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Advances in Mendelian Randomization Studies on the Causal Relationship Between Immune Cells and Psychiatric Disorders

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ABSTRACT

In recent years, the incidence of psychiatric disorders has been steadily increasing, posing significant challenges to both individual health and social stability. Emerging evidence has highlighted a close association between immune cells and the onset and progression of various psychiatric conditions. Traditional approaches for inferring causality, such as randomized controlled trials and observational studies, are often limited by feasibility, bias, and confounding factors. Mendelian randomization (MR), which leverages genetic variants as instrumental variables, provides a powerful alternative for assessing causal relationships between immune cells and psychiatric disorders. This review summarizes recent advances in MR studies investigating the causal links between immune cell profiles and psychiatric disorders, including anxiety, depression, and schizophrenia. By integrating current evidence from MR studies, this review aims to provide new insights and reference points for future research exploring the relationship between immune cells and psychiatric disorders.

Keywords: Causality; Immune cells; Mendelian randomization; Mental disorders; Neuroinflammation

INTRODUCTION

Psychiatric disorders represent a major global health burden and arise from complex interactions among genetic, neurobiological, and environmental factors.[1,2] Despite extensive research, the causal mechanisms underlying the development of psychiatric disorders remain incompletely understood. Traditionally, neurobiological processes such as dysregulation of neurotransmitters, including serotonin, dopamine, and cortisol, have been central to models of emotional regulation and stress response in psychiatric conditions.[3–5] In recent years, increasing attention has been directed toward the role of the immune system in mental health. Abnormal activation of immune cells and alterations in peripheral inflammatory cytokine levels have been shown to be closely associated with the pathogenesis of various psychiatric disorders.[6–8] For example, altered distributions and functional states of T lymphocyte subsets, including $CD4^+$ T cells, regulatory T cells, and T_H17 cells, have been associated with chronic low-grade inflammation and abnormal cytokine signaling, which may influence synaptic plasticity and neuronal survival. B cells may contribute to psychiatric

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phenotypes through antibody-mediated immune responses and cytokine production, while monocytes and other myeloid cells are involved in peripheral inflammatory activation and disruption of the blood-brain barrier. Immune signals originating from peripheral immune cells can interact with microglia in the central nervous system, thereby modulating neurodevelopment, stress responsiveness, and neurotransmitter systems.[9–11] These findings suggest that immune cell traits may play a mechanistic role in the development of psychiatric disorders.

Although observational studies have provided preliminary evidence for associations between immune cells and psychiatric disorders, they are often limited by the potential for reverse causation and confounding factors.[12] Randomized controlled trials (RCTs) are considered the gold standard for establishing causal relationships between exposures and diseases. However, RCTs are typically expensive, time-consuming, and prone to high failure rates. They also face practical limitations, such as the inability to randomize certain phenotypes (eg, pre-existing medical conditions), and are often constrained by small sample sizes.[13] To address the limitations of both RCTs and observational studies, Mendelian randomization (MR) has emerged as a powerful epidemiological approach for assessing causal relationships by using genetic variants as instrumental variables.[14] Therefore, this review aims to summarize recent MR studies investigating the causal associations between immune cells and various psychiatric disorders, to provide novel insights and guide future research in this field.

MATERIALS AND METHODS

Methodological Framework Of MR

MR is an epidemiological approach that uses genetic variants as instrumental variables to strengthen causal inference between exposures and outcomes. By leveraging the random allocation of genetic variants at conception, MR can reduce confounding and reverse causation, which are major challenges in psychiatric research where immune alterations may both influence and result from disease processes. The validity of MR relies on 3 core assumptions: genetic instruments must be strongly associated with the exposure, independent of confounders, and affect the outcome only through the exposure. In psychiatric applications, these assumptions are particularly relevant because immune-related genetic variants often participate in multiple biological pathways that overlap with neurodevelopmental and metabolic processes.[14]

