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# High rates of mood disorders in patients with chronic idiopathic eosinopenia

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ABSTRACT

*Background:* Mood disorders (MD) are multifactorial disorders. Identifying new biomarkers for the early diagnosis of MD and predicting response to treatment is currently a significant research topic. Both eosinopenia and MD are associated with increased activity of the hypothalamic-pituitary-adrenal axis. The present study, therefore, used a clear definition of chronic idiopathic eosinopenia (CIE) to determine the rate of MD in a large cohort of individuals with CIE.

*Methods:* This retrospective population-based, case-control study uses data of seven consecutive years from the database of Leumit Health Services (LHS) - a nationwide health maintenance organization in Israel.

*Results:* Participants were 13928 LHS members with CIE and 27858 negative controls. The CIE group exhibited significantly higher rates of MD than the control group throughout the whole study period, except for atypical depressive disorder at baseline.

*Conclusions:* CIE might be associated with a higher prevalence of MD. Further basic research should elucidate the pathophysiologic mechanisms linking CIE and MD.

## 1. Introduction

Chronic eosinophil count abnormalities in circulating blood are frequent. The most common anomaly, eosinophilia, is well-known. Its causes are varied and are mostly related to bacterial and parasitic infections, but may also be associated with allergic diseases, use of specific medications, endocrine abnormalities, hematopoietic and epithelial neoplasms, vasculitis and hypereosinophilic syndrome (Butt et al., 2017; Tzankov et al., 2023). Eosinopenia, the other abnormality in eosinophil count, is less researched, especially chronic eosinopenia. Most existing research is on eosinopenia that results from corticosteroid therapy and stress (Boumpas et al., 1991; Hong et al., 2020; Karakonstantis et al., 2018; Khoury et al., 2018).

Mood disorders (MD) are multifactorial (Lynch et al., 2020; Su and Si, 2022). Diagnosis of MD is based on phenotypic evaluation, which results in high misdiagnosis rates (Malhi and Mann, 2018). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), MD diagnosis requires the presence of five or more symptoms from the list of diagnostic criteria lasting for at least two weeks, with the patient demonstrating evident distress or functional impairment (American Psychiatric Association, 2013).

In recent decades, various pathophysiological hypotheses have been proposed for MD, including the inflammatory hypothesis and the hypothalamic-pituitary-adrenal axis (HPAA) over-activity hypothesis (Milaneschi et al., 2020; Stetler and Miller, 2011). Identifying new biological biomarkers for early diagnosis of MD and means of predicting response to antidepressant treatment have become attractive research topics in the field of depression in recent years.

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**Table 1**
Baseline clinical and laboratory data of individuals with chronic idiopathic eosinophilia compared to healthy controls.

