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Article

# Immune cell phenotypes and eating disorders: To find causal relationship through Mendelian randomization study

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**Abstract: Background:** Eating disorders are potentially persistent mental illnesses that can lead to death. Our study is determined to found out the casual relationship between immune cell phenotypes and eating disorders via Mendelian randomization (MR) method. **Aim:** To explore the causal relationship between 731 immune cell phenotypes and eating disorders. We conducted a two-sample Mendelian randomization (TSMR) analysis to find out the association between 731 immune cell phenotypes and eating disorders. **Materials and methods:** All the data we used in this study were obtained from GWAS. We conducted a TSMR analysis. We used 731 types of immune cells as exposure and eating disorders as outcome. Our analysis uses a variety of methods to ensure the robustness of the experiment. The inverse variance weighted (IVW) method was the main MR analysis method, we also proceeded sensitivity analyses to validate the robustness, heterogeneity and horizontal pleiotropy of the MR results. **Results:** Our study identified potential causal relationships between various immune cells and eating disorders. We identified 20 types of immune cells that are potentially causally linked to eating disorders linked to eating disorders. There are 7 types of immune cells that act as protective factors for eating disorders. **Conclusions:** There are 20 types of immune cells have possible relationship with eating disorders via MR method, which can provide more information for clinical practice.

**Keywords:** immune cell; phenotypes; causal relationship; Mendelian randomization study

## 1. Introduction

Eating disorders (EDs) are characterized by abnormal responses to food and weight-related stimuli and are associated with significant distress, impairment, and poor outcomes [1]. Empirical evidence is unequivocal in illustrating that the majority of patients with eating disorders will not fully recover during treatment [2]. Generally speaking, the most well-known to us eating disorders include bulimia nervosa and Anorexia Nervosa. However, there is no complete diagnostic method for eating disorders, and research on eating disorders is still limited. We look forward to providing more information about eating disorders through the exploration of immune cells.

Recent studies showed that eating disorders had a strong link with the immune cell phenotypes. In the realm of psychiatry, biological markers are seldom utilized, if at all, for the diagnosis of mental health disorders. Instead, clinicians predominantly depend on patients' medical histories and observed behavioral symptoms to pinpoint particular psychopathologies. This approach renders the diagnostic process highly subjective [3]. We explored the relationship between immune cells and eating

disorders. In recent research, some researchers found significant plasma proteome changes in Anorexia Nervosa patients, compared to healthy controls, and discovered differentially expressed proteins between the two disease subtypes. Which will be serving as a tool for better Anorexia Nervosa diagnosis and prognosis [4]. Researchers from Germany have found a close link between CCR4, CCR6 and CXCR4 expression and the adolescent mental health status in the study cohort as determined by the Strengths and Difficulties Questionnaire (SDQ) [5]. Some researchers also found that for female adolescent patients with Anorexia Nervosa, there is a dysfunction of intra- and intercellular inflammatory pathways characterized by higher levels of pro-inflammatory parameters in plasma and a decrease in one of the controlling cytoplasmic-nuclear pathways implicated in their modulation (i.e., PPARγ) with, in very early stage of the disease, no effect on oxidative stress markers plasma levels [6]. Researchers from Spain found that increased naive CD4 and B lymphocyte subsets are associated with body mass loss and drive relative lymphocytosis in anorexia nervosa patients [7]. In terms of diagnostic screening, some researchers have also proposed novel perspectives, they introduce DCM as an innovative and alternative approach to screening individuals at risk of eating disorders. That's because traditional screening methods mostly rely on predefined cutoff scores which have limitations of generalizability and may produce biased results when the cutoff scores are used in populations where the instruments or cutoff scores have not been validated [8]. Such studies have endeavored to delve into the mechanisms underlying eating disorders through the lens of immune cells. The insights gleaned from these researches have significantly enhanced our comprehension of the etiology of eating disorders and have furnished crucial hints for prospective therapeutic and preventive strategies. Despite the considerable endeavors of researchers, our knowledge of eating disorders remains limited. This shortfall could potentially stem from an insufficiency of research samples or constraints inherent in conventional research methodologies.

We employed the Mendelian randomization (MR) technique in our experiments. This was necessary because traditional statistical methods, which may be hampered by potential confounders and issues of reverse causality, were unable to accurately ascertain the observed associations. The MR approach was utilized to probe into the causal connections between various exposures and outcomes. In this method, genetic variants that are strongly linked to exposure levels serve as instrumental variables to gauge these causal relationships. Mendelian randomization enables the identification of potential causal factors for diseases and provides deeper insights into whether certain factors are causes or consequences of diseases [9–12]. Mendelian randomization has found extensive use across numerous disease—related studies. It has successfully pinpointed a multitude of pathogenic factors associated with various diseases [13–15].

In our study, a two-sample Mendelian randomization analysis was carried out to investigate potential causal links between various immune cell types and the risk of developing eating disorders. The objective of this study was to pave the way for innovative treatment strategies of eating disorders in the future. We hope that our findings will serve as a valuable resource for researchers in the field of eating disorders, offering them enhanced insights and information.

## 2. Materials and methods

### 2.1. Study design

In our study, we conducted a TSMR analysis, aiming to thoroughly evaluate and elucidate the potential causal relationships that may exist between a wide array of 731 distinct types of immune cell characteristics and the development or manifestation of eating disorders. Our aim is to delve deeper into the interplay between immunological factors and the pathogenesis of eating disorders, thereby providing a more robust foundation for understanding the underlying mechanisms and potentially informing future diagnostic and therapeutic strategies in this critical area of mental health research. In MR study, effective genetic instrumental variables must obey three key assumptions for causal inference: (1) genetic variation is directly associated with the exposure; (2) genetic variation is unrelated to potential confounders between the exposure and the outcome; (3) genetic variation does not influence the outcome through pathways other than the exposure [16]. The research design is shown in **Figure 1**.

