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Research paper

Association of anxiety disorder, depression, and bipolar disorder with autoimmune thyroiditis: A bidirectional two-sample mendelian randomized study

Jingyang Su [a,1], Jialin Zhang [b,1], Hanyu Zhu [b,1], Jinhua Lu [b,*]

[a] Department of General internal medicine, Tongde Hospital Affiliated to Zhejiang Chinese Medical University (Tongde Hospital of Zhejiang Province), Hangzhou 310012, China

[b] Department of Oncology, Hangzhou TCM Hospital of Zhejiang Chinese Medical University (Hangzhou Hospital of Traditional Chinese Medicine), 310007 Hangzhou, China

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ABSTRACT

Background: Anxiety disorder, depression, and bipolar disorder are common psychiatric disorders, and their association with autoimmune thyroiditis (AIT) has been of great interest. This study aimed to investigate the potential causal relationship between these psychiatric disorders and AIT.

Methods: We used publicly available summary statistics from large-scale genome-wide association studies to select, quality control and cluster genetic variant loci associated with anxiety disorder, depression, bipolar disorder and AIT as instrumental variables (IVs). The Mendelian randomization (MR) study mainly used inverse variance weighting (IVW) combined with MR-egger regression and weighted median estimation (WME) to estimate bidirectional causality between mental disorders and AIT. In addition, we conducted heterogeneity and multivariate tests to verify the validity of IVW.

Results: Two-sample bidirectional MR analysis revealed a positive causal link between depression and AIT. The forward MR analysis of IVW (OR 1.614, 95 % CI 1.104–2.358, $P = 0.013$) and WME (OR 2.314, 95 % CI 1.315–4.074, $P = 0.004$) demonstrated thatdepression potentially elevate the risk of AIT development, while, our investigation did not uncover a causal relationship between anxiety disorder, bipolar disorder and AIT. The results of reverse MR analysis showed that there was no significant causal relationship between AIT and anxiety disorder, depression, and bipolar disorder ($P > 0.05$).

Conclusions: The results of the forward MR analysis suggest a positive association between depression, and AIT risk, while indicating no support for a causal link between anxiety disorder or bipolar disorder and AIT risk based on the current data. Subsequent studies will be essential for elucidating the biological mechanisms and potential confounders underlying these associations.

1. Introduction

Autoimmune thyroiditis (AIT) stands as the most prevalent autoimmune endocrine disorder (Ruggeri et al., 2018), affecting an estimated 3–5 % of the general population (McLeod and Cooper, 2012). Predominantly afflicting women, its incidence escalates with advancing age (McLeod et al., 2014; Hollowell et al., 2002), soaring up to 20 % among elderly women (Surks et al., 2004). Furthermore, it serves as the primary cause of hypothyroidism. In the initial stages, AIT usually manifests with common hypothyroidism symptoms, such as mood disturbances, anxiety, or depression (van Zuuren et al., 2013), while, AIT can also precipitate hyperthyroidism.

Anxiety disorder, depression, and bipolar disorder are prevalent mental disorders with genetic and clinical overlap, suggesting that they may share common etiologic mechanisms (Tondo et al., 2017; Trede et al., 2005; Anttila et al., 2018). Research indicates a shared pattern of abnormal regional intrinsic brain activity in depression and bipolar disorder, particularly implicating the insula, medial prefrontal cortex, and cerebellum (Gong et al., 2020). The lifetime prevalence of anxiety disorder among individuals with bipolar disorder is estimated to be at

* Corresponding author.
E-mail address: 2021B461@zcmu.edu.cn (J. Lu).
[1] Jingyang Su, Jialin Zhang, and Hanyu Zhu contributed equally to this work.

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least 40 %, even exceeding 50 % (Seon et al., 2021; Kessler et al., 1997; Vieta et al., 2001). Recent evidence suggests that the comorbidity of anxiety disorder with bipolar disorder is as high as that of monophasic depression (Preti et al., 2016).