| Variable | Patients with CIE N = 13929 | Control Group N = 27858 | p |
|---|---|---|---|
| Sex; Female, n (%) | 11,207 (80.5 %) | 22,413 (80.5 %) | 1 |
| Age; (years) (mean ± SD) | 40.38 ± 15.98 | 40.01 ± 16.28 | 1 |
| Body mass index, kg/m$^2$ (mean ± SD) | 25.94 ± 5.66 | 25.92 ± 5.66 | 0.886 |
| Smoking, n (%) | 217 (12.9 %) | 451 (15.9 %) | 0.649 |
| Hypertension, n (%) | 962 (8.3 %) | 1901 (9.0 %) | 0.758 |
| Diabetes, n (%) | 681 (4.9 %) | 1468 (5.3 %) | 0.101 |
| **Laboratory** | | | |
| WBC, (cells × 10$^9$/L) (median [IQR]) | 5.97 [4.98–7.19] | 6.47 [5.37–7.78] | <0.001 |
| Neutrophils, (cells × 10$^9$/L) (median [IQR]) | 3.71 [2.18–6.88] | 4.20 [2.02–9.01] | 0.160 |
| Neutrophils, (%) (median [IQR]) | 60.00 [47.00–70.00] | 60.00 [43.00–73.00] | 0.923 |
| Lymphocytes, (cells × 10$^9$/L) (median [IQR]) | 1.69 [1.22–2.41] | 1.64 [1.13–2.50] | 0.385 |
| Lymphocytes, (%) (median [IQR]) | 28.75 [17.00–39.00] | 26.00 [15.00–40.00] | 0.085 |
| Eosinophils, (cells × 10$^9$/L) (median [IQR]) | 0.03 [0.02–0.04] | 0.08 [0.05–0.15] | <0.001 |
| Eosinophils, (%) (median [IQR]) | 0.38 [0.26–0.054] | 1.30 [0.80–2.30] | <0.001 |
| Basophils (cells × 10$^9$/L), (median [IQR]) | 0.02 [0.01–0.03] | 0.02 [0.01–0.03] | 0.414 |
| Basophils, (%) (median [IQR]) | 1.00 [1.00–1.00] | 1.00 [1.00–1.00] | 0.247 |
| Monocytes, (cells × 10$^9$/L) (median [IQR]) | 0.44 [0.30–0.70] | 0.45 [0.32–0.68] | 0.835 |
| Monocytes, (%) (median [IQR]) | 7.00 [5.00–9.00] | 7.00 [4.00–10.00] | 0.521 |
| Platelets (cells × 10$^9$/L) (median [IQR]) | 226.00 [189.00–266.00] | 237.00 [201.00–279.00] | <0.001 |
| MPV (fL) (median [IQR]) | 11.10 [10.50–11.80] | 11.10 [10.50–11.80] | 0.146 |
| Glucose (mg/dL), (median [IQR]) | 90.40 [83.90–99.70] | 91.40 [84.20–102.35] | 0.096 |
| TSH (0.35–4.94 mIU/L) (median [IQR]) | 1.76 [1.20–2.59] | 1.70 [1.13–2.46] | <0.001 |
| TPO (median [IQR]) | 10.30 [10.00–238.12] | 10.30 [10.00–85.85] | 0.664 |
| The number of patients who underwent the test | 1107 (7.95 %) | 2290 (8.22 %) | 0.401 |
| C-reactive protein (mg/L) (median [IQR]) | 2.50 [1.00–6.14] | 3.00 [1.10–7.50] | <0.001 |
| The number of patients who underwent the test | 10149 (72.86 %) | 19817 (71.14 %) | 0.003 |
| ESR (mm/h), (median [IQR]) | 18.00 [11.00–29.00] | 20.00 [11.00–32.00] | <0.001 |
| The number of patients who underwent the test | 6093 (43.74 %) | 11859 (42.57 %) | 0.027 |
| C3 (g/dL), (median [IQR]) | 117.00 [103.25–137.00] | 125.00 [108.00–144.00] | 0.006 |
| The number of patients who underwent the test | 1423 (10.21 %) | 2463 (8.84 %) | <0.001 |
| C4 (g/dL), (median [IQR]) | 29.00 [23.00–36.00] | 31.75 [26.00–39.00] | <0.001 |
| The number of patients who underwent the test | 1423 (10.21 %) | 2463 (8.84 %) | <0.001 |
| Antinuclear antibodies positive (>1:80), n (%) | 182 (1.3 %) | 245 (0.9 %) | <0.001 |
| The number of patients who underwent the test | 2781 (19.97 %) | 5132 (18.42 %) | <0.001 |
| Rheumatoid factor (0–20 IU/ml), (median [IQR]) | 10.00 [7.00–10.00] | 10.00 [7.00–10.00] | 0.885 |
| The number of patients who underwent the test | 2556 (18.35 %) | 4880 (17.52 %) | 0.038 |
| IgE (U/mL) (median [IQR]) | 24.40 [10.70–67.30] | 53.60 [19.50–174.50] | <0.001 |
| The number of patients who underwent the test | 741 (5.32 %) | 1613 (5.79 %) | 0.051 |

**Abbreviations**: C3 - complement component 3; C4 - complement component 4; CIE – chronic idiopathic eosinophilia; ESR - Erythrocyte Sedimentation Rate; IgE - Immunoglobulin E; IQR - interquartile range; MPV – mean platelet volume; TPO - Thyroid Peroxidase; TSH - thyroid stimulating hormone; WBC – white blood cells.

Eosinopenia is mainly seen as a secondary phenomenon and primary or idiopathic eosinopenia is considered an uncommon hematological finding. Chronic idiopathic eosinopenia (CIE) rarely has clinical consequences (Gleich et al., 2013).

HPAA represents a central neuroendocrine pathway in the response of one's body to psychosocial stress and is expressed in humans by elevated levels of blood cortisol (Ostinelli et al., 2021). The decrease in circulating eosinophil counts during HPAA activation was previously reported (Lengyel, 1964) and may be relevant to the emergence of depression.