Several MR designs are commonly applied. two-sample MR, based on summary statistics from independent GWAS, is widely used due to the availability of large psychiatric and immunological datasets. Bidirectional MR enables assessment of potential reverse causality, while multivariable MR allows the evaluation of independent effects of correlated immune cell traits.[15] Causal estimates are typically obtained using the inverse-variance weighted (IVW) method, with MR-Egger and weighted median approaches serving as sensitivity analyses to address potential violations of MR assumptions. Pleiotropy represents a key methodological concern in MR studies. Horizontal pleiotropy, in which genetic variants influence the outcome through pathways independent of the exposure, may bias causal estimates and is particularly relevant in immune-psychiatric research. In contrast, vertical pleiotropy does not violate MR assumptions. Sensitivity analyses and pleiotropy-robust methods are therefore essential for reliable inference.[16] In psychiatric research, medication use is an important source of confounding in observational studies, as psychotropic drugs may directly affect immune markers. Mendelian randomization largely mitigates this bias by using germline genetic variants that are not influenced by treatment exposure. However, residual horizontal pleiotropy cannot be fully excluded if genetic variants are related to drug response or metabolism, highlighting the need for pleiotropy-robust methods and sensitivity analyses in immune-psychiatric MR studies. Adequate statistical power is critical for MR analyses. Weak instruments can lead to biased or null results, and instrument strength is commonly assessed using the F-statistic, with values greater than 10 generally considered acceptable. This consideration is especially important in psychiatric MR studies, where effect sizes are often modest.[17]

Figure 1 illustrates the methodological framework of MR, including its core assumptions, potential sources of bias, and the analytical workflow applied in this study.

Key MR studies linking immune phenotypes to psychiatric disorders are summarized in Table 1.

Table 1. Key MR studies of immune phenotypes in psychiatric disorders.

Exposure	Outcome	Primary ancestry	Source	Sample size	Effect estimate (95% CI)	*p*	Reference
CD27 on IgD^+CD24^+ B cells	MDD	European	UK Biobank	3757/807 553	1.021 (1.011–1.031)	4.821×10^{-5}	Zhang et al[21]
HLA-DR^{++} monocytes	MDD	European	UK Biobank	3757/807 553	0.973 (0.948–0.998)	0.038	Zhang et al[21]
CRP	MDD	European	Published GWAS	204 402/230 214	r=0.152–0.362	<0.01	Kappelmann et al[24]
CRP	MDD	European	UK Biobank	204 402/480 359	1.020 (0.970–1.060)	0.500	Palmos et al[25]
Plasmablasts / plasma cells in B cells	GAD	European	FinnGen	3757/55 293	0.820 (0.750–0.910)	0.002	Ma et al[32]
CRP	Anxiety disorders	European	Lifelines cohort	55 098	β=0.002	0.037	Giollabhui et al[35]
$CD33^+$HLA-DR^+ myeloid cells	BD	European	UK Biobank	3757/807 553	1.022 (1.007–1.036)	0.007	Zhang et al[21]
$CD28^+CD45RA^-CD8^+$ T cells	BD	European	UK Biobank	3757/807 553	1.024 (1.008–1.041)	0.004	Zhang et al[21]
$CD62L^+$ myeloid dendritic cells	BD	European	UK Biobank	3757/807 553	0.926 (0.871–0.985)	0.014	Zhang et al[21]
IgD^-CD27^- B cells	BD	European	UK Biobank	3757/807 553	0.918 (0.880–0.956)	4.654×10^{-5}	Zhang et al[21]
sIL-2Rα	SCZ	European	PGC	8293/105 318	1.070 (1.010–1.120)	<0.05	Perry et al[49]
IL-6	SCZ	European	PGC	133 449/105 318	1.080 (1.030–1.120)	<0.05	Perry et al[49]
IL-9	SCZ	European	PGC	8293/105 318	1.060 (1.010–1.110)	<0.05	Perry et al[49]
$CD11c^+$ monocytes	SCZ	European	PGC	3757/130 644	1.060 (1.030–1.090)	0.027	Du et al[50]
CD25 on IgD^+CD38^- naïve B cells	SCZ	European	PGC	3757/130 644	1.030 (1.010–1.060)	0.042	Du et al[50]
CD86 on monocytes	SCZ	European	PGC	3757/130 644	1.040 (1.010–1.060)	0.042	Du et al[50]
Naïve $CD4^+$ %T cells	SCZ	European	PGC	3757/150 064	0.986 (0.979–0.992)	1.37×10^{-5}	Wang et al[17]
HLA-DR on $CD14^-CD16^-$	SCZ	European	PGC	3757/150 064	0.738 (0.642–0.849)	2.00×10^{-5}	Wang et al[17]
HLA-DR^{++} monocytes %monocytes	AN	European	PGC	3757/14 477	1.074 (1.032–1.119)	0.037	Li et al[55]
Basic fibroblast growth factor	AN	European	PGC	8293/14 477	0.403 (0.261–0.622)	4.03×10^{-5}	Chen et al[56]
$CD3^-$ lymphocytes %leukocytes	ASD	European	Published GWAS	3757/10 610	0.880 (0.810–0.950)	<0.001	Fang et al[57]
CCR2 on $CD14^-CD16^+$ monocytes	PTSD	European	Published GWAS	3757/174 659	1.059 (1.027–1.092)	0.008	Wang et al[58]