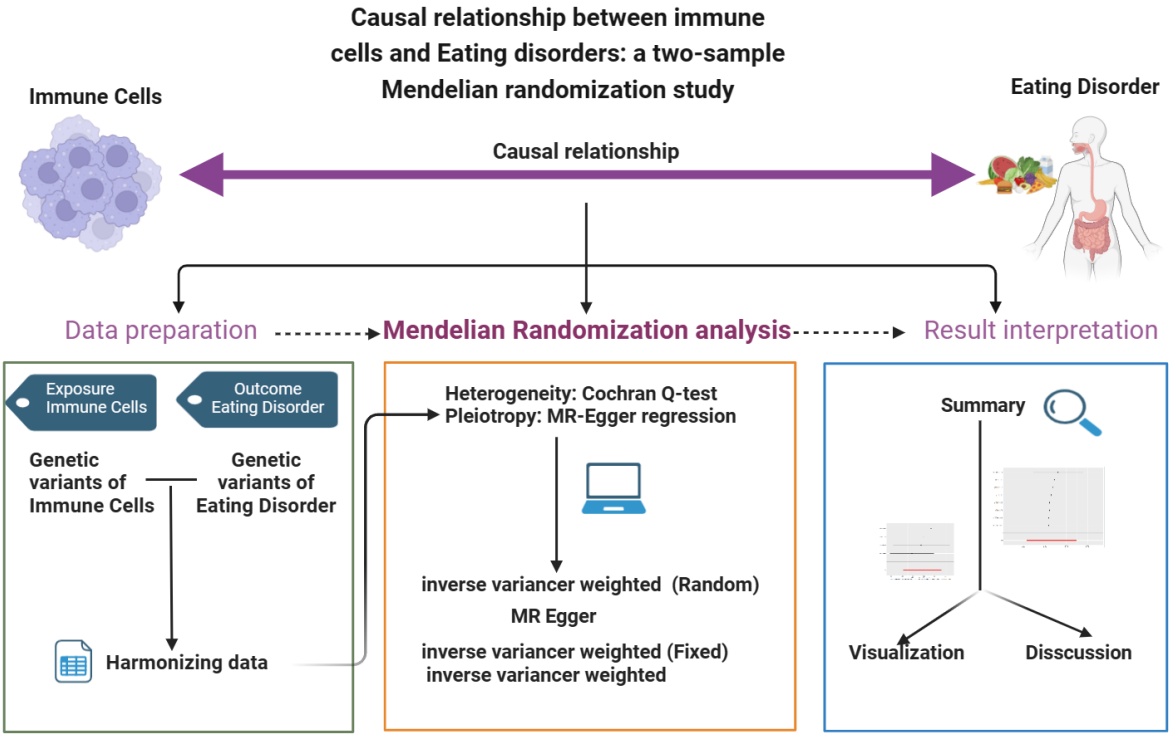



**Figure 1.** Schematic design showed the MR study process.

### 2.2. Data sources

The GWAS data pertaining to immune cells was sourced from a comprehensive study into the genetic attributes (with accession numbers from GCST0001391 to GCST0002121). In this study, the researchers undertook extensive analyses of a vast array of genetic variants. Their objective was to pinpoint the specific variations that are correlated with the characteristics of immune cells and sought to gain a deeper comprehension of how these genetic variations influence the overall functionality of the immune system [13]. Brief information is shown in **Table 1**.

Data of Eating disorders was obtained from GWAS (https://gwas.mrcieu.ac.uk/). The GWAS ID of the dataset is "finn-b-F5_EATING". Which contained males and females of European. Brief information is shown in **Table 1**.

**Table 1.** Detail information for the inclusion of exposure and outcome data in GWAS.

| | | | | | |
|---|---|---|---|---|---|
| Immune cells | 14,155,839 | 17,008 | 54,162 | European | NA |
| Eating disorders | 16,380,466 | 1874 | NA | European | NA |

NA: Not available.

### 2.3. Chief model in MR analyses

The Inverse Variance Weighted (IVW) model served as the primary analytical approach. This model enhances the precision of estimations. Additionally, we employed alternative methods such as Inverse Variance Weighted (Fixed Effects), Inverse Variance Weighted (Random Effects), and MR-Egger as supplementary techniques to corroborate our findings [17].

### 2.4. Selection of genetic IVs

SNPs that exhibited a robust association with immune cell traits were pinpointed by employing a stringent locus-wide significance threshold set at $p < 5 \times 10^{-8}$. In addition, the datasets underwent harmonization through the exclusion of variants in linkage disequilibrium (LD), with a criterion of $r^2 < 0.001$ within a 10,000 KB clumping distance. This meticulous procedure was instrumental in guaranteeing the independence of the selected instrumental variables (IVs) and in preventing the introduction of bias into the analytical process. We also removed incompatible alleles and palindromic SNPs.

### 2.5. Statistical analyses

In this study, the Cochran Q test was employed to assess the degree of heterogeneity among estimates of individual genetic variations. Furthermore, to scrutinize potential breaches of the Mendelian randomization (MR) assumptions that might arise from horizontal pleiotropy, the MR–Egger regression analysis was conducted.

### 2.6. Software and packages

In this study, all statistical analyses were performed utilizing the R software package within the R language environment (version 4.3.3). The predominant R package that was harnessed for these analyses was "TwoSampleMR," which was employed in version 0.5.8.

## 3. Results

### 3.1. Connection between eating disorders and immune cell phenotypes

In order to found out the causal impact of various immune cell types on eating disorders, a TSMR analysis was conducted. This analysis primarily utilized the Inverse

Variance Weighted (IVW) method as the key analytical approach, while also eliminating potential confounders and accounting for horizontal pleiotropy. The findings of our research suggest that there are 20 types of immune cells that exhibit potential causal associations with eating disorders. Regarding the reverse MR analysis with immune cells and eating disorders, the use of eating disorders as an exposure variable was not feasible in the reverse Mendelian randomization due to an insufficient number of single nucleotide polymorphisms (SNPs). This indicates that eating disorders do not exert an effect on the immune cells included in the study. Ultimately, the results reveal potential causal relationships between these 20 types of immune cells and eating disorders. Details are shown in **Figures 2** and **3**.