Previous studies have suggested that the development of autoimmune thyroiditis may be associated with anxiety disorder, depression, and bipolar disorder (Vonk et al., 2007; Siegmann et al., 2018; Engum et al., 2005). Observational studies have linked both hypothyroidism and hyperthyroidism to depression or bipolar disorder (Loh et al., 2019; Hong et al., 2018; Chakrabarti, 2011). Additionally, large cohort studies have demonstrated that even small variations in thyroid function within the normal range can increase the risk of depression (Williams et al., 2009; Medici et al., 2014; Kim et al., 2015). Based on the reviewed literature, we hypothesize that genetically related psychiatric disorders (anxiety disorder, depression, bipolar disorder) increase the risk of autoimmune thyroiditis, although this hypothesis remains controversial.

In a meta-analysis study, standardized depression and anxiety scale scores were significantly higher in patients with AIT, Hashimoto's thyroiditis, or subclinical or overt hypothyroidism, with an odds ratio (OR) of 3.56 (95 % CI, 2.14–5.94) and an OR of 2.32 (95 % CI, 1.40–3.85), respectively (Siegmann et al., 2018). In contrast, another study reported only a nonsignificant weak association between hypothyroidism and depression (OR, 1.24) (Wildisen et al., 2020). Unfortunately, the high costs and complexities associated with clinical trials impede the investigation of the effects of mental disorders on thyroid function. Moreover, confounding factors often arise in observational studies, leading to potential biases in research on mental disorders and AIT. In the absence of high-quality randomized controlled trials, Mendelian randomization (MR) offers a promising alternative method to assess the causal relationship between mental disorders and AIT.

In a recent study involving 497,726 participants from a U.K. Biobank, results suggest a tentative causal relationship between AIT and psychiatric disorders, including anxiety disorder, depression, and bipolar disorder (Soheili-Nezhad et al., 2023). Hypothyroidism was positively associated with the risk of developing anxiety disorder (OR 1.16, $P = 6.22 \times 10^{-8}$), depressive disorders (OR 1.31, $P = 5.29 \times 10^{-89}$), and bipolar disorders (OR 1.55, $P = 0.0038$). Similarly, hyperthyroidism was linked to an increased risk of anxiety disorder (OR 1.34, $P = 5.99 \times 10^{-6}$) and depression (OR 1.11, $P = 0.0034$). (Soheili-Nezhad et al., 2023). However, to date, there have been no Mendelian randomization studies examining the relationship between mental disorders (anxiety disorder, depression, bipolar disorder) and AIT. Thus, we conducted a two-sample bidirectional Mendelian randomization study based on genome-wide association study (GWAS) data to explore the causal relationship between anxiety, depression, bipolar disorder and the risk of AIT. MR studies utilize genetic variation as the instrumental variables, which allows for the exploration of causal relationships between exposure and outcome, thereby increasing the reliability of causal inference (Smith and Ebrahim, 2003). In addition, MR analyses take advantage of the stochastic nature of germline genetic variation at fertilization and the random assortment of alleles during meiosis to avoid confounders and reverse causality.

2. Methods

2.1. Study design

We conducted a two-sample bidirectional MR analysis using data from a large-scale GWAS to explore the potential causal relationship between mental disorders (anxiety disorder, depression, and bipolar disorder) and AIT. Initially, anxiety disorder, depression, and bipolar disorder were considered as exposure factors, while AIT served as the outcome indicator in the forward MR analysis. Subsequently, a reverse MR analysis was performed with AIT as the exposure factors and anxiety disorder, depression, and bipolar disorder as outcome indicators.

2.2. Data sources for mental disorders

Data related to mental disorders were sourced from the Psychiatric Genomics Consortium (PGC) database of published articles. We focused on a study population exclusively of European descent. The anxiety disorders dataset (Otowa et al., 2016) comprised 5580 cases and 17,310 controls, while the depression dataset (Howard et al., 2019) included 170,756 cases and 329,443 controls. Data for bipolar disorder were derived from the GWAS statistics of the Mullins et al. (Mullins et al., 2021), study, which involved 41,917 cases and 371,549 controls, as demonstrated in Table 1.

2.3. Data sources for autoimmune thyroiditis

The autoimmune thyroiditis GWAS data were obtained from the most recent Finnish database (https://r11.finngen.fi/), which encompasses a comprehensive cohort of 385,630 individuals. Within this population, 612 cases were diagnosed with autoimmune thyroiditis, as presented in Table 1.

