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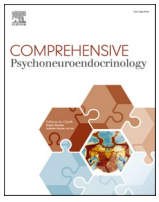

Causality effect of 21 metals in plasma and serum, 731 immunocytes, and schizophrenia: an intermediary Mendelian randomization study in East Asian populations

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A R T I C L E I N F O

Keywords:
Schizophrenia
Metals
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A B S T R A C T

Background: Multiple clinical studies have observed a close relationship between metals in plasma and serum, immunocytes, and schizophrenia; however, it remains unclear whether there is a genetic causal effect between metals in plasma and serum,immunocytes, and schizophrenia.
Objective: This study aimed to investigate the causal effects of metals in the plasma and serum on schizophrenia and the mediating role of immunocytes using Mendelian randomization methods in an East Asian population.
Methods: Summary results for 21 metals in plasma and serum,731 immunocytes and schizophrenia were acquired from publicly available genome-wide association studies (GWASs). GWAS data for metals, immunocytes, and schizophrenia were accessed between 2024 and 11–26 and 2024-12-02,Authors had no access to identifiable individual participant data. This study utilized two-sample Mendelian randomization (MR) analysis to establish causal relationships, which was achieved by employing various statistical methods, including inverse variance-weighted, simple mode, MR–Egger, weighted median, and weighted mode. Multiple sensitivity analyses, including heterogeneity tests, horizontal pleiotropy tests, MR-PRESSO tests, and leave-one-out analyses, were performed to confirm the reliability of the MR data. Finally, mediation analysis was employed to ascertain the immunocyte pathway that leads to schizophrenia from the metals in the plasma and serum. The study used anonymized summary-level GWAS data from public databases (e.g., GWAS Catalog, iEU Open GWAS), which do not contain personally identifiable information.
Results: The data of the East Asian population were analyzed by Mendelian randomization and two serum metallic traits that may reduce the risk of schizophrenia were identified: Serum iron (odds ratio (OR):0.54, 95 % confidence interval (CI):0.30–0.96, p = 0.036) and serum molybdenum levels (odds ratio (OR):0.54, 95 % confidence interval (CI):0.34–0.87, p = 0.011) corresponds to a 46 % reduction in schizophrenia risk. A baseline lifetime risk of 1 % in the general population, this translates to an absolute risk reduction of 0.46 %, with a number needed to treat (NNT) of approximately 217 individuals to prevent one case. They exhibited a negative causal relationship with the risk of Schizophrenia. Through mediation analysis, we identified a specific immunocyte subtype, CD33dim HLA DR + CD11b- Absolute Count, that not only correlates with serum iron levels but also shows a strong association with schizophrenia risk, suggesting a potential pathway through which serum iron may influence schizophrenia development. Serum iron levels showed a negative causal relationship in schizophrenia through the mediation of immunocytes with CD33dim HLA DR + CD11b- Absolute Count (mediation proportion:21 %).
Conclusions: This study identified a causal relationship between plasma and serum metals, immunocytes, and schizophrenia in an East Asian population through Mendelian randomization analysis, providing a new theoretical basis for the early detection, diagnosis, and treatment of schizophrenia.

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1. Introduction

Mental disorders(MD) are common and seriously affecting diseases. In 2019,970 million people were diagnosed with MD worldwide [1]. MD imposes a huge burden on individuals, societies and families of patients. [2–5]. MD includes many different kinds of illnesses, such as anxiety, depression, schizophrenia, anorexia nervosa, bipolar disorder, Autism, Persistent delusional disorders, dementia, phobia, and obsessive compulsive disorder. It is a serious MD that often presents with hallucinations, delusions, and extremely disorganized thinking and behavior, which can affect daily physical functioning and may eventually lead to disability [6]. Approximately 1 % of the global population will experience schizophrenia in their lifetime and about 5 % of these patients face increased physical health problems [7]. The complex etiology of schizophrenia complicates its early detection and timely diagnosis, while the diversity of symptoms and conditions challenges the effective implementation of treatment strategies [8]. To realize the early detection, accurate diagnosis, and effective treatment of schizophrenia,it is necessary to explore the etiological mechanisms and determine the related biomarkers.

As a ubiquitous component of the natural environment, metals can reach the human body through the air,drinking water, food, and medicine [9]. Metals entering the body produce a large number of free radicals through electron transfer, photochemical reactions and other processes, which can produce a variety of biological reactions including DNA damage, protein oxidation and lipid peroxidation [10]. When the free radicals produced by metals reach a certain threshold, they can cause irreversible damage to the human body and produce toxic effects in reproduction, immunity, metabolism, and other aspects, leading to a series of diseases [11,12]. Moreover, excessive free radicals produced by metals can also cause a huge toxic effect on immunocytes, and the free radicals induced by metals can also have a certain effect on schizophrenia [13,14].

Inflammatory factors have a quantitative impact on brain development, typically aiding in processes such as neurogenesis, neuronal migration, and synapse formation. However, excessive inflammatory responses can disrupt these processes and the release of large amounts of inflammatory factors in the brain increases the risk of schizophrenia [15–17].