There is no accepted definition of CIE. The present study defines CIE as a hematological condition characterized by at least two documented eosinophil counts lower than 0.05 cells × 10$^9$/L (Magen, E., Vinker-Shuster, M., Merzon, E., Green, I., Magen, I., Golan-Cohen, A., & Israel, A. (2024). Chronic idiopathic eosinopenia, allergic and autoimmune disorders. *The journal of allergy and clinical immunology. In practice*, S2213-2198(24)00341-6. Advance online publication. https://doi.org/10.1016/j.jaip.2024.03.048). This condition should not result from medication use and exist without a known infection or current illness. In veterinary medicine, eosinophilia (Gulland et al., 2012) and eosinopenia (Oh et al., 2022) are considered cost-effective diagnostic biomarkers pointing to suppression or activation of the HPAA or bloodstream infection (Abidi et al., 2008; Setterberg et al., 2004; Wibrow et al., 2011).

Unfortunately, there are, as yet no data suggesting the connection between immune dysregulation and hyperactivity of HPAA. Moreover, the database we used did not include data on levels of markers of HPAA that can support the objectivity of our claim. However, a recent study by Goltser-Dubner et al. (2023) shows that long-term perturbation in the expression of immune cell glucocorticoid response transcripts persists among young adults who develop PTSD following exposure to life threatening stress in childhood. This gene expression indicates chronic dysregulation of immune stress reactivity in PTSD, which is often associated with MD (Megan S Chesin, 2024, Alexandra Martalek, 2024).

Since both eosinopenia and MD are associated with dysregulation of the HPAA (Chin Fatt et al., 2023; Steffen et al., 2024), we assessed, in the present study, the rate of MD in a large cohort of individuals with CIE, where CIE is defined as above.

## 2. Materials and methods

### 2.1. Participants

This study is a retrospective population-based study using data from the electronic health records (EHRs) of Leumit Health Services (LHS), a large nationwide healthcare provider in Israel with about 720,000 members. The LHS EHR database is centrally managed and continuously updated regarding individuals' demographics, medical diagnoses, medical encounters, pharmacotherapy, hospitalizations, and laboratory tests. All LHS members have health insurance and healthcare access. According to the International Classification of Diseases 9th revision (ICD-9), a diagnosis is entered or updated during each physician visit. The validity of chronic diagnoses in the registry has been previously examined and confirmed as being high (Hamood et al., 2016; Rennert

**Table 2**
Rates of mood disorders in individuals with CIE vs. controls.

| | CIE N (%) n = 13929 | Controls N (%) n = 27858 | OR (95%CI) | p |
|---|---|---|---|---|
| ***AT BASELINE*** | | | | |
| F31 - F31.9 Bipolar affective disorder | 62 (0.45 %) | 56 (0.20 %) | 2.29 [1.59–3.28] | <0.001 |
| F32 - F33.9 Depressive episodes, single or recurrent | 277 (1.99 %) | 406 (1.46 %) | 1.37 [1.18–1.60] | <0.001 |
| 296.2–298.33 Major Depressive Disorder | 57 (0.41 %) | 68 (0.24 %) | 1.73 [1.21–2.46] | 0.002 |
| 296.82 Atypical depressive disorder | 25 (0.18 %) | 29 (0.10 %) | 1.73 [0.97–3.05] | 0.059 |
| ***AFTER* 1 YEAR** | | | | |
| F31 - F31.9 Bipolar affective disorder | 79 (0.56 %) | 71 (0.25 %) | 2.30 [1.67–3.17] | <0.001 |
| F32 - F33.9 Depressive episodes, single or recurrent | 347 (2.49 %) | 521 (1.86 %) | 1.34 [1.17–1.54] | <0.001 |
| 296.2–298.33 Major Depressive Disorder | 98 (0.70 %) | 84 (0.32 %) | 2.34 [1.75–3.14] | <0.001 |
| 296.82 Atypical depressive disorder | 27 (0.19 %) | 29 (0.10 %) | 1.86 [1.06–3.26] | 0.023 |
| ***AFTER 5 YEARS*** | | | | |
| F31 - F31.9 Bipolar affective disorder | 126 (0.90 %) | 103 (0.37 %) | 2.45 [1.89–3.19] | <0.001 |
| F32 - F33.9 Depressive episodes, single or recurrent | 739 (5.31 %) | 985 (3.52 %) | 1.45 [1.32–1.59] | <0.001 |
| 296.2–298.33 Major Depressive Disorder | 116 (0.83 %) | 107 (0.38 %) | 2.17 [1.67–2.83] | <0.001 |
| 296.82 Atypical depressive disorder | 49 (0.35 %) | 54 (0.19 %) | 1.82 [1.23–2.68] | 0.003 |
| ***AFTER 7 YEARS*** | | | | |
| F31 - F31.9 Bipolar affective disorder | 257 (1.84 %) | 139 (0.50 %) | 3.74 [3.04–4.61] | <0.001 |
| F32 - F33.9 Depressive episodes, single or recurrent | 988 (7.09 %) | 1119 (4.25 %) | 1.83 [1.67–1.99] | <0.001 |
| 296.2–298.33 Major Depressive Disorder | 147 (1.05 %) | 132 (0.47 %) | 2.24 [1.77–2.84] | <0.001 |
| 296.82 Atypical depressive disorder | 55 (0.40 %) | 67 (0.24 %) | 1.64 [1.13–2.37] | 0.007 |