2.4. Basic assumptions for instrumental variables

In employing single nucleotide polymorphisms (SNPs) as instrumental variables for exposure factors in MR analyses, three fundamental assumptions must be satisfied for the results to be deemed reliable. These assumptions are as follows: (1) the association assumption: SNPs are strongly correlated with exposure factors; (2) the independence assumption: SNPs remain independent of any confounding factors that may influence the relationship between exposures and outcomes; (3) the exclusivity assumption: SNPs exert their effects on outcomes solely through their impact on the exposure variables (Bowden and Holmes, 2019).

2.5. Selection of the instrumental variables

In this study, we first analyzed mental disorders as the exposure factor and AIT as the outcome indicator in a positive MR analysis. In the reverse MR analysis, AIT served as the exposure factor and mental disorders as the outcome indicator. During the SNP screening process, the criteria were adjusted due to the limited number of SNPs identified. Depending on the number of SNPs included, stringent criteria were employed ($p < 5 \times 10^{-6}$, linkage disequilibrium [LD] $r^2 < 0.01$, genetic distance = 10,000 KB) to identify significant SNPs associated with anxiety disorders, depression, and bipolar disorders from their respective databases. Although the thresholds were adjusted when the p-value of the screening was lowered to $p < 5 \times 10^{-6}$, this ensured the robustness of the analysis and preserved the integrity of the MR framework. No alterations to the main positive results were evident during the analysis, as shown in Fig. 1. To fulfill the first fundamental assumption of MR, the F statistic ($F = beta^2/se^2$) was computed for each SNP, with a threshold set at $F > 10$, indicative of a strong correlation between the instrumental variable and the exposure (Burgess and Thompson, 2011; Pierce et al.,

Table 1
Genetic summary data sources for psychiatric disorders and autoimmune thyroiditis.

Trait	Sample size	Population	ncase	ncontrol	Sex
Anxiety disorder	22,890	European	5580	17,310	Males and Females
Depression	500,199	European	170,756	329,443	Males and Females
Bipolar disorder	413,466	European	41,917	371,549	Males and Females
Autoimmune thyroiditis	385,630	European	612	385,018	Males and Females

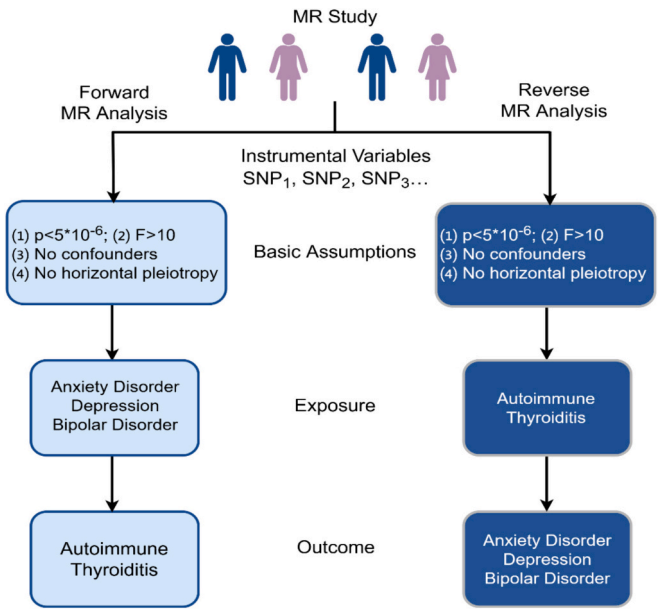

Fig. 1. Flowchart of bidirectional Mendelian randomization.

2011). The SNPs adhere to the principle that offspring alleles are randomly assigned from the parental generation and are unlikely to be influenced by environmental factors. Consequently, we can posit that the instrumental variable remains uncorrelated with potential confounders. Nevertheless, a meticulous process was undertaken wherein SNPs were filtered one by one to ascertain whether they exhibited associations with confounders, thereby fulfilling the criteria outlined in MR assumption 2 (Bowden and Holmes, 2019). In evaluating the third basic hypothesis of MR, intercept terms such as the Egger intercept were calculated using the MR-Egger regression model through the execution of "mr_pleiotropy_test" in R. A *p*-value exceeding 0.05 signifies the absence of horizontal pleiotropy, thereby affirming that the instrumental variables solely influence the outcome through the exposure, consistent with assumption 3 (Burgess and Thompson, 2017).