While the exact causes of schizophrenia remain partially understood, emerging evidence suggests a potential role of metal exposure in its pathogenesis, prompting further investigation into this association [18]. Mendelian randomization (MR) has emerged as a robust approach for inferring causal relationships by leveraging genetic variants as instrumental variables. Its reliability has been validated across diverse phenotypes, including immune dysregulation, metabolic disorders, and neuropsychiatric diseases. Notably, recent MR studies have elucidated bidirectional links between depression and immune-metabolic pathways, underscoring the utility of this method in disentangling complex etiology [19–24]. We hope that through this method, we can determine the potential relationship among metals, immunocytes, and schizophrenia and explore their biomarkers to provide direction and help for the next exploration of their pathogenesis.

2. Methods

2.1. Study design

We obtained GWAS datasets that included metals in plasma and serum, immunocytes, and schizophrenia. Two-sample MR analyses were then used to evaluate the causal relationship between metals in plasma and serum, immunocytes, and schizophrenia. Finally, a two-step MR analysis was employed to ascertain the mediation impact of immunocytes on the association between metals in plasma and serum and schizophrenia, and ethical review and informed consent were obtained from all GWAS study cohorts.

2.2. Data sources

Based on the experience of previous MR studies, the sample size of the GWAS summary data used in this study (e. g. metal exposure: 2,488 East Asian individuals, immune cells: 3,757 European individuals) has met the requirements for statistical efficacy of MR analysis. Weak instrument variable bias was assessed by the F statistic ($F > 10$), and all selected SNP F were significantly above the threshold, indicating that the instrument variable had sufficient strength to detect a causal effect between exposure and outcome. GWAS summary data for 21 metals in plasma and serum were obtained from the GWAS Catalog, and 2488 Chinese individuals were included in the association study [25]. The study accession numbers of time GWAS Catalog: GCST90001391-GCST90002121 provides the GWAS statistics for all immunocytes,It includes 3,757 individuals from Europe, including immunocytes from MFI, AC and RC, types, including B cells, circulating dendritic cells (cDC), mature T cells, monocytes, myeloid cells, TBNK (T cells, B cells, natural killer cells) and Treg panels [26]. The GWAS summary data for schizophrenia are available from the iEU Open GWAS databaseGWAS ID: ebi-a-GCST90018699 [27].

Although the immune cell GWAS data were derived from the European population (Sardinian cohort), Cross-population analysis may introduce genetic structure differences or environmental confounders (e. g., socioeconomic differences),we screened the SNP with allele frequency differences <5 % to reduce population stratification bias. Sensitivity analysis showed that the results remained robust when using the GWAS data for schizophrenia in East Asian populations (Supplementary materials). There are also similar studies using the same data as [28].

2.3. Instrument variables

For causal estimates derived from MR analysis to be considered trustworthy, the following three key assumptions must be satisfied: (1) IVs are correlated with exposure, (2) IVs are not correlated with confounding variables, and (3) IVs do not have a direct relationship with outcomes but affect outcomes through their influence on exposure. Therefore, we selected single nucleotide polymorphisms (SNPs) with large exposure-related effect sizes and high statistical significance as reliable instrumental variables (IVs) based on the principles of MR analysis. To avoid biased parameter estimates due to low statistical power and weak IVs during MR analysis, we applied different significance thresholds for associations under varying exposure conditions. A significance level of 1×10^{-5} was taken for the 21 metal traits used in exposed plasma and serum to extract IV for each metal trait, consistent with the threshold taken in previous experiments [25]. For immunocytes and schizophrenia, single nucleotide polymorphisms (SNP) with a genome-wide significance threshold of $p < 5 \times 10–5$ were selected as the effective IV associated with the exposure traits [26,27]. The independent SNP was screened by linkage disequilibrium (LD) clustering (r^2 threshold <0.001 within a 10,000 kb distance), based on the European 1000 Genomes reference panel. Despite the exposure data from East Asian populations, the use of the European reference panel conservatively controls the LD structure and reduces false-positive associations. Furthermore, the abnormal SNP was detected by MR-PRESSO and removed to ensure the independence of the instrumental variables. To satisfy the first assumption of MR analysis, increase the criteria for IV selection, and reduce the error due to instrumental variable selection, we calculated the F statistic (β^2/SE^2) for 21 metal traits in the exposed plasma and serum, and selected the instrumental variable with an $F > 10$ for the next analysis [25]. For plasma and serum metals, a significance threshold of 1×10^{-5} was chosen based on criteria from previous comparable studies to balance statistical stringency with the number of instrumental variables [25]. For immune cells and schizophrenia, a threshold of $5 \times 10–5$ was used, since the genetic architecture of these phenotypes often involves more productive loci, a slightly relaxed

threshold can retain more potent SNP [28,29]. All threshold choices were referred to the best practice guideline [30,32] for MR analysis. The MR analysis in this study utilized the TwoSampleMR package based on the R language [31]. Known phenotypic associations of the selected SNP were searched through the PhenoScanner database to exclude the SNP associated with known confounders of schizophrenia (e. g., BMI, smoking, socioeconomic status).