and Peterburg, 2001).

Data was collected using IBM Cognos Business Intelligence 10.1.1 BI Report Studio software (IBM Corp., Ottawa, ON, Canada). Query results were downloaded into a Microsoft Excel spreadsheet (v. 14; Microsoft Corp., Redmond, WA, US) for statistical analyses.

Baseline data regarding the studied population were extracted from January 1, 2014, to December 31, 2021. All the clinical diagnoses were based on ICD-9 codes. The study population consisted of all LHS members aged 12–99 years (mean age 40.38 ± 15.98 years) between January 1, 2014, and December 31, 2021. The diagnostic criteria for MD are primarily designed for adults and adolescents, making them more applicable and reliable for individuals 12 years and older. Moreover, eosinophil counts can vary by age. By 12 years old, these levels are more likely to have stabilized and be comparable to adult levels (Hartl et al., 2020). Additionally, by that age, diagnosis of MD also tends to be reliable (Miola et al., 2022; Solmi et al., 2022).

We retrieved data from the LHS electronic database for patients with at least three blood counts with eosinophils <0.05 cells × $10^9$/L for two consecutive years. Patients were considered as having comorbid MD if their record included two ICD-9-CM diagnosis codes in the range of 296.21–296.36 within one year. This approach was shown to have 61.4% sensitivity and 94.3% specificity for identifying patients with MD (Doktorchik et al., 2019).

Exclusion criteria for this study consisted of any systemic autoimmune disease, hematological disease or malignancy, as well as acute or chronic liver disease, chronic heart failure, kidney failure, history of surgery or major physical trauma during the previous three months, any acute or chronic infection, use of antibiotics within the previous two months, treatment with any corticosteroid or immunosuppressive medication, total white blood count (WBC) < 4.5 cells × $10^9$/L, lymphocyte count of <1.5 cells × $10^9$/L, active treatment with thionamides and any anti-inflammatory or antiseizure medications that may affect blood counts.

Historically, patients with CIE have undergone comprehensive immune tests, including antinuclear antibody (ANA), thyroid peroxidase (TPO) antibodies, rheumatoid factor, and complement levels, to rule out underlying autoimmune or systemic diseases. Nowadays, in routine clinical practice, comprehensive immune immunological profiling is applied only when specific symptoms or clinical suspicions of autoimmune or systemic conditions are present. Regarding the participants in the current study, the decision to perform these tests was based on clinical indications and physician discretion.

The control group included randomly selected subjects from the same electronic database in a ratio of 2:1. Controls were matched individually by age, sex, socioeconomic status (SES), and sector. The 2:1 ratio of controls to cases was chosen based on several considerations aimed at enhancing the statistical power of our study, while maintaining a balance between robustness and feasibility. Specifically, this ratio allows for a more accurate estimation of the association between CIE and MD by increasing the precision of the estimated effect sizes and confidence intervals.

The decision was also influenced by practical considerations. A higher number of controls increases the likelihood of detecting true associations, particularly in a retrospective study where the variability in historical data have the potential to dilute significant findings. Additionally, using a larger control group helps to better account for potential confounders and variability in the general population, which is crucial for studies involving complex traits such as MD and hematological conditions.

We considered a range of ratios and concluded that a 2:1 ratio offers a good compromise between achieving sufficient statistical power and the resource constraints inherent in handling large datasets, especially when considering the extensive data management and analysis involved.