2.6. Statistical analysis

After harmonizing the effect alleles from GWAS for anxiety disorder, depression, bipolar disorder, and AIT, we primarily employed three MR methods: inverse variance weighted (IVW) test, MR-Egger regression, and weighted median estimation (WME), to evaluate the potential causal relationship between mental disorders and the risk of developing AIT. The IVW method served as the primary analytical approach, while MR-Egger regression and WME were utilized as supplementary methods to support IVW estimation (Bowden et al., 2016). The heterogeneity of IVW was assessed using the Cochrane Q statistic. A *p*-value >0.05 indicates homogeneity, which ensures the reliability of the results (Burgess and Thompson, 2017; Bowden et al., 2016). If a p-value <0.05 indicates heterogeneity, a random-effects model was applied for IVW, and combining the WME results was necessary to enhance reliability (Burgess et al., 2013; Bowden et al., 2019). In contrast, MR-Egger regression accounted for the presence of an intercept term (Bowden et al., 2015), corrected for multivariate bias, and detected directional pleiotropy but was susceptible to instrumental variable assumptions. A close-to-zero egger intercept in linear regression suggests the absence of directional pleiotropy. The weighted median method, aggregating data from multiple genetic variants into a single causal estimate, required that over 50 % of weights originate from validated instrumental variables to ensure reliable causal effect estimates (Bowden et al., 2016). Additionally, to enhance the robustness of MR estimation, we identified outliers potentially influencing MR estimation through forest plots, scatter plots, funnel plots, and leave-one-out analyses.

The MR analysis was conducted using the R package "TwoSampleMR" (version 0.5.11) within the R software environment (version 4.3.3).

3. Results

3.1. Mendelian randomization analysis

After a series of quality control procedures, we obtained MR data with anxiety, depression, and bipolar disorder as exposure factors and AIT as an outcome indicator. We first merged the anxiety-related dataset with the AIT dataset, resulting in 6 SNPs for analysis. Similarly, merging the depression and AIT datasets led to the exclusion of five palindromes (rs261909, rs2876520, rs4730387, rs547488, rs751996), yielding 171 SNPs. Using the same quality control measures, merging bipolar disorder with AIT involved removing duplicate SNPs (rs76769832) and excluding 29 palindromes (rs10791849, rs11062170, rs1204834, rs12233703, rs12407573, rs12625702, rs13417268, rs146950761, rs149002246, rs1646022, rs197120, rs1998820, rs2011302, rs2299098, rs255373, rs28360326, rs2921552, rs2962370, rs35985675, rs56014219, rs62489493, rs72745470, rs72800727, rs77426572, rs7895364, rs7937640, rs7940866, rs880447, rs9883919), resulting in 160 SNPs for analysis. The f-statistics for all these SNPs exceeded 10, as detailed in (***Supplementary Material:*** Tables 1, 2, 3).

In contrast, for the reverse MR study with AIT as an exposure factor and mental disorders as outcome indicators, 3 datasets were collected. In the AIT and bipolar disorder datasets, 6 SNPs were extracted after excluding 2 palindromic sequences (rs1020998, rs8073475). Similarly, 6 SNPs were screened in the AIT and depression datasets. For the AIT and anxiety disorder dataset, 5 SNPs were included in the final analysis. The f-values of these SNPs also exceeded 10, indicating reliable results without substantial bias, as delineated in (***Supplementary Material: table 4***).

The causal relationship between psychiatric disorders (anxiety disorder, depression, bipolar disorder) and AIT was analyzed by two-sample bidirectional MR. (1) Forward MR study: There was a positive causal association between depression and AIT, with the results of IVW was [(odds ratio, OR) 1.614, 95 % confidence interval (CI) 1.104–2.358, $P = 0.013$] and the WME was (OR 2.314, 95 % CI 1.315–4.074, $P = 0.004$). Anxiety disorders (OR 0.884, 95 % CI 0.666–1.173, $P = 0.393$) and bipolar disorders (OR 1.101, 95 % CI 0.898–1.351, $P = 0.355$) were not significantly causally associated with an increased risk of AIT. (2) Reverse MR studies: Reverse MR analysis did not support a causal relationship between genetic susceptibility to AIT and psychiatric disorders (anxiety disorders, depression, bipolar disorder). IVW analysis of the primary outcome showed no causal relationship between AIT and anxiety disorders (OR 1.021, 95 % CI 0.924–1.127, $P = 0.685$), depression (OR 1.004, 95 % CI 0.987–1.022, $P = 0.630$), or bipolar disorder (OR 0.969, 95 % CI 0.931–1.008, $P = 0.118$), as detailed in Table 2.