2.4. Statistical analysis

2.4.1. Two-sample MR

The MR method was employed to assess the causative associations among 21 metals in plasma and serum, immunocytes, and schizophrenia, and different methods, including IVW, MR-gger, Wald ratio, Simple mode, and weighted median, were applied to determine the causality of exposure and outcome (where only the Wald ratio for traits with only one snp). However, we preferred to use IVW as the main method, which can provide the highest level of statistical advantage and reduce a large number of errors exist, supplemented by other methods [32]. Based on the MR analysis, it was found that when $p < 0.05$, there was a statistically significant causal association between the exposure factors and outcome factors. Given the exploratory nature of this study and the limited prior evidence on metal-immunocyte-schizophrenia pathways, we prioritized reporting nominal p-values to avoid over-correction for multiple comparisons, which may obscure biologically plausible associations. This approach aligns with similar Mendelian randomization studies in psychiatric genetics [33–35].

2.4.2. Reverse MR analysis

To investigate the potential causative impact of schizophrenia on the observed metals in the plasma and serum (PIVW <0.05), we conducted a reverse MR analysis.

2.4.3. Mediation analysis

Our study conducted a two-step MR for mediation analysis to examine if immununocytes act as mediators in the pathway from metals in plasma and serum to schizophrenia. In order to calculate the indirect mediation effect of 21 metals in plasma and serum on schizophrenia, we used the coefficient product method as our main method to calculate the mediation effect, as follows: mediation effect = beta1 × beta2 (beta1 is beta value between 21 metals in plasma and 731 immunocytes, beta2 is beta value between 731 immunocytes and schizophrenia). The overall effect of the 21 metals in the plasma and serum on schizophrenia was determined in a previous two-sample MR analysis. The direct effect is the difference between the overall effect and the mediating effect, so the proportion of metals in plasma and serum mediating the total effect in schizophrenia was estimated by dividing the indirect effect by the overall effect.

2.4.4. Sensitivity analysis

To test the accuracy of the data, we performed heterogeneity tests using MR-Egger and IVW techniques. Heterogeneity between IV was assessed using the Cochran Q test, where a p-value greater than 0.05 indicates the the absence of substantial heterogeneity. Furthermore, a p-value greater than 0.05 indicates that horizontal pleiotropy is absent by using the MR-Egger regression equation. Finally, we performed a leave-one-out method sensitivity analysis to determine whether a single SNP had a significant effect on the causal estimates.(S1-S4).

3. Results

Fig. 1 depicts the research flowchart.

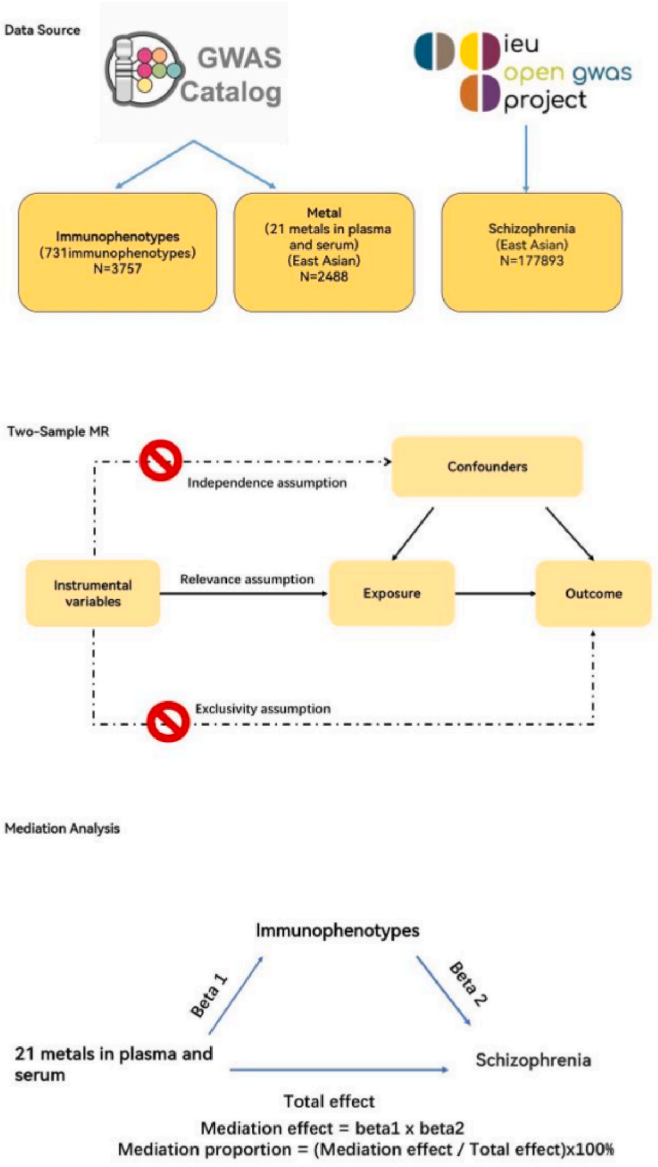

Fig. 1. Flowchart of this research.

3.1. The overall causal effects of 21 metals in plasma and serum on schizophrenia

The IVs of the 21 metals in our plasma and serum showed strong intensity (lowest F statistic = 19.64, above the common threshold of 10) and were therefore applied to the following MR analysis.