| exposure | method | nsnp | OR (95% CI) | pval |
|---|---|---|---|---|
| CD39+ resting CD4 regulatory T cell %resting CD4 regulatory T cell \|\| id:ebi-a-GCST90001484 | Inverse variance weighted (multiplicative random effects) | 7 | 0.89 (0.80 to 1.00) | 4.038306e-02 |
| CD39+ resting CD4 regulatory T cell %resting CD4 regulatory T cell \|\| id:ebi-a-GCST90001484 | Inverse variance weighted | 7 | 0.89 (0.80 to 1.00) | 4.038306e-02 |
| CD39+ resting CD4 regulatory T cell %resting CD4 regulatory T cell \|\| id:ebi-a-GCST90001484 | MR Egger | 7 | 0.91 (0.73 to 1.13) | 4.157057e-01 |
| CD39+ resting CD4 regulatory T cell %resting CD4 regulatory T cell \|\| id:ebi-a-GCST90001484 | Inverse variance weighted (fixed effects) | 7 | 0.89 (0.80 to 0.99) | 3.666770e-02 |
| Secreting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001493 | Inverse variance weighted (multiplicative random effects) | 6 | 1.08 (1.01 to 1.16) | 3.440543e-02 |
| Secreting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001493 | Inverse variance weighted | 6 | 1.08 (1.01 to 1.16) | 3.440543e-02 |
| Secreting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001493 | MR Egger | 6 | 1.08 (0.97 to 1.21) | 2.270443e-01 |
| Secreting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001493 | Inverse variance weighted (fixed effects) | 6 | 1.08 (1.01 to 1.15) | 1.518436e-02 |
| Activated & resting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001499 | Inverse variance weighted (multiplicative random effects) | 6 | 0.93 (0.86 to 0.99) | 3.531289e-02 |
| Activated & resting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001499 | Inverse variance weighted | 6 | 0.93 (0.86 to 0.99) | 3.531289e-02 |
| Activated & resting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001499 | MR Egger | 6 | 0.93 (0.83 to 1.03) | 2.299373e-01 |
| Activated & resting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001499 | Inverse variance weighted (fixed effects) | 6 | 0.93 (0.87 to 0.99) | 1.545458e-02 |
| Activated & secreting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001502 | Inverse variance weighted (multiplicative random effects) | 8 | 1.07 (1.01 to 1.13) | 2.777314e-02 |
| Activated & secreting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001502 | Inverse variance weighted | 8 | 1.07 (1.01 to 1.13) | 2.777314e-02 |
| Activated & secreting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001502 | MR Egger | 8 | 1.05 (0.97 to 1.15) | 2.714073e-01 |
| Activated & secreting CD4 regulatory T cell %CD4 regulatory T cell \|\| id:ebi-a-GCST90001502 | Inverse variance weighted (fixed effects) | 8 | 1.07 (1.01 to 1.13) | 1.887288e-02 |
| Monocytic Myeloid-Derived Suppressor Cells Absolute Count \|\| id:ebi-a-GCST90001530 | Inverse variance weighted (multiplicative random effects) | 5 | 1.14 (1.05 to 1.23) | 1.078758e-03 |
| Monocytic Myeloid-Derived Suppressor Cells Absolute Count \|\| id:ebi-a-GCST90001530 | Inverse variance weighted | 5 | 1.14 (1.03 to 1.26) | 1.213221e-02 |
| Monocytic Myeloid-Derived Suppressor Cells Absolute Count \|\| id:ebi-a-GCST90001530 | MR Egger | 5 | 0.94 (0.58 to 1.52) | 8.086825e-01 |
| Monocytic Myeloid-Derived Suppressor Cells Absolute Count \|\| id:ebi-a-GCST90001530 | Inverse variance weighted (fixed effects) | 5 | 1.14 (1.03 to 1.26) | 1.213221e-02 |
| Effector Memory CD8+ T cell %CD8+ T cell \|\| id:ebi-a-GCST90001555 | Inverse variance weighted (multiplicative random effects) | 4 | 1.12 (1.02 to 1.24) | 2.364824e-02 |
| Effector Memory CD8+ T cell %CD8+ T cell \|\| id:ebi-a-GCST90001555 | Inverse variance weighted | 4 | 1.12 (1.00 to 1.25) | 4.402700e-02 |
| Effector Memory CD8+ T cell %CD8+ T cell \|\| id:ebi-a-GCST90001555 | MR Egger | 4 | 1.17 (1.01 to 1.35) | 1.712033e-01 |
| Effector Memory CD8+ T cell %CD8+ T cell \|\| id:ebi-a-GCST90001555 | Inverse variance weighted (fixed effects) | 4 | 1.12 (1.00 to 1.25) | 4.402700e-02 |
| Effector Memory CD4-CD8- T cell Absolute Count \|\| id:ebi-a-GCST90001569 | Inverse variance weighted (multiplicative random effects) | 4 | 1.34 (1.01 to 1.78) | 4.279068e-02 |
| Effector Memory CD4-CD8- T cell Absolute Count \|\| id:ebi-a-GCST90001569 | Inverse variance weighted | 4 | 1.34 (1.01 to 1.78) | 4.279068e-02 |
| Effector Memory CD4-CD8- T cell Absolute Count \|\| id:ebi-a-GCST90001569 | MR Egger | 4 | 1.21 (0.59 to 2.50) | 6.553488e-01 |
| Effector Memory CD4-CD8- T cell Absolute Count \|\| id:ebi-a-GCST90001569 | Inverse variance weighted (fixed effects) | 4 | 1.34 (1.10 to 1.64) | 3.961853e-03 |
| Effector Memory CD4-CD8- T cell %CD4-CD8- T cell \|\| id:ebi-a-GCST90001570 | Inverse variance weighted (multiplicative random effects) | 4 | 1.20 (1.01 to 1.43) | 4.077315e-02 |
| Effector Memory CD4-CD8- T cell %CD4-CD8- T cell \|\| id:ebi-a-GCST90001570 | Inverse variance weighted | 4 | 1.20 (1.01 to 1.43) | 4.077315e-02 |
| Effector Memory CD4-CD8- T cell %CD4-CD8- T cell \|\| id:ebi-a-GCST90001570 | MR Egger | 4 | 1.12 (0.74 to 1.70) | 6.370601e-01 |
| Effector Memory CD4-CD8- T cell %CD4-CD8- T cell \|\| id:ebi-a-GCST90001570 | Inverse variance weighted (fixed effects) | 4 | 1.20 (1.03 to 1.41) | 2.194730e-02 |
| CD25 on IgD+ CD38- B cell \|\| id:ebi-a-GCST90001780 | Inverse variance weighted (multiplicative random effects) | 3 | 1.38 (1.23 to 1.55) | 4.499064e-08 |
| CD25 on IgD+ CD38- B cell \|\| id:ebi-a-GCST90001780 | Inverse variance weighted | 3 | 1.38 (1.08 to 1.76) | 9.902203e-03 |
| CD25 on IgD+ CD38- B cell \|\| id:ebi-a-GCST90001780 | MR Egger | 3 | 1.25 (0.64 to 2.44) | 6.263700e-01 |
| CD25 on IgD+ CD38- B cell \|\| id:ebi-a-GCST90001780 | Inverse variance weighted (fixed effects) | 3 | 1.38 (1.08 to 1.76) | 9.902203e-03 |
| CD25 on IgD- CD38dim B cell \|\| id:ebi-a-GCST90001789 | Inverse variance weighted (multiplicative random effects) | 3 | 1.28 (1.14 to 1.43) | 2.006675e-05 |
| CD25 on IgD- CD38dim B cell \|\| id:ebi-a-GCST90001789 | Inverse variance weighted | 3 | 1.28 (1.04 to 1.57) | 1.723923e-02 |
| CD25 on IgD- CD38dim B cell \|\| id:ebi-a-GCST90001789 | MR Egger | 3 | 1.12 (0.71 to 1.76) | 7.105608e-01 |
| CD25 on IgD- CD38dim B cell \|\| id:ebi-a-GCST90001789 | Inverse variance weighted (fixed effects) | 3 | 1.28 (1.04 to 1.57) | 1.723923e-02 |