AN: anorexia nervosa; ASD: autism spectrum disorder; BD: bipolar disorder; CCR2: C-C chemokine receptor type 2; CD: cluster of differentiation; CI: confidence interval; CRP: C-reactive protein; GAD: generalized anxiety disorder; GWAS: genome-wide association study; HLA-DR: human leukocyte antigen–DR isotype; IgD: immunoglobulin D; IL: interleukin; MDD: major depressive disorder; MR: Mendelian randomization; PGC: Psychiatric Genomics Consortium; PTSD: post-traumatic stress disorder; SCZ: schizophrenia; sIL-2Rα: soluble interleukin-2 receptor α.

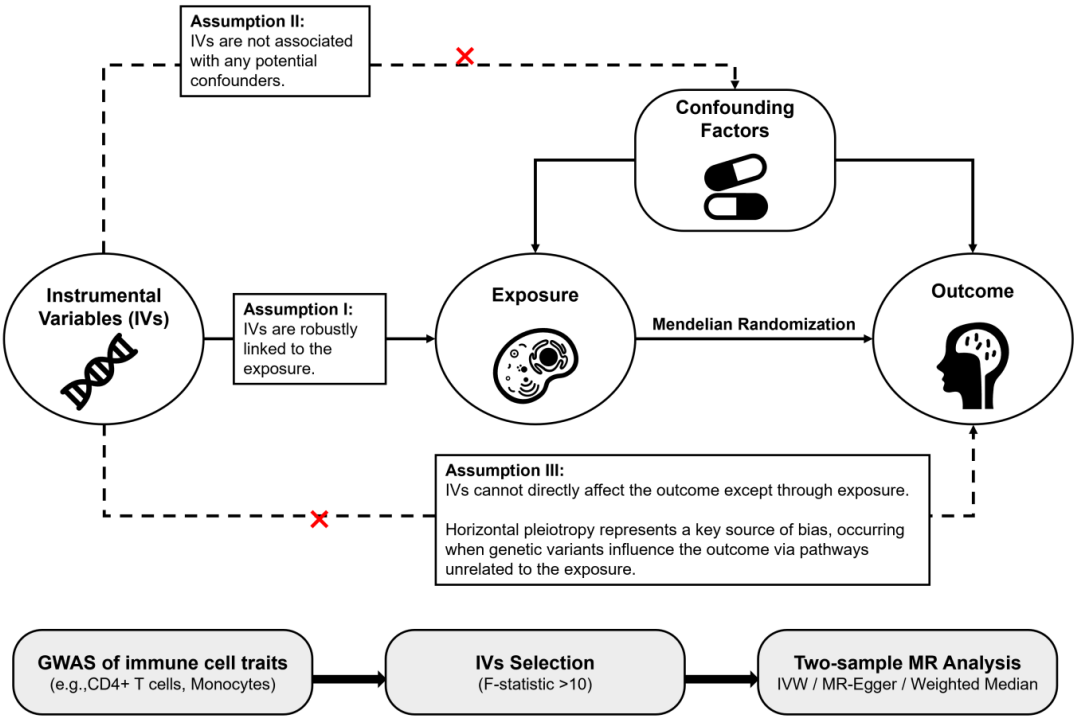

Figure 1. Overview of MR framework.

RESULTS

Immune Cells and Depression

Depression is a common psychiatric disorder primarily characterized by persistent and markedly low mood, often accompanied by a range of behavioral and physiological disturbances.[18] Recent studies have increasingly highlighted the involvement of the immune system in the pathogenesis of depression. Stress-related signals can be transmitted from the central nervous system to immune cells, influencing the physiological mechanisms underlying stress-related behaviors.[19] Immune cells differentiate into distinct lineages that regulate both pro-inflammatory and anti-inflammatory responses, with each cell type characterized by a specific cytokine profile and immunological function.[20]

A large-scale MR study systematically evaluated the causal effects of 731 immune cell phenotypes on major depressive disorder. The results suggested that genetically predicted alterations in several B cell-related traits were associated with increased susceptibility to depression, whereas specific monocyte and $CD4^+$ T cell phenotypes appeared to exert protective effects, highlighting a potential role of adaptive immune regulation in depression vulnerability.[21] Specifically, at the symptomatic or disease state level, abnormal activation of $CD4^+$ T cells has been linked to anhedonia,[22] while elevated levels of $CD20^+$ B cells have been associated with the onset of depressive disorders.