Our MR results showed that among the 21 metals in the plasma and serum of the East Asian population, two metals had a strong causal relationship with schizophrenia, and both were negatively associated with the development of schizophrenia (OR> 1, $p < 0.05$), resulting in serum iron levels and serum molybdenum levels, respectively. We selected the results of the IVW method to show, Where the causal effect of Seruim iron levels on schizophrenia was (odds ratio (OR): 0.54, 95 % confidenceinterval(CI):0.30–0.96, p = 0.036), Seruim molybdenun levels The causal effect on schizophrenia is (oddsratio (OR): 0.54, 95 % confidenceinterval(CI):0.34–0.87, p = 0.011) (Fig. 2), shows the results of the two IVW methods in plasma in the East Asian population, Then according to the dataA baseline lifetime risk of 1 % in the general population [7], We calculated thea number needed to treat (NNT) of approximately 217 individuals to prevent one case. We performed sensitivity test (including heterogeneity test, pleiotropic test) and

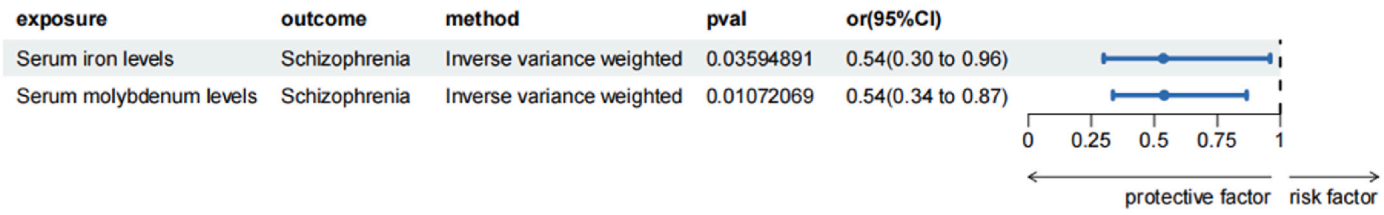

Fig. 2. Forest plots depicting the causal impacts of 21 metals in our plasma and serum on SCZ. OR, odds ratio; CI, confidence interval.

leave-one-method sensitivity analysis, To determine whether a single SNP has a significant effect on the causal relationships. then we serum the two positive relationships with schizophrenia metal and schizophrenia in reverse MR analysis, found no positive results, both schizophrenia to the plasma and serum metal, but also met the next step can be MR mediation analysis conditions.

3.2. The overall causal effect of immunocytes on schizophrenia

The MR results showed that 13 out of 731 immunocytes were causally related to schizophrenia. The effects on schizophrenia were inconsistent, with both positive and negative correlations. They are respectively: HLA DR + + monocyte Absolute Count(oddsratio (OR):0.26,95 %confidenceinterval(CI):0.09–0.78, p = 0.016), CD33dim HLA DR + CD11b− Absolute Count (OR:0.32, 95 %CI:0.11–0.89, p = 0.029)CD14− $CD16^{+}$ monocyte%monocyte(OR:0.12, 95 % CI:0.02–0.90, p = 0.039), B cell%CD3− lymphocyte(OR = 1.62, 95 % CI:1.11–2.35, p = 0.011), Natural Killer%CD3− lymphocyte(OR = 0.62, 95 %CI0.43–0.88, P = 0.008) and 13 species (Fig. 3).Immunocytes with an OR> 1 were identified as possible risk factors for the onset of Sschizophrenia, while those with an OR <1 were identified as possible protective factors for schizophrenia.

3.3. The overall causal effect of Seruim iron levels and Seruim molybdenum levels on 731 immunocytes

The MR results of metals in plasma and serum with immunocytes showed that both exposures of Seruim iron levels and Seruim molybdenum levels had multiple meaningful results for 731 immunocytes; among them, Seruim iron levels were positive for 22 different immunocytes (e. g., the MR results of Seruim iron levels for Granulocytic Myeloid Derived Suppressor Cells Absolute Count showed that (OR: 1.10, 95 %CI:1.01–1.20, p = 0.033)), While Seruim molybdenum levels were positive for 24 different immunocytes (such as Seruim molybdenum levels MR results for CD33 on CD33 + HLA DR + CD14dim (OR: 1.14, 95 %CI:1.04–1.25, p = 0.007))(Figs. 4 and Fig. 5).

3.4. The results of the mediation analysis

With the goal of understanding the fundamental processes involved in the development and development of schizophrenia by 21 metals in plasma and serum, we performed mediation analysis by MR analysis with Seruim iron levels and Seruim molybdenun levels as exposure, 731 immunocytes as outcome and 731 immunocytes as exposure and schizophrenia as outcome. To calculate the indirect mediating effect of metals on schizophrenia outcome, we used the coefficient product method as our primary method, which is the indirect effect of metals in plasma and serum on outcome through immunocytes (beta1 × beta2). The direct effect is the estimate of the plasma and serum metal effect in schizophrenia alone (beta3) on the outcome, and the total effect is the sum of direct and indirect effects (beta3 + beta1 × beta2). Therefore, the proportion of the total effects mediated by each immune effect was estimated by dividing the indirect effect by the total effect [beta1 × beta2/(beta3 + beta1 beta2)].

