0.766$, respectively) (Table 1; Fig. 1), with no evidence for horizontal pleiotropy for the association of PTSD with T2D in the all-SNP analysis. The analysis examining the effects of T2D on PTSD produced negative findings; specifically, no causal associations reached statisitical significance. Cochran's Q test suggested pointed at some heterogeneity in IVs (Table 1).

Discussion

Two-sample MR analysis indicated that genetically determined PTSD confers a higher risk of developing T2D. PTSD may be linked to the development of diabetes through the physiological and behavioral changes associated with it. First, the initial trauma leads to propagation of chronic stress. This, in turn, contributes to the dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA). The HPA axis dysregulation, which is characterized by an initial increase in cortisol secretion followed by the establishment of low cortisol levels, may promote some degree of systemic inflammation [27, 28], particularly neuroinflammation. Subsequenty, neuroinflammation causes neuronal apoptosis and abnormal glutamate transmission in the central nervous system, especially in

Table 1 Analysis of bidirectional associations between PTSD and T2D

Exposure	Outcome	Method	P_IV	b (se)	OR [95%CI]	N_IV	Q_P	I^2	Egger_intercept	P_pleiotropy	*P*
PTSD	T2D	IVW	1.00E-05	0.035 (0.013)	1.04 [1.01–1.06]	23	1.32E-03	0.536	NA	NA	8.60E-03
PTSD	T2D	WM	1.00E-05	0.019 (0.013)	1.02 [0.99–1.04]	23	NA	NA	NA	NA	0.132
PTSD	T2D	MR-Egger	1.00E-05	-0.009 (0.031)	0.99 [0.93–1.05]	23	3.85E-03	0.48	0.011	0.128	0.766
T2D	PTSD	IVW	5.00E-08	-0.016 (0.039)	0.98 [0.91–1.06]	232	0.058	0.131	NA	NA	0.687
T2D	PTSD	WM	5.00E-08	0.022 (0.064)	1.02 [0.90–1.16]	232	NA	NA	NA	NA	0.729
T2D	PTSD	MR-Egger	5.00E-08	-0.027 (0.091)	0.97 [0.82–1.16]	232	0.053	0.131	0.001	0.894	0.768

IVW: inverse variance weighted; WM: weighted median; OR: odds ratio; CI: confidence interval; N_IV: number of instrumental variables; Q_P: Cochran's P value of heterogeneity analysis.