[23] Pro-inflammatory immune cells can secrete various inflammatory markers implicated in the pathophysiology of depression. For example, an MR analysis by Kappelmann et al[24] reported a genetic correlation between C-reactive protein (CRP) levels and depressive symptoms, potentially reflecting a causal relationship between metabolic dysregulation and features such as anhedonia, fatigue, appetite changes, and feelings of worthlessness. In contrast, a study by Palmos et al[25] found no evidence supporting a direct causal effect of CRP on depression. These seemingly inconsistent results are likely driven by a combination of methodological and biological factors. Variability in the genetic instruments used to proxy CRP may capture different aspects of inflammatory activity, such as acute versus chronic inflammatory processes, thereby yielding heterogeneous causal estimates. Differences in statistical power across studies, together with the potential influence of residual horizontal pleiotropy, may also contribute to the divergent findings. Collectively, these observations highlight the need for

further studies combining refined Mendelian randomization approaches with experimental investigations to better elucidate the immunological mechanisms underlying depression and to evaluate the causal relevance of inflammatory markers as potential therapeutic targets.

Although most MR studies on depression have focused on peripheral immune cell subsets due to the availability of large-scale GWAS data,[26] innate immune mechanisms (particularly microglia) are widely recognized as central mediators of immune-related depression pathology. Microglia are the resident immune cells of the central nervous system and play a pivotal role in neuroinflammation, synaptic pruning, and stress-induced neural plasticity. Activation of microglia can be triggered by peripheral inflammatory signals, including cytokines released by myeloid cells, T cells, and B cells, thereby linking systemic immune alterations to central nervous system dysfunction.[27,28] From an MR perspective, genetically predicted alterations in peripheral immune cell traits may influence depression risk indirectly through microglia-mediated neuroimmune pathways. Therefore, although microglia-specific MR analyses remain limited, their established biological role provides important mechanistic context for interpreting MR findings involving peripheral immune cells and inflammatory markers.