The final results identified that Seruim iron levels and Seruim molybdenun levels have a pathway associated with schizophrenia, among which the Seruim iron levels in the schizophrenia pathway were affected by the strong negative correlation of CD33dim HLA DR + CD11b-Absolute Count (its mediation effect was 0.129 and its mediation proportion was 0.207). Seruim molybdenun levels affected schizophrenia through CD19 on IgD + CD24 + B cells (since the direction of beta values in its two-step MR, inconsistent positive and negative effects, Delete it without consideration). We tested the MR analysis of serum iron levels on CD33dim HLA DR + CD11b-Absolute Count (assessing the

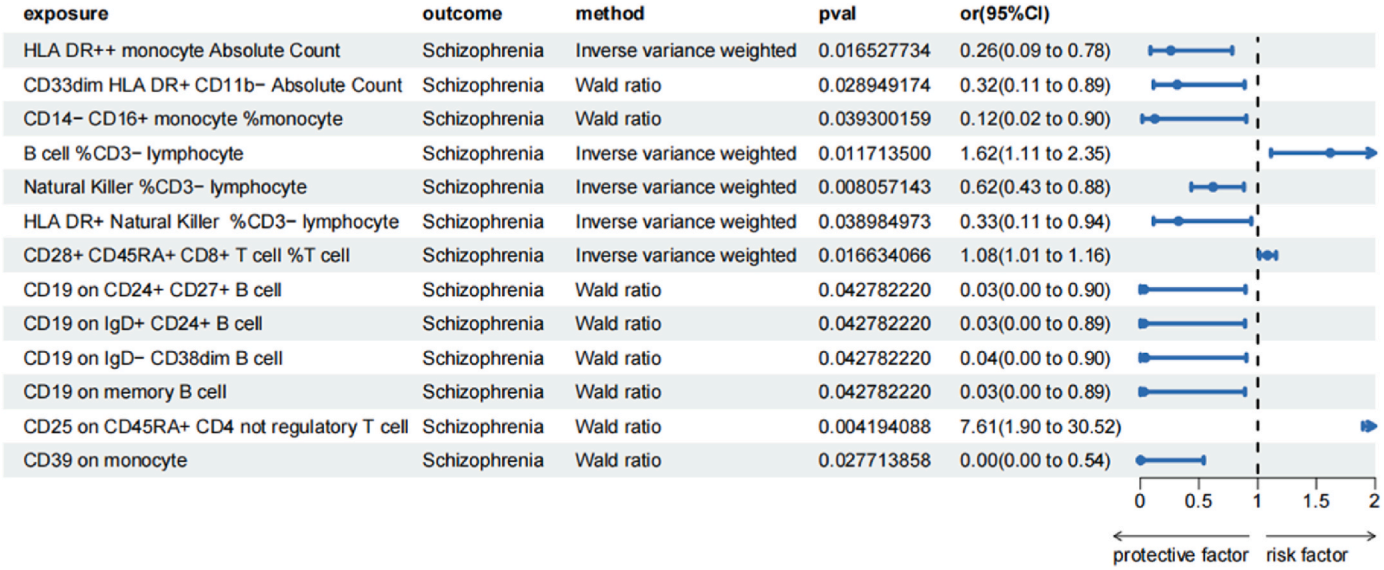

Fig. 3. Forest plots depicting the causal impacts of immunocytes on SCZ. OR, odds ratio; CI, confidence interval.

exposure	outcome	method	pval	or(95%CI)
Serum iron levels	Plasma Blast−Plasma Cell Absolute Count	Inverse variance weighted	0.045683662	0.95(0.90 to 1.00)
Serum iron levels	IgD− CD38+ B cell Absolute Count	Inverse variance weighted	0.010892857	0.94(0.89 to 0.98)
Serum iron levels	CD20− B cell Absolute Count	Inverse variance weighted	0.040726178	0.95(0.90 to 1.00)
Serum iron levels	IgD− CD38+ B cell %lymphocyte	Inverse variance weighted	0.046580452	0.93(0.87 to 1.00)
Serum iron levels	CD20− B cell %lymphocyte	Inverse variance weighted	0.038725134	0.95(0.90 to 1.00)
Serum iron levels	Granulocytic Myeloid−Derived Suppressor Cells Absolute Count	Inverse variance weighted	0.033069144	1.10(1.01 to 1.20)
Serum iron levels	CD33dim HLA DR+ CD11b− Absolute Count	Inverse variance weighted	0.019086488	0.89(0.81 to 0.98)
Serum iron levels	T cell %lymphocyte	Inverse variance weighted	0.048071106	1.05(1.00 to 1.11)
Serum iron levels	CD3− lymphocyte %leukocyte	Inverse variance weighted	0.007399904	0.93(0.88 to 0.98)
Serum iron levels	Natural Killer %lymphocyte	Inverse variance weighted	0.031142847	0.95(0.90 to 1.00)
Serum iron levels	Granulocyte Absolute Count	Inverse variance weighted	0.042007010	1.06(1.00 to 1.12)
Serum iron levels	CD62L on monocyte	Inverse variance weighted	0.039200523	1.06(1.00 to 1.13)
Serum iron levels	CD66b on Granulocytic Myeloid−Derived Suppressor Cells	Inverse variance weighted	0.047082471	1.09(1.00 to 1.19)
Serum iron levels	CD28 on CD45RA+ CD4+ T cell	Inverse variance weighted	0.006922620	1.09(1.02 to 1.16)
Serum iron levels	CD86 on monocyte	Inverse variance weighted	0.031064224	0.93(0.86 to 0.99)
Serum iron levels	CD127 on granulocyte	Inverse variance weighted	0.015007996	0.93(0.87 to 0.99)
Serum iron levels	CD33 on Granulocytic Myeloid−Derived Suppressor Cells	Inverse variance weighted	0.000925825	1.16(1.06 to 1.27)
Serum iron levels	CD40 on CD14+ CD16− monocyte	Inverse variance weighted	0.047669601	0.95(0.89 to 1.00)
Serum iron levels	CD64 on CD14− CD16−	Inverse variance weighted	0.014001188	0.94(0.89 to 0.99)
Serum iron levels	CCR2 on CD62L+ myeloid Dendritic Cell	Inverse variance weighted	0.013779593	1.08(1.02 to 1.16)
Serum iron levels	HLA DR on CD33− HLA DR+	Inverse variance weighted	0.033545070	0.92(0.85 to 0.99)
Serum iron levels	CD8 on CD39+ CD8+ T cell	Inverse variance weighted	0.027954782	0.94(0.88 to 0.99)