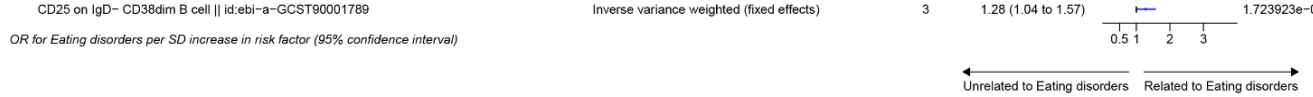
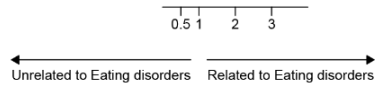



**Figure 2.** The forest plot of the MR result (Immune cells to eating disorders).

| exposure | method | nsnp | OR (95% CI) | pval |
|---|---|---|---|---|
| CD27 on IgD+ CD38− unswitched memory B cell \|\| id:ebi-a-GCST90001801 | Inverse variance weighted (multiplicative random effects) | 5 | 1.12 (1.02 to 1.24) | 1.578780e−02 |
| CD27 on IgD+ CD38− unswitched memory B cell \|\| id:ebi-a-GCST90001801 | Inverse variance weighted | 5 | 1.12 (1.02 to 1.24) | 2.117009e−02 |
| CD27 on IgD+ CD38− unswitched memory B cell \|\| id:ebi-a-GCST90001801 | MR Egger | 5 | 1.21 (0.85 to 1.72) | 3.664817e−01 |
| CD27 on IgD+ CD38− unswitched memory B cell \|\| id:ebi-a-GCST90001801 | Inverse variance weighted (fixed effects) | 5 | 1.12 (1.02 to 1.24) | 2.117009e−02 |
| CD27 on memory B cell \|\| id:ebi-a-GCST90001805 | Inverse variance weighted (multiplicative random effects) | 7 | 1.12 (1.01 to 1.25) | 3.895428e−02 |
| CD27 on memory B cell \|\| id:ebi-a-GCST90001805 | Inverse variance weighted | 7 | 1.12 (1.00 to 1.26) | 4.825239e−02 |
| CD27 on memory B cell \|\| id:ebi-a-GCST90001805 | MR Egger | 7 | 1.19 (0.83 to 1.71) | 3.817069e−01 |
| CD27 on memory B cell \|\| id:ebi-a-GCST90001805 | Inverse variance weighted (fixed effects) | 7 | 1.12 (1.00 to 1.26) | 4.825239e−02 |
| CD38 on transitional B cell \|\| id:ebi-a-GCST90001819 | Inverse variance weighted (multiplicative random effects) | 5 | 1.17 (1.03 to 1.32) | 1.223137e−02 |
| CD38 on transitional B cell \|\| id:ebi-a-GCST90001819 | Inverse variance weighted | 5 | 1.17 (1.01 to 1.34) | 3.050352e−02 |
| CD38 on transitional B cell \|\| id:ebi-a-GCST90001819 | MR Egger | 5 | 1.07 (0.86 to 1.33) | 5.842428e−01 |
| CD38 on transitional B cell \|\| id:ebi-a-GCST90001819 | Inverse variance weighted (fixed effects) | 5 | 1.17 (1.01 to 1.34) | 3.050352e−02 |
| CD3 on secreting CD4 regulatory T cell \|\| id:ebi-a-GCST90001855 | Inverse variance weighted (multiplicative random effects) | 3 | 0.90 (0.81 to 0.99) | 3.270488e−02 |
| CD3 on secreting CD4 regulatory T cell \|\| id:ebi-a-GCST90001855 | Inverse variance weighted | 3 | 0.90 (0.81 to 1.00) | 4.796387e−02 |
| CD3 on secreting CD4 regulatory T cell \|\| id:ebi-a-GCST90001855 | MR Egger | 3 | 1.12 (0.75 to 1.67) | 6.695438e−01 |
| CD3 on secreting CD4 regulatory T cell \|\| id:ebi-a-GCST90001855 | Inverse variance weighted (fixed effects) | 3 | 0.90 (0.81 to 1.00) | 4.796387e−02 |
| CD3 on CD4 regulatory T cell \|\| id:ebi-a-GCST90001868 | Inverse variance weighted (multiplicative random effects) | 3 | 0.90 (0.82 to 0.99) | 2.842885e−02 |
| CD3 on CD4 regulatory T cell \|\| id:ebi-a-GCST90001868 | Inverse variance weighted | 3 | 0.90 (0.81 to 1.00) | 4.626433e−02 |
| CD3 on CD4 regulatory T cell \|\| id:ebi-a-GCST90001868 | MR Egger | 3 | 1.11 (0.75 to 1.65) | 6.921421e−01 |
| CD3 on CD4 regulatory T cell \|\| id:ebi-a-GCST90001868 | Inverse variance weighted (fixed effects) | 3 | 0.90 (0.81 to 1.00) | 4.626433e−02 |
| CD80 on myeloid Dendritic Cell \|\| id:ebi-a-GCST90002035 | Inverse variance weighted (multiplicative random effects) | 4 | 1.23 (1.04 to 1.44) | 1.293073e−02 |
| CD80 on myeloid Dendritic Cell \|\| id:ebi-a-GCST90002035 | Inverse variance weighted | 4 | 1.23 (1.03 to 1.47) | 2.542154e−02 |
| CD80 on myeloid Dendritic Cell \|\| id:ebi-a-GCST90002035 | MR Egger | 4 | 1.08 (0.65 to 1.79) | 8.013926e−01 |
| CD80 on myeloid Dendritic Cell \|\| id:ebi-a-GCST90002035 | Inverse variance weighted (fixed effects) | 4 | 1.23 (1.03 to 1.47) | 2.542154e−02 |
| CD80 on CD62L+ myeloid Dendritic Cell \|\| id:ebi-a-GCST90002036 | Inverse variance weighted (multiplicative random effects) | 3 | 1.31 (1.21 to 1.42) | 9.355137e−11 |
| CD80 on CD62L+ myeloid Dendritic Cell \|\| id:ebi-a-GCST90002036 | Inverse variance weighted | 3 | 1.31 (1.07 to 1.60) | 8.325983e−03 |
| CD80 on CD62L+ myeloid Dendritic Cell \|\| id:ebi-a-GCST90002036 | MR Egger | 3 | 1.17 (0.71 to 1.94) | 6.471214e−01 |
| CD80 on CD62L+ myeloid Dendritic Cell \|\| id:ebi-a-GCST90002036 | Inverse variance weighted (fixed effects) | 3 | 1.31 (1.07 to 1.60) | 8.325983e−03 |
| CD4RA on Terminally Differentiated CD4+ T cell \|\| id:ebi-a-GCST90002099 | Inverse variance weighted (multiplicative random effects) | 3 | 0.90 (0.86 to 0.94) | 1.458536e−05 |
| CD4RA on Terminally Differentiated CD4+ T cell \|\| id:ebi-a-GCST90002099 | Inverse variance weighted | 3 | 0.90 (0.82 to 0.99) | 2.326823e−02 |
| CD4RA on Terminally Differentiated CD4+ T cell \|\| id:ebi-a-GCST90002099 | MR Egger | 3 | 0.89 (0.78 to 1.02) | 3.337799e−01 |
| CD4RA on Terminally Differentiated CD4+ T cell \|\| id:ebi-a-GCST90002099 | Inverse variance weighted (fixed effects) | 3 | 0.90 (0.82 to 0.99) | 2.326823e−02 |
| CD8 on CD28− CD8+ T cell \|\| id:ebi-a-GCST90002120 | Inverse variance weighted (multiplicative random effects) | 3 | 0.76 (0.59 to 0.99) | 4.504259e−02 |
| CD8 on CD28− CD8+ T cell \|\| id:ebi-a-GCST90002120 | Inverse variance weighted | 3 | 0.76 (0.59 to 0.99) | 4.504259e−02 |
| CD8 on CD28− CD8+ T cell \|\| id:ebi-a-GCST90002120 | MR Egger | 3 | 0.14 (0.02 to 1.22) | 3.254886e−01 |
| CD8 on CD28− CD8+ T cell \|\| id:ebi-a-GCST90002120 | Inverse variance weighted (fixed effects) | 3 | 0.76 (0.60 to 0.97) | 2.790228e−02 |
| CD8 on CD39+ CD8+ T cell \|\| id:ebi-a-GCST90002121 | Inverse variance weighted (multiplicative random effects) | 5 | 0.83 (0.71 to 0.96) | 1.057587e−02 |
| CD8 on CD39+ CD8+ T cell \|\| id:ebi-a-GCST90002121 | Inverse variance weighted | 5 | 0.83 (0.69 to 0.99) | 4.143381e−02 |
| CD8 on CD39+ CD8+ T cell \|\| id:ebi-a-GCST90002121 | MR Egger | 5 | 0.74 (0.36 to 1.54) | 4.859771e−01 |
| CD8 on CD39+ CD8+ T cell \|\| id:ebi-a-GCST90002121 | Inverse variance weighted (fixed effects) | 5 | 0.83 (0.69 to 0.99) | 4.143381e−02 |