Immune Cells and Anxiety Disorders

Anxiety disorders are among the most prevalent psychiatric conditions globally, affecting approximately 4% of the world's population.[29] Emerging evidence suggests that immune system dysregulation plays a critical role in the development of anxiety disorders. Most studies have reported that individuals with anxiety disorders exhibit heightened inflammatory responses, characterized by elevated levels of pro-inflammatory cytokines in peripheral blood, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α).[30] Furthermore, the activation and functional alterations of immune cells, such as monocytes and T cells, may influence neurotransmitter systems, thereby contributing to changes in mood and the manifestation of anxiety symptoms.[31]

MR analyses have revealed causal relationships between immune cells and anxiety disorders. Notably, an increased proportion of plasmablasts (PB) / plasma cells (PC) among B cells in peripheral blood has been associated with a reduced risk of generalized anxiety disorder (GAD).[32] Variations in the PB / PC ratio within B cells are known to influence the strength and quality of immune regulation and response. A higher PB / PC ratio may help maintain immune homeostasis, support coordinated immune activity, and thereby exert a protective effect on overall health status.[33] Animal studies have demonstrated that anxiety-related activation of the sympathetic nervous system can disrupt B cell development within the bone marrow through neuro-mesenchymal units, mediated by altered CXCL12 signaling. Notably, restoration of B cell development in this model was accompanied by improvements in anxiety-like behaviors, suggesting a bidirectional interaction between anxiety and adaptive immunity.[34] These findings offer biological plausibility for MR-identified associations between B cell traits and anxiety disorders, although translational validation in human populations remains necessary.

In addition, genetic risk scores for CRP have been found to correlate with anxiety disorder diagnoses. MR analyses have provided weak but suggestive evidence for a potential causal association between elevated CRP levels and anxiety disorders.[35] Elevated CRP could reflect a low-grade inflammatory state characterizing specific anxiety subtypes, such as late-onset or metabolically burdened forms of anxiety, which have been observed in large population-based cohorts.[36,37] From a clinical perspective, these findings suggest that immune-related markers may contribute to biological stratification rather than serve as standalone diagnostic tools. However, due to the small effect sizes observed, further large-scale and mechanistic studies are required to validate these findings and to clarify the specific roles of immune cells and inflammatory markers in the pathophysiology of anxiety.

Immune Cells and Bipolar Disorder

Bipolar disorder (BD) is a psychiatric condition characterized by the presence of both manic and hypomanic episodes and depressive episodes.[38] Observational and epidemiological studies have reported associations between BD and immune-related comorbidities, including autoimmune diseases, metabolic disorders, and chronic low-grade inflammation. In addition, elevated levels of pro-inflammatory cytokines have been observed during acute mood episodes, suggesting a state-dependent relationship between immune activation and disease severity.[39] However, these associations are inherently

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limited by potential confounding factors, medication effects, and reverse causation, as immune alterations may arise as a consequence of mood episodes rather than contributing to disease onset.

MR provides a framework to address these limitations by leveraging genetically proxied immune traits to infer causal relationships. MR analyses have revealed a weak but significant genetic correlation between BD and immune-related diseases, with BD being positively correlated with celiac disease, Crohn's disease, and psoriasis.[40] Additionally, 20 immune cell types, including $CD33^{+}HLA\text{-}DR^{+}$ cells and $CD28^{+}CD45RA^{-}CD8^{+}$ T cells, are associated with an increased risk of BD; whereas 15 immune cell types, including $CD62L^{+}$ myeloid dendritic cells and $IgD^{-}CD27^{-}$ B cells, are associated with a decreased risk of BD.[21] The biological plausibility of these MR findings is supported by known neuroimmune mechanisms. Immune-derived cytokines and chemokines can cross or signal across the blood-brain barrier, modulate monoaminergic neurotransmission, activate microglia, and promote neuroinflammatory and oxidative stress pathways. Such processes can impair neuroplasticity and contribute to structural and functional alterations in brain regions implicated in mood regulation, thereby providing mechanistic insight into how immune dysregulation may causally influence BD pathophysiology.[41,42]