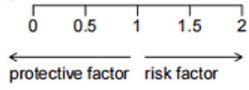

Fig. 4. Forest plots depicting the causal impacts of Serum iron levels on immunocytes. OR, odds ratio; CI, confidence interval.

exposure	outcome	method	pval	or(95%CI)
Serum molybdenum levels	CD4 regulatory T cell %CD4+ T cell	Inverse variance weighted	0.029860128	0.93(0.87 to 0.99)
Serum molybdenum levels	CD4 regulatory T cell %T cell	Inverse variance weighted	0.026368047	0.93(0.87 to 0.99)
Serum molybdenum levels	Activated & resting CD4 regulatory T cell %CD4+ T cell	Inverse variance weighted	0.032067096	0.93(0.87 to 0.99)
Serum molybdenum levels	CD25++ CD4+ T cell %CD4+ T cell	Inverse variance weighted	0.030290029	0.93(0.87 to 0.99)
Serum molybdenum levels	CD25++ CD4+ T cell %T cell	Inverse variance weighted	0.022876723	0.93(0.87 to 0.99)
Serum molybdenum levels	CD25++ CD45RA− CD4 not regulatory T cell %T cell	Inverse variance weighted	0.030601245	0.93(0.87 to 0.99)
Serum molybdenum levels	Central Memory CD4+ T cell %CD4+ T cell	Inverse variance weighted	0.045133521	0.93(0.88 to 1.00)
Serum molybdenum levels	Central Memory CD4+ T cell %T cell	Inverse variance weighted	0.033346353	0.93(0.87 to 0.99)
Serum molybdenum levels	CD19 on IgD+ CD24+ B cell	Inverse variance weighted	0.047787430	1.07(1.00 to 1.14)
Serum molybdenum levels	CD27 on CD20− CD38− B cell || id:ebi−a−GCST90001797	Inverse variance weighted	0.023484135	0.93(0.87 to 0.99)
Serum molybdenum levels	IgD on IgD+ CD24+ B cell	Inverse variance weighted	0.015318567	1.08(1.02 to 1.16)
Serum molybdenum levels	IgD on unswitched memory B cell	Inverse variance weighted	0.012083260	1.09(1.02 to 1.16)
Serum molybdenum levels	CD34 on Hematopoietic Stem Cell	Inverse variance weighted	0.027172730	1.11(1.01 to 1.22)
Serum molybdenum levels	CD28 on CD45RA− CD4 not regulatory T cell	Inverse variance weighted	0.046936508	0.93(0.86 to 1.00)
Serum molybdenum levels	CD45 on granulocyte	Inverse variance weighted	0.037980376	0.93(0.87 to 1.00)
Serum molybdenum levels	CD25 on CD45RA− CD4 not regulatory T cell	Inverse variance weighted	0.030028760	0.93(0.87 to 0.99)
Serum molybdenum levels	CD33 on CD33+ HLA DR+ CD14dim	Inverse variance weighted	0.007578411	1.14(1.04 to 1.25)
Serum molybdenum levels	CD33 on CD33dim HLA DR+ CD11b+	Inverse variance weighted	0.019007449	1.12(1.02 to 1.23)
Serum molybdenum levels	CD33 on CD33dim HLA DR+ CD11b−	Inverse variance weighted	0.021076610	1.12(1.02 to 1.22)
Serum molybdenum levels	CD33 on CD66b++ myeloid cell	Inverse variance weighted	0.035522418	1.11(1.01 to 1.23)
Serum molybdenum levels	CD33 on Monocytic Myeloid−Derived Suppressor Cells	Inverse variance weighted	0.035123101	1.11(1.01 to 1.22)
Serum molybdenum levels	CD33 on CD33+ HLA DR+	Inverse variance weighted	0.008088440	1.14(1.03 to 1.25)
Serum molybdenum levels	CD33 on CD33+ HLA DR+ CD14−	Inverse variance weighted	0.009407140	1.14(1.03 to 1.25)
Serum molybdenum levels	CD4 on HLA DR+ CD4+ T cell	Inverse variance weighted	0.047729236	1.07(1.00 to 1.15)

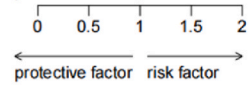

Fig. 5. Forest plots depicting the causal impacts of Serum molybdenum levels on immunocytes. OR, odds ratio; CI, confidence interval.

effect of directional pleiotropy, we applied the MR-Egger regression method). Both pleiotropic and heterogeneity tests using the MR-Egger intercept term (Cochran Q and MR-PRESSO) were used to quantify the pleiotropic level of outcome in the MR analysis) and the leave-for-one method.