*OR for Eating disorders per SD increase in risk factor (95% confidence interval)*




**Figure 3.** The forest plot of the MR result (Immune cells to eating disorders).

### 3.2. Sensitivity analysis result

The heterogeneity test results indicate that our analysis exhibits no significant heterogeneity, as evidenced by Q_pval results consistently exceeding 0.05. This finding underscores the robustness of our study. Additionally, the pleiotropy assessment reveals no apparent pleiotropic effects. The Egger_intercept results are proximate to zero, and the associated pval results are all above 0.05, further substantiating the robustness of our research findings. Details are shown in Supplementary materials.

### 3.3. Leave-one-out plot detection result

Owing to the result of the Leave-one-out plot analysis, we ascertained that the inference regarding the potential causal connection between 20 types of immune cells and eating disorders is reliable and robust. The utilization of a diverse array of Mendelian randomization (MR) methods contributed to the precision and efficacy of our findings. Details are shown in **Figures 4–8**.

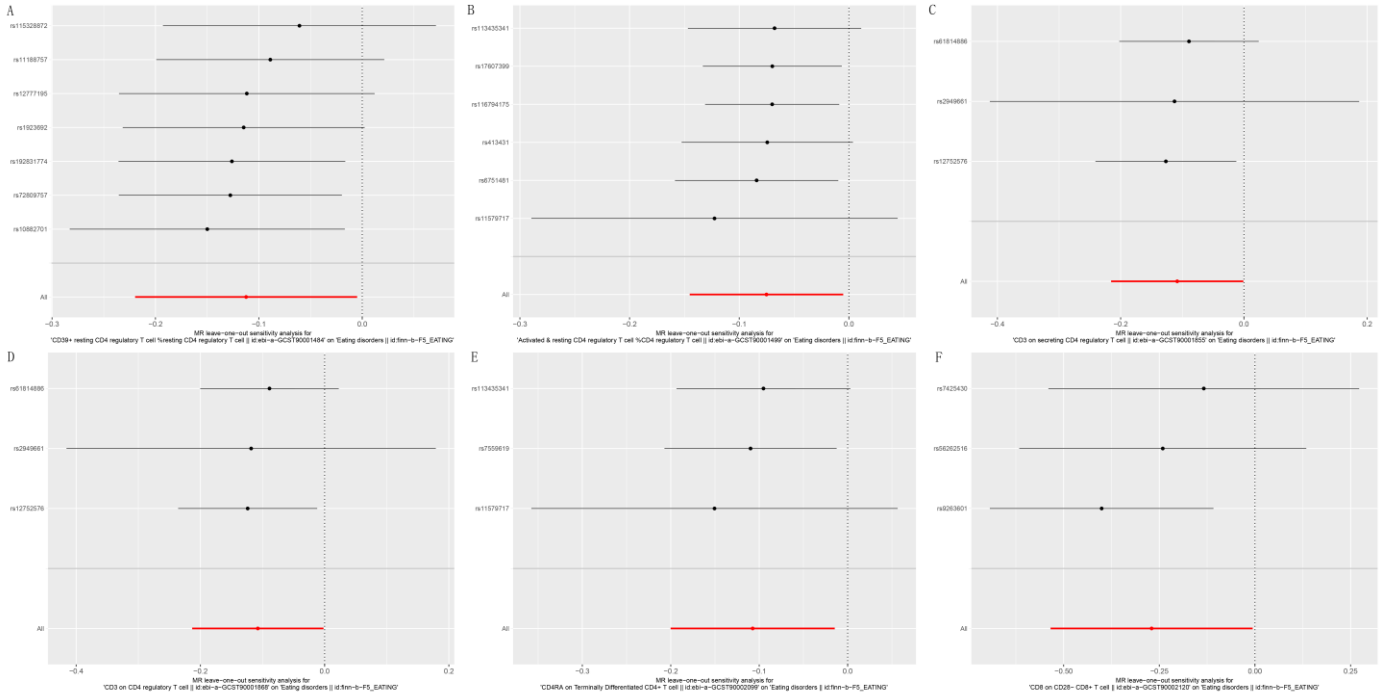



**Figure 4.** Leave-one-out plot result (Immune cells to eating disorders: As protection factors). **(A)** CD39+ resting CD4 regulatory T cell %resting CD4 regulatory T cell; **(B)** Activated & resting CD4 regulatory T cell %CD4 regulatory T cell; **(C)** CD3 on secreting CD4 regulatory T cell; **(D)** CD3 on CD4 regulatory T cell; **(E)** CD4RA on Terminally Differentiated CD4+ T cell; **(F)** CD8 on CD28− CD8+ T cell.