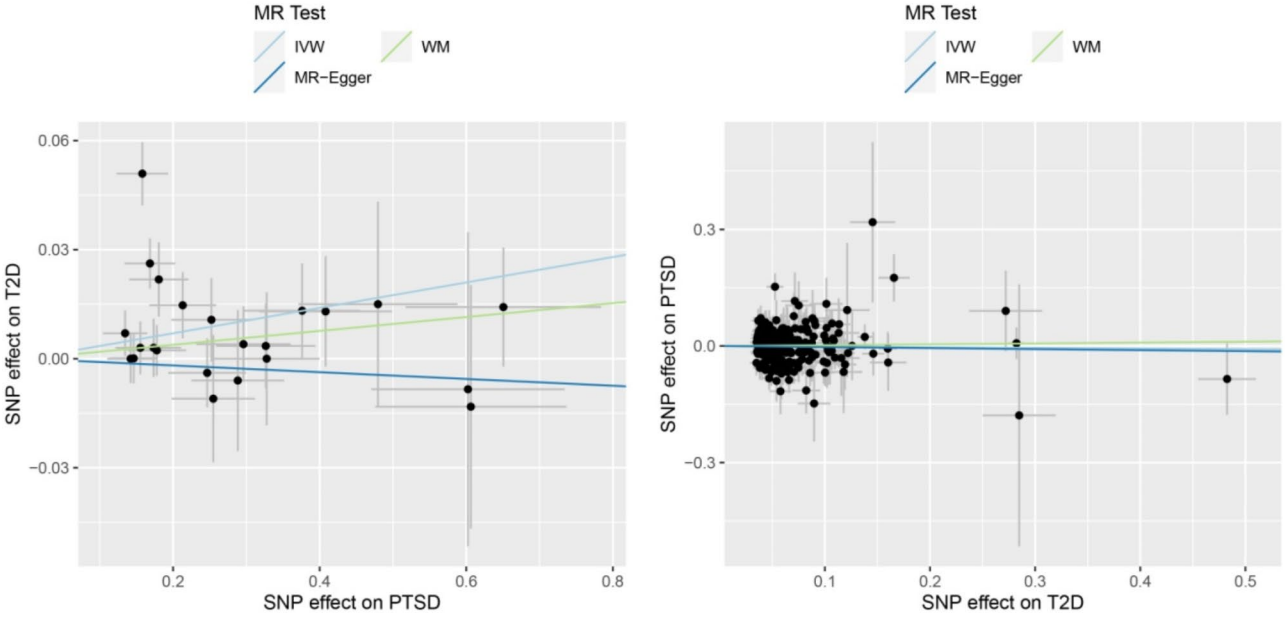

Fig. 1 Causal associations between PTSD and T2D. Scatter plot for the SNP effect size estimate. Relationship between the SNP effect size estimate of exposure (x-axis) and the corresponding effects size estimate of outcome (y-axis). The trait on the x-axis denotes exposure, the trait on the y-axis denotes outcome, and each cross point represents an instrumental variant. The dots and short lines through the dots denote the effect sizes (**b**) and the 95%CI of exposure on an outcome. IVW: inverse variance weighted; WM: Weighted median

the appetite center. This leads to weight gain and potentially results in insulin resistance and reduced glucose intolerance [29].

Chronic stress also can trigger an increase in peripheral immune inflammation. This can be followed by dysregulation of the gut microbiota, which in turn further impacts the body's metabolic state. Multiple studies have demonstrated that inflammatory markers, such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-alpha (TNF-α), interferon (IFN), and C-reactive protein (CRP), are elevated in peripheral blood and cerebrospinal fluid (CSF) of PTSD patients [30, 31]. Inflammation not only promotes weight gain but also insulin resistance. These conditions further boost the levels of pro-inflammatory cytokines, thereby creating a vicious circle [32]. Furthermore, stress, even when it is merely perceived rather than objectively real, can directly initiate an abnormal neuroendocrine response. This includes inappropriate insulin secretion, leading to more significant fluctuations in blood glucose concentration and contributing to insulin resistance [33, 34]. Behaviorally, persistent negative posttraumatic emotions frequently give rise to unhealthy habits such as overeating, smoking, alcohol abuse, and sedentary lifestyle. These habits are well-established risk factors for T2D [35].

To mitigate the risk of developing diabetes and related morbidities in PTSD sufferers, it is essential to identify these potential mechanisms that promote T2D and implement relevant interventions.

It should be noted that our study has certain limitations. Firstly, our study was restricted to subjects from the European population. As a result, the study findings cannot be readily generalized to other ethnic groups. Secondly, the relationship between PTSD and T2D was examined in a pairwise manner. There is a need to identify and explore other factors that mediate the causal link between PTSD and T2D.

Conclusion

In conclusion, PTDS may increase the risk of T2D. Individuals suffering from PTSD should be screened for T2D and its precursor, metabolic syndrome. Treatment plans for PTSD should incorporate measures designed to prevent T2D.

Author contributions

FZ conceived the project, supervised the study and analyzed the data. F.Z., Y.S., A.B., H.C.,W.H. wrote the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Informed consent

Not applicable.

Competing interests
The authors declare no competing interests.

Animal studies
Not applicable.

Approval of the research protocol
Not applicable.

Approval date of registry and the registration no. of the study/trial
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Conflict of interest
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