4. Discussion

MR analyses used genetic variation as an instrumental variable to elucidate potential causal relationships between exposure and outcome. We identified a complex association between schizophrenia and metal ions in serum by MR analysis of 21 metals in plasma and serum for schizophrenia and the mediators of immunocytes therein.

Our MR results showed that the concentration of serum iron in the East Asian population was inversely correlated with schizophrenia and was a protective factor against schizophrenia. It was also found that CD33dim HLA DR + CD11b-Absolute Count has an important mediating role (20.7 % of mediators). Iron is only a negligible proportion of our body weight (about 1–3 g in adults), but it is critical for many physiological functions [36]. And after clinical data show maternal iron deficiency, will greatly increase the risk of offspring schizophrenia, Beverly J Insel and others to hemoglobin concentration as a marker of iron content, found low hemoglobin concentration of pregnant women gave birth to children, children in adulthood probability of schizophrenia greatly exceeds the high hemoglobin concentration of women gave birth to children [37]. Researchers have also studied the anemia of patients with chronic schizophrenia in a Chinese population, and found that the proportion of anemia in chronic schizophrenia patients was very high in the Chinese Han population [38]. While some studies have found that the concentration of iron in the blood also affects the concentration of some immunocytes, evidence is lacking [39]. Our results precisely confirm that the iron concentration does affect the concentration of the immunocytes. immunocytes (myeloid immune cells) can also affect the generation of red blood cells in terms of cellular immunity, and even it can lead to a severe hematopoietic disease: aplastic anemia [40]. This may also indicate a potential close link between immune immunocytes in serum iron and schizophrenia. All MR methods (IVW, MR-Egger, weighted median) showed consistent directionality (serum iron OR <1), and the confidence interval of the IVW results did not span 1, supporting the conclusion robustness. The slope of MR-Egger was not significantly different from IVW to further verify the reliability of the causal effect.

There are many possible reasons why immunocytes can affect schizophrenia. First, the possibility is the involvement of the autonomic nervous system in the brain and immune system, and second, the activation of the immune system by psychological stress and emotions [41]. Regarding the involvement of the autonomic nervous system in the link between the brain and the immune system, sympathetic and lymphoid organs innervated by peptiderergic nerve fibers are able to promote certain immune responses mediated by neurotransmitters and hormones such as norepinephrine and substance P, thereby increasing immunocytes [42]. As for the activation of the immune system by psychological stress and emotion, it is well known that psychological stress and emotion will activate the HPA axis, increase the levels of circulating glucocorticoids and lead to immune function suppression [43]. Importantly, studies have found that iron concentration also affects changes in mood, and observations suggest that lower iron concentration are associated with depressed mood, functional fatigue and poor memory [44]. So this may be a potential factor in iron concentration affecting immunocytes, as shown by our results.

Immunocytes are essential for the early detection of susceptibility to schizophrenia and for preventing its development. Previous studies in schizophrenia patients showed that subgroups with elevated inflammation showed decreased microglia in the subependymal region, increased peripheral immunocytes, and altered gene expression of neurogenesis markers [45]. Jennie G Pouget et al. found a genetic correlation between six immune disorders and schizophrenia [46]. There is evidence that schizophrenia is characterized by reduced activation and neuroprotection of the immune inflammatory response (IRS) and the compensatory immune regulatory system (CIRS) [47]. Our findings also identified a causal association between 731 immunocytes and schizophrenia in East Asian populations.

The CD33dim HLA DR + CD11b-cells are a myeloid cell subtype, and it is hypothesized that HLA-DR may reduce the risk of schizophrenia through its subtype, HLA-DRB 1. A previous study using the Tunisian population found that the highly protective allele against schizophrenia in HLA-DRB 1 was DRB 1 * 13 ($P = 0.013$) [48]. Although we did not find any studies on the relationship between CD11b and schizophrenia in humans, it significantly increased CD11b expression in schizophrenia rats [49]. This also indicates that the CD11b-cell may be negatively associated with schizophrenia, which also confirms the accuracy of our experimental results, in addition, CD33 inhibited the expression of proinflammatory cytokines, including IL-1 β and TNF- α [50,51]. Therefore, CD33 may reduce the incidence of schizophrenia by reducing the inflammatory response.

CD33dim HLA DR + cells in the central nervous system (CNS) by HLA-DR molecules such as myantigen, activate autoreactive T cells, and then trigger nerve inflammation and neuronal damage, this mechanism is demonstrated in multiple sclerosis (MS), HLA-DR15 haplotype as the core genetic risk factor for MS, so we can reasonably guess it may have potential mechanism in schizophrenia (may be caused by neuronal damage). Furthermore, memory B cells synergistically activate brain-taxis CD4 + T cells through HLA-DR-dependent signaling to drive disease progression. The experimental autoimmune encephalomyelitis (EAE) model using HLA transgenic mice confirmed that the HLA-related antigen presentation mechanism is the core link of T cell-mediated CNS autoimmunity, providing the possibility to guess the underlying mechanism of schizophrenia [52–55].