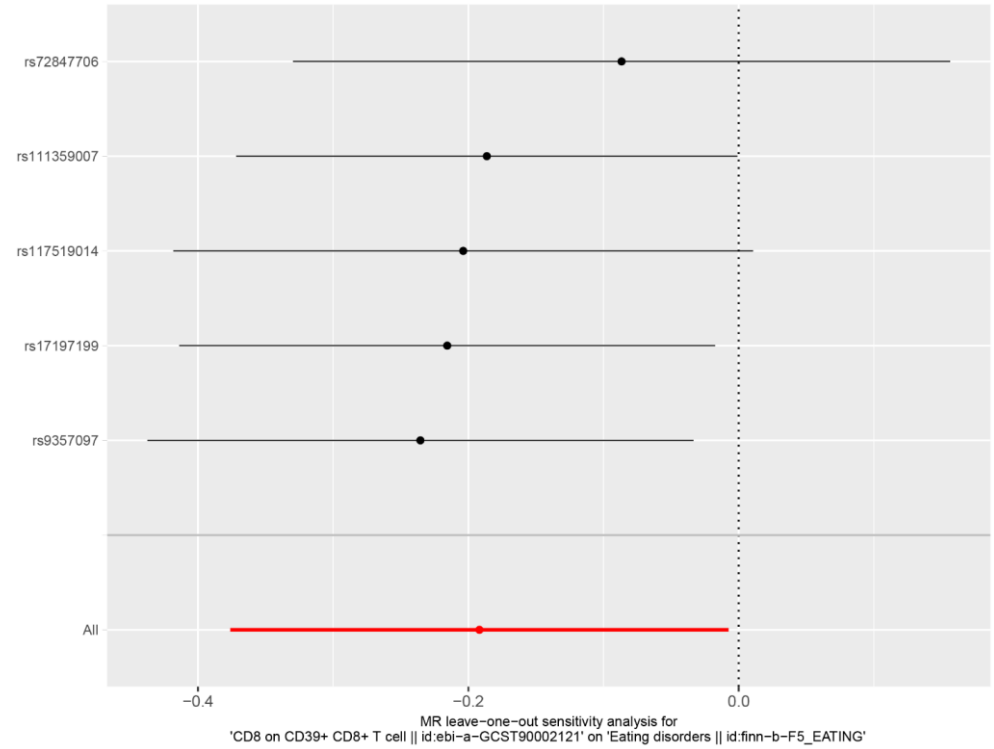



**Figure 5.** Leave-one-out plot result (Immune cells to eating disorders: As protection factors).

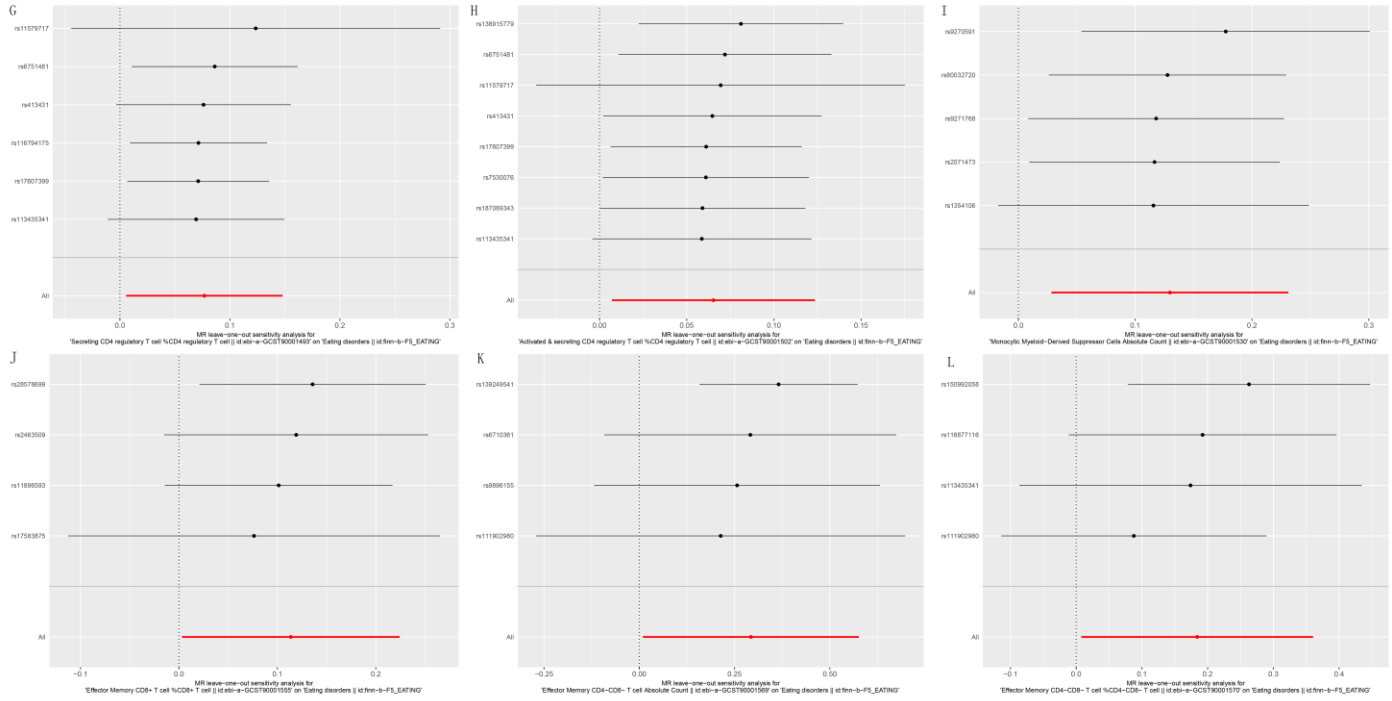



**Figure 6.** Leave-one-out plot result (Immune cells to eating disorders: As risk factors). (G: Secreting CD4 regulatory T cell %CD4 regulatory T cell, H: Activated & secreting CD4 regulatory T cell %CD4 regulatory T cell, I: Monocytic Myeloid-Derived Suppressor Cells Absolute Count, J: Effector Memory CD8+ T cell %CD8+ T cell, K: Effector Memory CD4−CD8− T cell Absolute Count, L: Effector Memory CD4−CD8− T cell %CD4−CD8− T cell).