### 2.2. Ethical considerations

This study was conducted following the Code of Ethics of the World Medical Association. The study was approved by the institutional review committees of the Asaf-HaRofe Medical Center and the LHS (approval number: 393-20- LEU). Due to the retrospective nature of this study and the fact that the data used for the study was in digital files and anonymous, the need for informed consent was waived.

### 2.3. Assessment of blood eosinophil counts

In the LHS's central laboratory, absolute peripheral blood eosinophil counts were measured with an automated hematology analyzer (XT-2000i, Sysmex, Kobe, Japan). Automated hematology analyzers are generally reliable for eosinophil counts, providing high accuracy and consistency (Chinudomwong et al., 2021; Ferrero-Vacher et al., 1997). The Sysmex XT-2000i uses fluorescent flow cytometry and

hydrodynamic focusing technologies, along with sophisticated algorithms, to provide highly reliable eosinophil counts (Hill et al., 2009).

Eosinopenia was defined by a cutoff of less than $0.05 \times 10^9$/L, which is the most commonly used definition (Hirosawa et al., 2020; Lin et al., 2021).

### 2.4. Statistical analyses

Standard descriptive statistics were used to present the demographic characteristics of individuals included in the study. Continuous data are presented as either mean ± SD or median with an interquartile range (IQR), depending on the data distribution. The two-sided Wilcoxon rank sum test was used to compare continuous variables, and Fisher's exact test was used to compare categorical variables. All tests were two-sided, with statistical significance set at $P < 0.05$. The odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression analysis. Statistical analyses were performed with R v. 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

### 3.1. Demographic, clinical, and laboratory characteristics of the study participants

Age, sex, clinical, and laboratory data of the 13929 individuals with CIE and 27858 controls without a diagnosis of CIE are shown in Table 1. There were no significant differences in sex, age, and BMI distribution between the two groups.

As may be seen in Table 1, total IgE levels were significantly lower in the CIE group than in the control group. The CIE group demonstrated lower levels of C-reactive protein, C3, C4, WBC, and platelet counts than the control group. TSH levels were slightly but significantly higher in the CIE group than in the control group.

Antinuclear antibody (ANA) was detected in 182 individuals (1.3 %) from the CIE group and in 245 controls (0.9 %) ($p < 0.001$).

### 3.2. Mood disorders in individuals with CIE compared to controls without CIE

The prevalence of MD in individuals with CIE compared to controls without CIE is shown in Table 2. Significant differences were found in the rate of MD between the two groups during the seven study years.

The differences between the rates of mood disorder, both unipolar and bipolar, between the CIE group and the controls were significant at baseline. They remained significant after one, five, and seven years. The most robust and consistent results at all time points were found for bipolar affective disorder" (Table 2).

The rates of MD differ significantly from the control group throughout the study period (Table 2), except for 296.82 - Atypical Depressive Disorder at baseline ($P = 0.059$).

## 4. Discussion

The main finding of the present study is the association throughout the study period of CIE with a higher prevalence of MD, both unipolar and bipolar, and especially with bipolar affective disorder. This study is consistent with previous studies that described various changes in peripheral blood leukocyte distribution in patients with MD, including secondary eosinopenia (Darko et al., 1988; Foley É et al., 2023).

CIE is considered a rare clinical condition (Chusid, 2018). In the present study, of the 720000 members of LHS who were screened for CIE over 10 years, and after excluding the secondary forms of eosinophil depletion, 13928 (1.93 %) were identified with CIE. In a United Kingdom study, CIE was present in 44,112 individuals, who constitute 5% of the general population of 775,231 (Shah et al., 2016). This study concluded that low eosinophil counts are associated with increased short-term incidence of heart failure and coronary death. Conversely, in a review Gleich et al. (2013) argue that in most mammals (humans and animal models) with CIE, the condition has no apparent health consequences.

In our study, the observed association between CIE and higher rates of MD suggests a potential clinical relevance of CIE that extends beyond the traditionally understood scope of this condition. We propose several explanations for our findings: One possibility is that due to limited prior research focusing on the psychiatric implications of CIE, these implications may have been under-recognized. Another possibility is that our study's robust methodology, featuring a large sample and detailed data analysis, from a well-maintained electronic health record system, reveals associations not evident in previous smaller or less detailed studies. Yet another possibility is that the variations in the prevalence and impact of CIE observed in our findings stem from the differences in the demographic and geographic characteristics of our study population, including genetic, environmental, and lifestyle factors,

Although speculative, the possibility exists that CIE results from autoimmune processes that destroy eosinophils in the peripheral blood, mediated by activation of IgE, IgG, and anti-IgA autoantibodies (Kolkhir et al., 2022).