3.2. Sensitivity analysis

In our sensitivity analysis, we first applied Cochran's Q test to evaluate the heterogeneity of the IVW and MR-Egger regression analysis results. The MR analysis revealed that the *p*-values for anxiety disorders, depression, and AIT were all >0.05, indicating no significant heterogeneity in these cases. However, there was noted heterogeneity between bipolar disorder and AIT. To enhance the reliability of the data, we employed a random effects model for the IVW analysis between bipolar disorder and AIT and selected a random effects model for balancing the heterogeneity in the results. We also included the WME results for supplementary data, as depicted in Table 2.Additionally, we generated leave-one-out and funnel plots. The symmetry of the funnel plot indicates a relatively low risk of bias. Sensitivity analyses using the leave-

Table 2
The causal effect of different psychiatric disorders and autoimmune thyroiditis.

Exposure	Outcome	IVW				MR-Egger				Weighted median	
		OR (95 % CI)	P	Q	P	OR (95 % CI)	P	Q	P	OR (95 % CI)	P
Anxiety disorder	AIT	0.884 (0.666–1.173)	0.393	4.170	0.525	0.835 (0.353–1.975)	0.702	4.150	0.386	0.809 (0.568–1.154)	0.242
Depression	AIT	1.614 (1.104–2.358)	0.013	165.238	0.589	1.583 (0.343–7.306)	0.557	165.237	0.567	2.314 (1.315–4.074)	0.004
Bipolar disorder	AIT	1.101 (0.898–1.351)	0.355	208.558	0.005	0.794 (0.357–1.768)	0.573	207.656	0.005	1.123 (0.845–1.492)	0.425
AIT	Anxiety disorder	1.021 (0.924–1.127)	0.685	2.110	0.716	0.838 (0.566–1.239)	0.440	1.063	0.786	1.006 (0.892–1.135)	0.585
AIT	Depression	1.004 (0.987–1.022)	0.630	7.926	0.160	0.975 (0.937–1.014)	0.271	4.829	0.305	0.997 (0.979–1.015)	0.747
AIT	Bipolar disorder	0.969 (0.931–1.008)	0.118	12.930	0.024	0.898 (0.785–1.029)	0.195	9.764	0.045	0.960 (0.927–0.994)	0.023

AIT, autoimmune thyroiditis; Q, Cochran Q; P, *p* value.

Table 3
Horizontal pleiotropy in different psychiatric disorders and autoimmune thyroiditis.

Exposure	Outcome	Egger_intercept	P value
Anxiety disorder	AIT	0.011	0.897
Depression	AIT	0.001	0.980
Bipolar disorder	AIT	0.020	0.409
AIT	Anxiety disorder	0.071	0.382
AIT	Depression	0.013	0.185
AIT	Bipolar disorder	0.033	0.318

one-out SNP-by-SNP method did not identify any single SNP that had a substantial impact on the MR analysis results, suggesting robustness in our MR analysis findings. Furthermore, we reviewed scatter plots where each point represents an instrumental variable, and each horizontal solid line in the forest plot represents a single SNP estimated using the Wald ratio method. Notably, the MR-Egger intercept method showed that the Egger intercepts for all endpoints were close to 0, with *p*-values exceeding 0.05, indicating the absence of horizontal pleiotropy, as described in Table 3. Leave-one-out plots, scatter plots, funnel plots, and forest plots are available in the ***Supplementary Material: Fig. S1–24***.

4. Discussion

Thyroid dysfunction is mostly in the form of autoimmune origins (likeAIT), and numerous evidences suggest that this phenomenon is related to the inflammatory response and the pathophysiology of the immune system and psychiatric disorders (Rudzki and Maes, 2020; Benros et al., 2014). The genetically determined interplay between thyroid dysfunction and psychiatric disorders may hold immunological significance in elucidating disease pathogenesis (Soheili-Nezhad et al., 2023). Several potential mechanisms for AIT have been proposed, including the concurrent presence of anti-central nervous system autoantibodies in thyroid disease, the binding of thyroid peroxidase (TPO) antibodies to human astrocytes, and the increased secretion of monocyte- and T-lymphocyte-derived cytokines, among others (Soheili-Nezhad et al., 2023; Leyhe and Müssig, 2014). The pathogenesis of AIT due to psychiatric disorders is likely to proceed along two main pathways, as illustrated in Fig. 2.