Immune Cells and Schizophrenia

Schizophrenia (SCZ) is a highly heritable psychiatric disorder that is closely associated with the dysfunction of multiple brain systems.[43] Existing epidemiological surveys have revealed correlations between the immune system and mental and psychological disorders.[44,45] The immune status of SCZ patients is characterized by an imbalance of helper T (T_H) cell subtypes, specifically a reduction in T_H1 cytokines and an increase in T_H2 cytokines, which is closely related to the dysregulation of inflammatory mediators.[46] Pro-inflammatory cytokines, produced by immune accessory cells in infected areas, may induce changes in endocrine regulation, autonomic nervous system function, and behavioral manifestations. Typical inflammatory mediators include interleukins, tumor necrosis factor, and CRP.[47] Studies have shown that serum levels of soluble interleukin-2 receptor (sIL-2R), IL-6, IL-8, and IL-10 are significantly higher in SCZ patients than in healthy controls.[48]

MR analyses provide convergent evidence supporting a causal role of immune dysregulation in SCZ. Specifically, genetically predicted increases in pro-inflammatory cytokines, including sIL-2Rα, IL-6, and IL-9, have been causally associated with SCZ risk, indicating a state of immune activation.[49] At the cellular level, MR studies further highlight the involvement of activated myeloid and lymphoid compartments. Increased expression of activation markers on monocytes, such as CD11c and CD86, as well as altered B cell and T cell phenotypes, have been linked to elevated SCZ risk.[50] In contrast, higher proportions of naïve $CD4^{+}$ T cells and certain $HLA\text{-}DR^{-}$ cell populations appear to exert a protective effect,[17] suggesting that imbalance between immune activation and immune regulation may be central to disease susceptibility. Within this framework, B cells may represent a critical link between peripheral immune alterations and neurobiological processes relevant to SCZ. Beyond their roles in antibody production and antigen presentation, B cells secrete cytokines and chemokines that modulate monocyte and T cell responses.[51,52] Notably, the B-1a cell subtype has been implicated in brain development, particularly in regulating oligodendrocyte precursor cell proliferation and myelination. Dysregulation of B-1a cells may therefore contribute to disrupted neural connectivity and impaired signal transmission, providing a biologically plausible mechanism linking immune abnormalities to SCZ pathogenesis.[53]

Immune Cells and other Psychiatric Disorders

In addition to the aforementioned mental and psychological disorders, MR analyses have also identified potential causal relationships between immune cells and other conditions such as anorexia nervosa (AN), autism spectrum disorder (ASD), and post-traumatic stress disorder (PTSD).

In AN, MR analyses suggest that increased proportions of HLA-DR–expressing monocytes are causally associated with higher disease risk, implicating antigen presentation and innate immune activation in disease susceptibility.[54,55] Genetically predicted fibroblast growth factor levels show a negative causal association with AN, highlighting potential links between immune-related growth signaling and metabolic–psychiatric interactions.[56] For ASD, a neurodevelopmental disorder with early-life onset, MR studies have identified multiple immune phenotypes

with putative causal effects, particularly involving regulatory T-cell and lymphocyte-related traits.[57] These findings support the hypothesis that immune regulation may influence neurodevelopmental trajectories, rather than reflecting secondary inflammatory consequences. PTSD represents a stress-related psychiatric condition in which bidirectional MR analyses indicate reciprocal causal relationships between T-cell traits and PTSD risk, alongside downstream effects of PTSD on dendritic cell phenotypes.[58] This bidirectionality underscores the dynamic interplay between immune regulation and trauma-related psychopathology.