Notably, 80.5 % of our individuals with CIE were females. We have no scientific explanation for the female sex predominance in our CIE group. One may hypothesize that estrogens can decrease bone marrow eosinophil numbers, interfering significantly with TGC-induced eosinophil blood mobilization (Douin-Echinard et al., 2011).

Eosinophils have been implicated in many pathological conditions, notably allergic, autoimmune, and inflammatory diseases, characterized by eosinophil accumulation in tissues. Chronic mental stress can activate the hypothalamic-pituitary-adrenal axis and the sympathoadrenal medullary system, causing CIE (McCarty et al., 1988; Roth et al., 2012).

Recent literature suggests that HPAA hyperactivity is present in a significant subset of patients with MD, estimated at approximately 30–50% of cases (Ceruso et al., 2020).

Therefore, increased cortisol secretion is considered a biological marker for MD, both in terms of presence and severity (Dziurkowska and Wesolowski, 2021; Kennis et al., 2020). Moreover, HPAA activity was suggested to be a predictor of clinical response to antidepressant treatment (Fischer et al., 2017). Previous pre-clinical and clinical studies have demonstrated significant involvement of stress-induced immune responses in depressive and anxiety disorders (Debnath et al., 2021; Druzhkova et al., 2022). The authors of these studies could not find large-scale epidemiological studies linking low eosinophil counts to MD. Neither could they find clinical studies assessing the relationship between eosinophil suppression due to HPAA activation and MD. Several neuropeptides, which act as neurotransmitters or neuromodulators in the nervous system, may influence the immune system. Still, their role in directly controlling immunoglobulin production, especially IgE, is not as well-established as their influence on Th2 pathway and eosinophil homeostasis (Kalantaridou et al., 2007; Ramirez et al., 2016; Watts, 2005).

Notably, in our study, the OR of the difference between the CIE group and the controls concerning bipolar affective disorders was found to be especially robust ($OR = 2.29$ [1.59–3.28], $p < 0.001$). The observation that people with bipolar disorder demonstrate a significantly higher rate of CIE, may be related to immune activation and neuroinflammation in these patients, suggesting that bipolar disorder may be the mood disorder most influenced by inflammatory mechanisms. (Hochman et al., 2023; Pereira et al., 2021; Solmi et al., 2021).

Notably, recent findings suggest an association between eotaxin-1/CCL11 and aging, neurogenesis impairment, neurodegeneration, and psychiatric disorders (Teixeira et al., 2018). Moreover, in patients with bipolar disorder, immune dysregulation of the eotaxin/CCL11 pathway was found to affect brain pathophysiological mechanisms relevant to the clinical manifestations of the disorder (Barbosa et al., 2013; Panizzutti et al., 2015).

Our study lasted till December 2021, when COVID-19 may have

already influenced the rates of MD observed. We therefore analyzed the COVID-19 infection rates within our study cohorts to determine if the pandemic might have differentially affected the groups in our study. Up to December 2021, COVID-19 infection was documented in 3726 (25.01%) patients with CIE and in 7238 (24.29%) subjects from the control group. The odds ratio (OR) for infection between these groups was 1.04 [95% CI 0.99 to 1.09], with a p-value of 0.098. This analysis suggests that there were no significant differences in the rate of COVID-19 infection between the CIE and control groups. Therefore, while the pandemic's broader effects—such as increased psychological stress and changes in healthcare access may have influenced mood disorder prevalence, the direct impact of COVID-19 infection does not appear to have biased our findings.

We suggest that CIE may have the following clinical implications: 1. Potential biomarker: the association between CIE and autoimmunity in previous research suggests that eosinophil counts could serve as a biomarker for immune system dysregulation (Magen et al., 2024). This may be relevant in patients with MD, as there is growing evidence of immune system involvement in psychiatric conditions. 2. Prediction of treatment response: In patients with autoimmune diseases, CIE was associated with poor response to treatment (Kolkhir et al., 2020). If a similar pattern exists in MD, monitoring eosinophil levels could help predict treatment outcomes and guide therapeutic decisions. 3. Personalized treatment strategies: if CIE in MD are linked to specific patient characteristics and treatment responses, monitoring eosinophil levels in patients with MD may help develop more personalized treatment approaches; 4. Potential for early intervention in MD: CIE could serve as an early warning sign, allowing for more timely interventions. 5. Research opportunities: The potential link between CIE and MD opens up new avenues for research into the immunological aspects of psychiatric conditions, which could lead to novel treatment strategies.