AIT encompasses two presentation phenotypes: hyperthyroidism (like Graves-Basedow disease) and hypothyroidism (such as Hashimoto's thyroiditis). In Graves-Basedow disease (GBD), there is a characteristic infiltration of thyroid T-lymphocytes (TLs) and aberrant activation of B-lymphocytes (BLs), leading to a breakdown of thyroid immune tolerance. This breakdown occurs through the synthesis and heightened secretion of autoantibodies directed against the TSH receptor (TSHR) (Bartalena et al., 2022). In Hashimoto's thyroiditis (HT), there is not only a cellular immune response characterized by an abundance of inflammatory mediators that destroy thyroid tissue and impair thyroid function, but also the presence of autoantibodies against TPO and

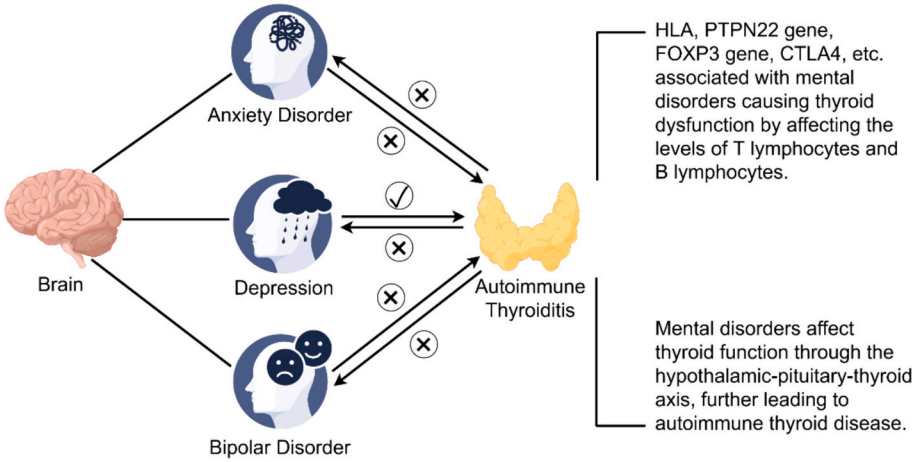

Fig. 2. Causal relationship between mental disorder and autoimmune thyroiditis and related pathogenesis.

thyroglobulin (Tg) (Ragusa et al., 2019). AIT is believed to have a genetic predisposition, with over 60 % of GBD patients having a family history of the disease (Vargas-Uricoechea, 2023). Indeed, AIT may be associated with an accumulation of genes related to GBD and HT. As mentioned earlier, the progression of AIT may be influenced by the effects of T lymphocytes and B lymphocytes mediated by the human leukocyte antigen (HLA) system, the PTPN22 gene, the Cytotoxic T Lymphocyte-Associated Factor 4 (CTLA4) gene, the FOXP3 gene, and others (Vargas-Uricoechea, 2023). Abnormal T-cell infiltration and B-lymphocyte overactivity in the thyroid leads to an immune response resulting in thyroid dysfunction.

The reciprocal relationship between autoimmune diseases and mental disorders has been notably linked to the HLA gene (Liu et al., 2021). Findings from the study revealed a noteworthy overexpression of HLA among patients with a familial history of psychiatric disorders (Rösler et al., 1983). Additionally, elevated HLA levels were observed in patients with schizophrenia and in patients with acute bipolar disorder experiencing depressive episodes (Boukouaci et al., 2021). HLA genes not only heighten the susceptibility to depression and anxiety disorder but also impact autoimmune functioning (Cheng et al., 2024). HLA polymorphisms (SNP) govern the diversity of HLA and its correlation with various diseases. HLA regulates cytokine synthesis and secretion, presents antigens to T-lymphocytes for recognition and response, and modulates the initiation of a cell-mediated immune response, thereby influencing the differentiation level of T-lymphocytes in the thymus, consequently leading to autoimmune diseases (Sollid et al., 2014; Wamala et al., 2016; Mehraji et al., 2017). HLA erroneously identifies thyroid autoantigens as “foreign” entities, triggering an immune response (CD4+/CD8+) mediated by autoreactive T-lymphocytes. In the presence of other factors such as environmental stimuli or infections, T- and B-lymphocytes activate and amplify the immune response, promoting the synthesis and secretion of relevant cytokines and autoantibodies, ultimately culminating in the development of AIT (Sollid et al., 2014; Wamala et al., 2016).