CD11b (integrin α M) plays an important role in immune cell migration, especially when crossing the blood-brain barrier (BBB). CD11b promotes the adhesion and migration of immune cells by binding to ligands such as ICAM-1, which is crucial for the immune monitoring and inflammatory response of the central nervous system (CNS) [56,57]. However, the low expression of CD11b in CD33dim cells may limit the ability of these cells to penetrate the BBB and thus affect their function in the CNS and a function in the pathogenesis of schizophrenia.

This study based data from a large-scale GWAS cohort using two-sample MR analysis, mediation MR analysis, in addition, we utilized a two-step MR study and mediation analysis to establish a pathway linking serum iron concentration to immunocytes-mediated schizophrenia. East Asian populations were used as plasma and serum data sources for metals and schizophrenia, thus ensuring a high statistical efficacy in specific populations. The results were derived from genetic instrumental variables and causal inferences by using various MR analysis methods. The final MR results were not affected by horizontal pleiotropy or by other potential confounders.

However, this experiment also has some limitations, as we selected the sample based on the East Asian population, this leads to our lack of universality to other populations; second, the lack of demographic information led to our lack of an analysis of schizophrenia stratified by age and sex, thus limiting our understanding of how causal relationships change between different age groups and the sexes. At the same time, we found that although serum iron and molybdenum are protective against schizophrenia, the effect size was moderate, but according to previous studies, although the effect size is small, they still have certain clinical significance due to their large population base [22]. Since this paper is an exploratory study, this multiple testing correction was not performed, The observed effect size (46 % risk reduction) aligns with iron's role in neurodevelopment and immune regulation, though replication in larger cohorts is needed to confirm causality. Although this study follows the core assumptions of MR analysis, the following limitations should be noted: firstly, the screening of instrumental variables depends on the

public GWAS data, which may miss some functional SNP; secondly, despite the pleiotropic effects through sensitivity analysis, residual confounding cannot be completely excluded; finally, the limited data of East Asian population may affect the generalization of the results. Future further validation is needed by combining across ethnic cohorts and experimental studies. Since this experiment is a theoretical experiment, there is a lack of clinical and experimental data to support it, and it is difficult to explain the different results of iron concentrations at different locations (plasma and serum); further validation is needed by additional empirical studies performed in experimental and clinical settings.

This study faced an important limitation when analyzing the causal relationship between serum metals, immune cells and schizophrenia: there is no public GWAS data on immune cells in East Asian population. Therefore, we used the immune cell GWAS data from the European Sardinian population. Although cross-population analysis may introduce genetic structure differences or environmental confounders (e. g. socioeconomic differences), this study was adopted Sensitivity verification to minimize the error, Other studies have also used the analysis of different population data sources [28]. The mediation analysis in this study revealed the potential pathway of CD33dim HLA DR + CD11b-immune cells between serum iron and schizophrenia (mediator ratio of 21 %). To be clear, this finding is exploratory rather than conclusive. The mediation analysis was based on the strong assumption of 'no unmeasured confounding', while the relationship of the immune system with schizophrenia may involve other unincluded cell types or molecular pathways (e. g., cytokines, complement system). As the immune cell data are derived from European populations, the mediating effects may be influenced by population-specific regulatory mechanisms. For example, the expression level of CD33 may be regulated by differential epigenetic modifications in different populations. Thus, these results provide a hypothesis-generating framework for subsequent mechanistic studies. In the future, the specific role of CD33dim HLA DR + CD11b-cells in iron metabolism and neuroinflammation should be verified through experimental studies (such as animal models or cell experiments).

In summary, the causal relationship between schizophrenia and the concentration of metal ions in the blood and the possible intermediary pathways are complex, which strengthens our understanding of the role of immune regulation and the effects of metals on the human body in the development of the disease and brings new insights and potential directions for those who explore the diagnosis and treatment of schizophrenia. The above studies can help to provide more precise and advanced therapeutic targets for the disease as in other studies, so as to better serve the clinical patients [58].

5. Conclusion

In conclusion, our findings reveal a complex interplay between serum metal concentrations, particularly iron, and immunocyte activity in influencing schizophrenia risk, underscoring the importance of further research into these biological pathways. We found that serum iron ion concentration may negatively affect schizophrenia through the CD33dim HLA-DR + CD11b-Absolute Count (mediator 20.7 %) pathway. These results provide new value to the mechanisms that cause and advance schizophrenia.

CRediT authorship contribution statement

Yunchang Yang: Conceptualization. **Yaofeng Wang:** Data curation. **Yunqin Sun:** Formal analysis.

Data avaliability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Further inquiries can be directed to the corresponding author.

Ethics declarations

All studies were approved by local ethics committees, and all participants provided written, informed consent. Informed consent was obtained from all participants and/or their LAR. This study was conducted in accordance to relevant guidelines and regulations.

Consent to participate,consent to publish declarations

Not applicable.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2025.100304.

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