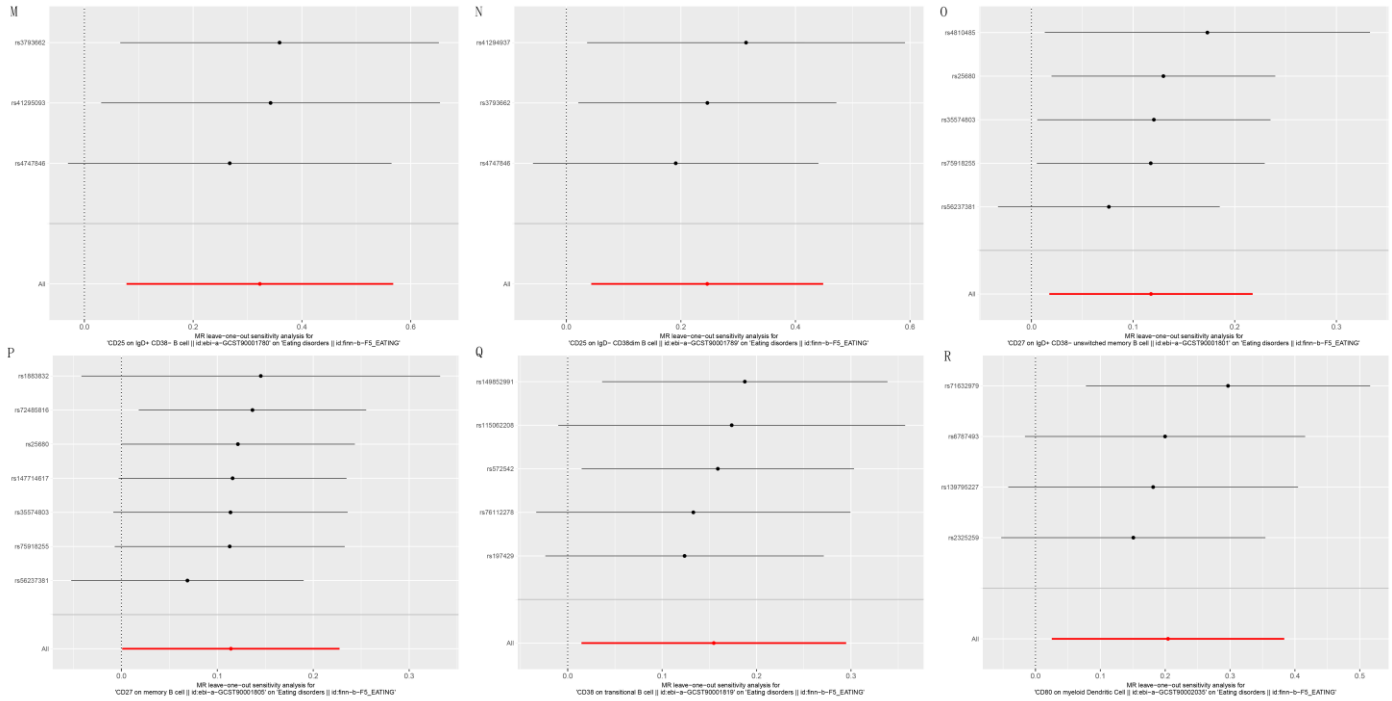



**Figure 7.** Leave-one-out plot result (Immune cells to eating disorders: As risk factors). (M: CD25 on IgD+ CD38− B cell, N: CD25 on IgD− CD38dim B cell, O: CD27 on IgD+ CD38− unswitched memory B cell, P: CD27 on memory B cell, Q: CD38 on transitional B cell, R: CD80 on myeloid Dendritic Cell).