The PTPN22 gene ranks as the second most susceptible gene to autoimmune diseases following HLA. PTPN22 gene activity inhibits T-lymphocytes by down-regulating regulatory T cells (Tregs) amplification or through transcription factors such as FOXP3, while simultaneously influencing B-lymphocyte differentiation and proliferation, and augmenting the escape of self-reactive B-lymphocytes into the periphery resulting in AIT (Burn et al., 2011; Tizaoui et al., 2022; Bogusławska et al., 2022). Treg reduces inflammatory brain damage and white matter destruction due to psychiatric disorders, and Treg hypofunction is part of the progression of psychiatric disorders (Poletti et al., 2017; Corsi-Zuelli et al., 2021; Freier et al., 2010). FOXP3 is a major regulator of Tregs, studies also have revealed unveiled a potential link between AIT and FOXP3–3279 SNPs (Corsi-Zuelli et al., 2021; Lee et al., 2015). Moreover, two separate meta-analyses have indicated that the FOXP3-related rs3761549 and rs3761548 loci exhibit significant associations with GBD susceptibility (Tan et al., 2021; Li et al., 2020). Concurrently, the rs3761548 SNP has shown a significant association with HT, with patients harboring this SNP demonstrating significantly elevated levels of serum TPO-expressing antibodies (Kalantar et al., 2019). Besides, the CTLA4 gene acts as a suppressor of T-lymphocyte activation; consequently, reduced CTLA4 expression can trigger an immune response characterized by cytokine overactivity and autoantibody self-destruction, as well as induce psychiatric disorders (Narooie-Nejad et al., 2017; Xiaoheng et al., 2017; Liu et al., 2011; Miyamoto et al., 2020). The findings also identified common risk factors for major depression, schizophrenia, and bipolar disorder in the CTLA4 gene in the Chinese population (Liu et al., 2011).

On the other hand, AIT stemming from mental disorders is linked with abnormal regulation of the hypothalamic-pituitary-thyroid axis (HPT), as documented in the literature on mental health (Hirtz et al., 2021; Gutiérrez-Mariscal et al., 2008; Bauer and Whybrow, 2001; Bauer et al., 2008). In 1949, Asher introduced the concept of “crazy mucus edema,” which brought a new era of altered mental status in hypothyroid patients (Tayde et al., 2017). Indeed, approximately 1 % to 4 % of people with affective disorders may exhibit overt hypothyroidism, while 4 % to 40 % may present with subclinical hypothyroidism (SCH) (Kotkowska and Strzelecki, 2022). Depression stands out as one of the most prevalent psychiatric conditions associated with thyroid dysfunction (Lass et al., 2008). Thyroid abnormalities can manifest in patients at an early stage of depression (Peng et al., 2023). Data from a study revealed that 26.6 % of people diagnosed with depression exhibited abnormal thyroid function (Kafle et al., 2020). Meanwhile, a multicenter investigation demonstrated that 13.2 % of major depressive disorder patients suffered from hypothyroidism, in contrast to 1.6 % with hyperthyroidism (Fugger et al., 2018). Depression exerts a suppressive effect on the HPT axis, which interacts intricately with the aminergic system (Swaab et al., 2005). Depressed patients usually have higher thyrotropin-releasing hormone (TRH) concentrations in cerebrospinal fluid (Hage and Azar, 2012; Fountoulakis et al., 2006), alongside sluggish negative feedback regulation of thyrotropin (TSH) (Loosen and Prange Jr., 1982). This phenomenon is associated with elevated cortisol levels damaging hippocampal tissue (Hirtz et al., 2021), leading to a loss of inhibitory feedback in TRH-secreting neurons (Jackson, 1998). Amygdala TRH neurons influence anxiety. Stress from persistent anxiety and depression causes changes in the cerebral cortex and hypothalamus, which affect immune system function causing AIT (Mohammadpour et al., 2019). Both anti-thyroglobulin and TPO antibody levels are elevated in patients with psychiatric disorders and are associated with exacerbation of psychiatric disorders and increased risk of suicide. Results of observational studies suggest that bipolar disorder is associated with abnormal thyroid function (Hu et al., 2013; Bauer et al., 2016; Nuñez and Frye, 2019). Lithium is currently the preferred treatment for bipolar disorder, while it affects thyroid functional status (Ferensztajn-Rochowiak et al., 2021). However, our study did not find a causal relationship between anxiety disorder, bipolar disorder and AIT.