### *4.1. Limitations*

This study has all the limitations inherent to its database-derived retrospective and descriptive nature.

Diagnosis of MD was based on the DSM-5 criteria. This may constitute a limitation in view of recent debates in literature that suggest that the DSM-5 criteria for major depression disorder (MDD) may be overly simplistic and advocating for a more nuanced diagnostic approach that better captures the complexity and variability of MDD (Maj, 2013).

Unfortunately, no data on blood levels of eosinophil-homing chemokine eotaxin-1/CCL11 in patients with CIE was available for the current study. Elevated eotaxin-1/CCL11 may activate and degranulate eosinophils, which could explain the high rate of CIE observed in this study among patients with MD (Hassani et al., 2020).

Additionally, the database may include inaccurate clinical records and missing data, creating bias and making follow-up impossible. The inclusion of only baseline data in our study was a constraint imposed by the retrospective nature of our data. Clearly, a future study is needed that captures the variability and changes over time using a longitudinal design, where repeated measurements of these parameters can be collected and analyzed.

Another limitation was the fact that patients with MD were maintained on antidepressant medication, which may affect eosinophil numbers. However, to the best of our knowledge, there are no studies showing suppressive effects of antidepressants on eosinophil counts. Also, no data is available on the possible impact of CIE on MD severity and response to treatment. Moreover, over-the-counter purchases of anti-inflammatory drugs, that could influence eosinophil counts and associated MD symptoms may not be reliable since patients may not always report such purchases to their caretakers. Additionally, undiagnosed or unreported infectious diseases affecting blood count results cannot be excluded.

Since ANA, TPO antibodies, rheumatoid factor, and complement levels were performed only is some patients with CIE and not always in the same patients, any statistical analysis involving these specific tests may have selection bias. Consequently, conclusions drawn from these specific tests may be limited and not generalizable to all patients with CIE.

Notably, while statistical differences in acute phase reactants between the CIE and control groups are significant, these results reflect differences at the group-level rather than at the individual level. Thus, one cannot draw individual-specific diagnostic or therapeutic insights from these results. The purpose of including these measurements was to identify potential systemic inflammatory markers that may be associated with CIE.

For the results to contribute more effectively to precision medicine, individual-specific data and analyses are more appropriate. Future studies should focus on longitudinal measurements of these reactants in individual patients. Such an approach may help in understanding the variability of the findings at the individual level. Thus, caution should be exercised when interpreting the current results.

Furthermore, to provide more insights into the general health conditions of patients with MD, and into the link between CIE and MD, it is necessary to assess acute phase reactants in CIE patients with MD and in age- and gender-matched, healthy controls.

## 5. Conclusions

Our study indicates that CIE may be associated with high rates of MD, both unipolar and bipolar, in the short and the long term, which means a possible involvement of inflammatory mechanisms, especially in bipolar disorder. This observation needs further confirmation in large-scale replicative studies. Further pre-clinical and clinical research should investigate the pathophysiological mechanisms underlying the association between CIE and MD. At the present time it seems that in clinical practice, eosinopenia is overlooked, and its meaning is elusive.

## Data availability

The data used in this study is available on reasonable request from Dr. Eli Magen allergologycom@gmail.com or Dr. Ariel Israel aisrael@leumit.co.il.

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## CRediT authorship contribution statement

**Eli Magen:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Akim Geishin:** Methodology, Writing – review & editing. **Abraham Weizman:** Conceptualization, Writing – review & editing. **Eugene Merzon:** Formal analysis, Methodology, Data curation, Writing – review & editing. **Ilan Green:** Project administration, Data curation, Writing – review & editing. **Israel Magen:** Data curation, Methodology, Project administration, Writing – review & editing. **Avi Yakov:** Methodology, Data curation, Writing – review & editing. **Iris Manor:** Data curation, Project administration, Writing – review & editing. **Shai Ashkenazi:** Formal analysis, Writing – review & editing, Supervision. **Shlomo Vinker:** Data curation, Methodology, Writing – review & editing. **Ariel Israel:** Formal analysis, Supervision, Writing – review & editing.

## 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.

## Data availability

Data will be made available on request.

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