DISCUSSION

Shared Immune Pathways and Translational Implications

Beyond disease-specific findings, the MR studies summarized in this review identify convergent immune pathways that may contribute to the development of multiple psychiatric disorders. Across studies, adaptive immune traits, particularly T cells, are consistently implicated in psychiatric disease susceptibility. In addition to their peripheral immune functions, monocytes, macrophages, and helper T cells play important roles within the central nervous system by contributing to neurogenesis, cognitive maintenance, and the regulation of learning and behavior.[59] Under physiological conditions, immune cells dynamically cross the blood–brain barrier to support brain homeostasis and plasticity, whereas this process may be disrupted in psychiatric disorders. Interactions between neurons and leukocytes can influence brain structure and function in mood disorders.[60] Accumulating evidence suggests that immune cells may affect white matter microstructure and that these effects may be partly modulated by psychotropic treatments,[61,62] supporting circulating immune cells as potential biomarkers.

At the molecular level, cytokine- and chemokine-related pathways, particularly inflammatory signaling involving IL-6 and TNF-α, are repeatedly identified in MR studies of depression and anxiety. Genetically predicted inflammatory activity appears to affect specific symptom dimensions or clinical subtypes rather than exerting uniform effects across all patients. Supporting this view, elevated TNF-α levels have been reported in atypical depression, whereas findings in melancholic depression are less consistent and may reflect greater activation of the hypothalamic-pituitary-adrenal axis, which can suppress peripheral inflammation.[63,64] In line with these observations, several studies have explored immune molecular profiles to distinguish bipolar disorder from major depressive disorder. TNF-α, CCL3, CCL4, CCL5, and CCL11 are more strongly associated with bipolar disorder, whereas IL-4, IL-6, and IL-10 show closer associations with major depressive disorder.[65] These findings indicate that immune pathways may underlie shared disease mechanisms while also offering potential value for clinical stratification.

Despite the increasing statistical power of large-scale GWAS, several limitations should be considered when interpreting MR studies on immune cells and psychiatric disorders. First, most GWAS data underlying MR analyses are derived predominantly from individuals of European ancestry, which may introduce population bias and limit the generalizability of findings across ethnic groups.[66] Second, many studies rely on large resources such as the UK Biobank, where partial sample overlap between exposure and outcome GWAS may introduce bias, including winner's curse effects, despite efforts to mitigate this issue. Third, although multiple sensitivity analyses have been applied, horizontal pleiotropy cannot be fully excluded, and genetic instruments may not capture all relevant biological exposures.[67] Fourth, the available MR evidence is largely based on adult populations, and its applicability to pediatric or adolescent psychiatric disorders remains unclear. In addition, most studies do not perform sex-stratified analyses, despite known sex differences in immune regulation and psychiatric vulnerability. Finally, ethical considerations related to genetic causal inference in psychiatry warrant careful consideration when translating MR findings into clinical or public health contexts.

MR provides an important genetic framework for clarifying causal relationships between immune cells and mental and psychological disorders. By leveraging large-scale GWAS data, MR helps prioritize immune-related traits, such as inflammatory markers and specific T- and B-cell subsets, as potential translational biomarkers and therapeutic targets for disorders including depression, anxiety, BD, and SCZ. Importantly, MR complements evidence from randomized controlled trials and animal studies by strengthening causal inference, refining hypotheses, and identifying immune pathways that warrant experimental or clinical validation. From a clinical perspective, MR findings encourage psychiatrists

to view immune dysregulation not merely as a correlate, but as a potentially causal and modifiable component of psychiatric risk. Future translational efforts should focus on targeted MR analyses of specific immune biomarkers, integration of genetically supported immune targets into clinical trials, and validation of these markers across diverse populations and age groups.

STATEMENT OF ETHICS

This study was based on previously published studies and publicly available summary-level genetic data. No new human participants, personal data, or animal experiments were involved; therefore, ethical approval was not required.

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Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

No new data were generated or analyzed in this review. The data discussed in this article are derived from previously published studies and publicly available databases, which can be accessed through the original publications and corresponding repositories.

AI ASSISTANCE DISCLOSURE

No artificial intelligence (AI) tools were used in the preparation of this manuscript.

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