We conducted the first MR analysis examining the association between mental disorders (anxiety disorder, depression, bipolar disorder) and AIT. The results of the forward MR analysis revealed a causal link between depression and AIT, indicating an increased risk of AIT with these conditions. However, from a genetic perspective, anxiety disorder and bipolar disorder did not show any impact on the development of AIT. Meanwhile, reverse MR analysis did not identify a causal relationship between AIT and anxiety disorder, depression, or bipolar disorder.

We contribute to enhancing readers' comprehension of the potential genetic link between psychiatric disorders and AIT, while also offering valuable insights for early intervention and treatment strategies for patients with these psychiatric disorders. For instance, proactive screening and treatment of psychiatric disorders can mitigate the risk of developing AIT, and monitoring the expression levels of relevant genes or regulating hormone secretion in the HPT axis can enhance the clinical management of psychiatric disorders. Because SNPs are randomly generated, MR studies reduce the confounding bias of observational studies, such as human bias, and allow for reverse causality studies to increase the confidence of causal inference. MR studies reveal the potential risk factors of AIT patients in a more efficient way and reduce the cost and time consumption to a large extent, which is favorable for preclinical studies and does not violate ethical requirements. Our study also has limitations. Genetic variants sometimes have a small effect on exposure factors, which may lead to lower statistical power of MR analysis and risk of false-negative results, on the other hand, it was confirmed that the extraction of a larger number of compliant SNPs is beneficial to increase the reliability of the results. Due to the limitation of the dataset, the number of patients with anxiety disorders as well as AIT in our study was small, to the extent that it was necessary to lower the *p*-value of the inclusion criteria before the number of eligible SNPs could be further increased, which may be slightly biased. AIT subdivision can also be categorized into a variety of disorders, and our study has

only conducted a preliminary MR study of mental disorder problems and AIT, and future studies should focus on more specific analyses, such as examining the association of mental disorders with various forms of hypothyroidism or hyperthyroidism in autoimmune thyroid disorders. Enhanced exploration of the more detailed pathogenesis of psychiatric disorders (anxiety disorder, depression, bipolar disorder) that increase the prevalence of AIT.

5. Conclusion

We conducted the first bidirectional Mendelian randomization study of anxiety disorder, depression, bipolar disorder and autoimmune thyroiditis. Depression increases the risk of AIT, while no causal relationship has been found between anxiety disorders, bipolar disorder and AIT. Psychiatric disorders lead to AIT mainly through the expression of related genes affecting the levels of T and B lymphocytes or through the hypothalamic-pituitary-thyroid axis affecting the feedback regulation mechanism to induce thyroid dysfunction. We look forward to more clinical and experimental research data to validate the relationship between psychiatric disorders and AIT. In the meantime, we need to focus on more updated and larger data sets to explore whether there is a causal relationship between other psychiatric disorders and AIT.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Study design and manuscript writing were done by Jingyang Su, Jialin Zhang. Literature search and data collection were done by Jingyang Su and Hanyu Zhu. Figures, table, data analysis Jingyang Su, Jialin Zhang, Jinhua Lu. Manuscript revision and article polish were done by Hanyu Zhu and Jinhua Lu. Manuscript finalization and funds support were done by Jinhua Lu. All authors read and approved the final manuscript.

CRediT authorship contribution statement

Jingyang Su: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Jialin Zhang:** Writing – original draft, Resources, Data curation, Conceptualization. **Hanyu Zhu:** Writing – original draft, Validation, Resources, Data curation. **Jinhua Lu:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Data availability

All the data used in the current research are publicly available GWAS summary data.

Anxiety disorder, depression, and bipolar disorder data were obtained from the Psychiatric Genomics Consortium (PGC) database of published articles. The autoimmune thyroiditis GWAS data were obtained from the most recent Finnish database (https://r11.finngen.fi/). The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.09.132.

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