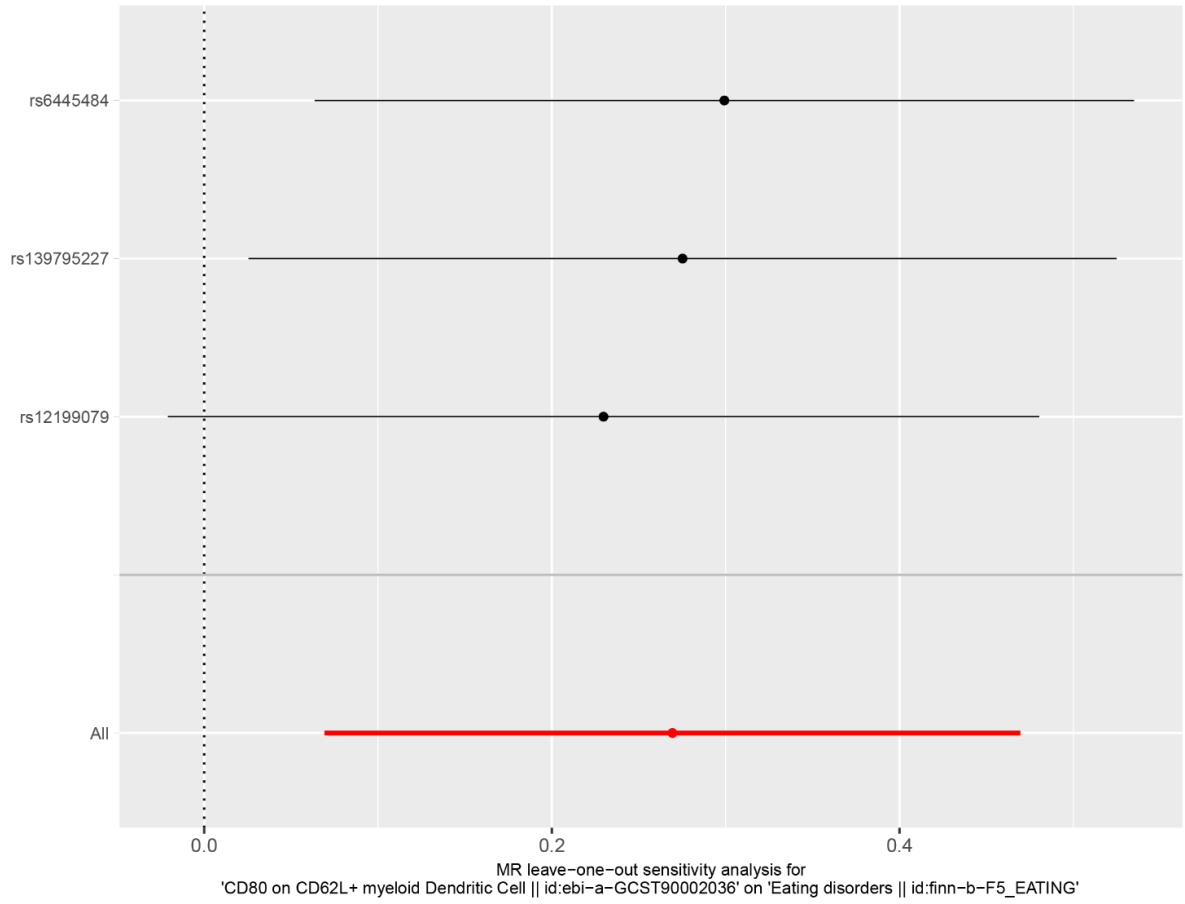



**Figure 8.** Leave-one-out plot result (Immune cells to eating disorders: As risk factors).

## 4. Discussion

In this study, we investigate the causal relationships between 731 genetically proxied immune cell traits and eating disorders through a Mendelian randomization design. Our study suggests that CD39+ resting CD4 regulatory T cell %resting CD4 regulatory T cell, Activated & resting CD4 regulatory T cell %CD4 regulatory T cell, CD3 on secreting CD4 regulatory T cell, CD3 on CD4 regulatory T cell, CD4RA on Terminally Differentiated CD4+ T cell, CD8 on CD28− CD8+ T cell and CD8 on CD39+CD8+T cell are associated with a reduced risk of eating disorders. While phenotypes of Secreting CD4 regulatory T cell %CD4 regulatory T cell, Activated & secreting CD4 regulatory T cell %CD4 regulatory T cell, Monocytic Myeloid-Derived Suppressor Cells Absolute Count, Effector Memory CD8+ T cell %CD8+ T cell, Effector Memory CD4−CD8− T cell Absolute Count, Effector Memory CD4−CD8− T cell %CD4−CD8− T cell,CD25 on IgD+ CD38− B cell, CD25 on IgD− CD38dim B cell, CD27 on IgD+ CD38− unswitched memory B cell, CD27 on memory B cell, CD38 on transitional B cell, CD80 on myeloid Dendritic Cell and CD80 on CD62L+ myeloid Dendritic Cell increases the risk of Eating disorders. To our knowledges, this study represents the first MR investigation for exploring causal links between immune cell traits and eating disorders. These findings can provide help for future clinical practice.

Our study is exploratory, leveraging a two-sample MR analysis based on openly published large GWAS datasets, which enhances its statistical efficiency. The goal was to elucidate the connection between immune cell traits and eating disorders, potentially offering new perspectives on the pathophysiology of these disorders and identifying novel risk factors or protective mechanisms. Notably, our study did not exhibit horizontal pleiotropy or heterogeneity, indicating the robustness of our results.

The immune system's involvement in eating disorders is complex and multifaceted. Regulatory T cells (Tregs), particularly the CD4+ subset, are crucial in maintaining immune tolerance and preventing autoimmune responses [18,19]. Our finding that increased proportions of CD39+ resting CD4+ Tregs and other CD4+ Treg subsets correlate with a reduced risk of eating disorders suggests that these cells might play a protective role, potentially by modulating inflammatory responses that could contribute to the pathogenesis of these disorders.

On the other hand, immune cells such as monocytic MDSCs [20], which are known for their immunosuppressive properties, were associated with an increased risk of eating disorders. This paradoxical finding might indicate that while these cells suppress immune responses, their presence in higher numbers could reflect an underlying state of chronic inflammation or immune dysregulation, contributing to eating disorder pathology [21].

Effector memory T cells, both CD8+ and CD4−CD8−, were also linked to increased risk. These cells are involved in the rapid response to previously encountered antigens and their heightened presence might suggest a state of immune activation or chronic immune stress, potentially influencing neural circuits involved in eating behavior [22].

B cell markers such as CD25 and CD27, which are indicative of activated and memory B cells, were also associated with an increased risk of eating disorders. This

could point towards a role of humoral immunity and possibly autoantibodies in the development of these conditions. Similarly, the expression of activation markers like CD80 on myeloid dendritic cells, which are pivotal in antigen presentation and T cell activation, suggests that heightened immune activation and antigen presentation might contribute to the risk of developing eating disorders. Our findings also corroborate existing literature on the vital role of immune cells in mental health [23–29], particularly highlighting Tregs' function in suppressing neuroinflammation and maintaining nervous system health [30]. Clinically, these insights suggest potential strategies for modulating the immune system to treat eating disorders and May become an early screening biomarker, potentially improving patient outcomes.

Despite the robustness of our findings, several limitations must be acknowledged. Firstly, our analysis was confined to data from European populations, which limits the generalizability of our results to other ethnic groups. Future studies should aim to include more diverse populations to validate and extend our findings. Secondly, the broad categorization of eating disorders in our study precludes the ability to distinguish between different types, such as anorexia nervosa, bulimia nervosa, and binge-eating disorder. Each subtype may have distinct pathophysiological mechanisms and immune profiles. Further research should aim to disaggregate these disorders to understand subtype-specific immune mechanisms. Our study identified specific immune cell types as potential risk or protective factors in eating disorders opens new avenues for therapeutic interventions. Our findings suggest that modulating the activity of these immune cells could be a promising approach for developing novel treatments and early detection methods.

In conclusion, our study provides novel insights into the potential causal relationships between immune cell traits and eating disorders. These findings highlight the importance of immune regulation in the pathogenesis of eating disorders and suggest new avenues for research and therapeutic intervention. Future studies should continue to explore these relationships in diverse populations and across different types of eating disorders to further elucidate the underlying mechanisms.

## 5. Conclusion

Through the application of the Mendelian randomization method, it has been identified that there are 20 distinct types of immune cells that may potentially be associated with eating disorders. This discovery has the potential to offer valuable insights and additional information that could prove beneficial in guiding clinical practice and enhancing our understanding of the underlying mechanisms linking immune function to the development of eating disorders. By providing clinicians with a broader perspective on the immunological factors that may contribute to these conditions, this research may aid in the development of more targeted and effective treatment strategies in the future.

**Supplementary materials:** Heterogeneity test result and Pleiotropy test result are shown in Supplementary materials (Table S1-Table S2).

**Author contributions:** Write the manuscript, KZ; perform the quality assessment, KZ; design the project, KZ; perform the statistical analysis, KZ; revision of the

manuscript, ZD and YT; review the results, ZD and YT; conceptualization, KZ; methodology, KZ; writing—review and editing, ZD and YT; visualization, KZ. All authors have read and agreed to the published version of the manuscript.

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**Data availability statement:** The datasets presented in this study can be found in online repositories (https://gwas.mrcieu.ac.uk/). The names of the repository/repositories a can be found in the article.

**Ethical approval:** Not applicable.

**Conflict of interest:** The authors declare no conflict of interest.

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