

ORIGINAL PAPER

Pro- and Anti-Inflammatory Cytokine Profiles in Young Adults With Major Depressive Disorder

Surachat Buddhisa^a, Sureewan Bumrunghai^b, Keeratirawatn Thitiponkunanon^a, Wichaya Manachaichan^a, Nattaphol Prakobkaew^{a,*}

^a Department of Medical Technology, Faculty of Allied Health Sciences, Burapha University, Chonburi, Thailand.

^b Division of Biopharmacy, Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani, Thailand.

* Corresponding author: *nattaphol@go.buu.ac.th*

Received: 19 May 2026 / Revised: 17 August 2026 / Accepted: 20 August 2026

Abstract. Major depressive disorder (MDD) is a common psychiatric disorder associated with immune dysregulation and chronic low-grade inflammation. However, simultaneous alterations of pro- and anti-inflammatory cytokines in young adults with MDD remain incompletely characterized. This study investigated serum levels and detectability of interleukin-6 (IL-6), interferon-gamma (IFN- γ), and interleukin-10 (IL-10) in young adults with MDD and healthy controls (HC). A total of 135 participants aged 18–30 years, including 22 patients with MDD and 113 HC, were enrolled. Demographic characteristics, body mass index and white blood cell counts were assessed. Serum cytokines were measured using enzyme-linked immunosorbent assay. All three cytokines were detectable in significantly higher proportions of patients with MDD than HC (IL-6, 59.1% vs. 10.6%, $p < 0.0001$; IFN- γ , 81.8% vs. 57.5%, $p = 0.0339$; IL-10, 100% vs. 83.2%, $p = 0.0422$). Among participants with detectable cytokines, IFN- γ and IL-10 concentrations were significantly higher in the MDD group ($p = 0.0002$ and $p = 0.0048$, respectively), whereas IL-6 concentrations did not differ ($p = 0.5033$). IL-10 correlated positively with IFN- γ (Spearman $r = 0.3101$, $p = 0.0064$), but not IL-6 ($r = 0.2983$, $p = 0.1569$). These findings indicate differential cytokine alterations consistent with systemic immune dysregulation in MDD. However, the cross-sectional design and small MDD group limit interpretation and do not establish causality or biomarker status. Larger longitudinal studies incorporating disease severity and treatment outcomes are warranted to determine the clinical relevance and potential biomarker utility of these cytokine alterations.

Keywords: Major depressive disorder, inflammation, cytokines, interleukin-6, interferon- γ , interleukin-10

1. Introduction

Major depressive disorder (MDD) is a psychiatric disorder characterized by persistent changes in thoughts, emotions, and behaviors that may lead to self-harm and suicide. Depression is a common mental disorder and a major public health concern worldwide. According to the World Health Organization (WHO), approximately 332 million people worldwide experience depression, corresponding to an estimated 5.7% of adults. (<https://www.who.int/news-room/fact-sheets/detail/depression>). In Thailand, MDD has been reported across all age groups, with prevalence rates varying according to age and population characteristics. Previous studies have documented prevalence rates ranging from 7.0–21.4% among adolescents and young adults aged 19–22 years, approximately 12.0% among adults over 30 years of age, and up to 39.1% among individuals older than 40 years. Among middle-aged and older adults, prevalence rates ranging from 6.5% to 29.2% have also been reported (Wangtongkum et al. 2008; Charoensakulchai et al. 2019; Singkhorn et al. 2021; Pengpid et al. 2023; Liangruenrom et al. 2025). These findings indicate that MDD affects individuals throughout the lifespan and remains a significant health burden in the Thai population. Despite its high prevalence and substantial impact on quality of life, the biological mechanisms underlying MDD remain incompletely understood.

In addition to psychological, environmental, and social factors, increasing evidence suggests that immune dysregulation and neuroinflammation contribute to the pathophysiology of MDD. Communication between the immune system and the central nervous system plays an important role in regulating mood, cognition, and behavior. Dysregulation of this interaction may promote neuroinflammatory processes that contribute to the development and progression of depressive symptoms (Zhao et al. 2025; Jiao et al. 2025; Sălcudean et al. 2025; Hole et al. 2025). Several studies have reported elevated circulating levels of pro-inflammatory cytokines in patients with MDD, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), interleukin-1 β (IL-1 β), and interferon-gamma (IFN- γ) (Rethorst et al. 2012; Felger and Lotrich 2013; Haapakoski et al. 2015; Strawbridge et al. 2017; Petralia et al. 2020; Zhan et al. 2020; ElgellaieAsmahan et al. 2022; Chen et al. 2024). These cytokines can influence brain function through multiple mechanisms. Pro-inflammatory cytokines activate indoleamine 2,3-dioxygenase (IDO), which redirects tryptophan metabolism from serotonin synthesis toward the kynurenine pathway, resulting in reduced serotonin availability and increased production of neuroactive metabolites. In addition, inflammatory mediators may alter norepinephrine and dopamine signaling, impair neuroplasticity, and dysregulate the hypothalamic–pituitary–adrenal (HPA) axis, all of which have been implicated in depression (Yu et al. 2023; Cui et al. 2024; Sălcudean et al. 2025). Although most studies have focused on pro-inflammatory cytokines, anti-inflammatory cytokines may also play an important role in MDD. Interleukin-10 (IL-10) is a key immunoregulatory cytokine that suppresses excessive inflammatory responses and maintains immune homeostasis. Alterations in IL-10 levels have been reported in patients with depression, suggesting that both pro-inflammatory and anti-inflammatory pathways may be involved in the complex immune response associated with MDD (Hassamal

2023; Poletti et al. 2024; Ren et al. 2026; Cortes-Altamirano et al. 2026).

Young adults are commonly affected by MDD. However, data on circulating inflammatory cytokine profiles in this population remain limited. Although previous studies have reported alterations in individual inflammatory cytokines in MDD, fewer studies have simultaneously characterized both pro-inflammatory and anti-inflammatory cytokine responses. Therefore, the present study aimed to characterize the circulating cytokine profile of young adults aged 18–30 years with MDD by examining the pro-inflammatory cytokines IL-6 and IFN- γ and the anti-inflammatory cytokine IL-10, compared with healthy controls. Characterizing these cytokine alterations may provide further insight into systemic immune dysregulation associated with MDD and help clarify the potential clinical significance of inflammatory responses in young adults with depression.

2. Methodology

2.1 Specimens

The study was approved by the Ubon Ratchathani University Research Ethics Committee (UBU-REC-69/2567) and written informed consent was obtained from all participants prior to enrollment. A total of 135 participants aged 18–30 years were recruited and classified into two groups: healthy controls (HC) and patients with major depressive disorder (MDD). Demographic and lifestyle characteristics, including sex, underlying diseases, family history, exercise habits, alcohol consumption, and smoking status, were collected using a structured questionnaire. The HC group comprised individuals without a history of chronic disease or psychiatric disorders, whereas the MDD group comprised participants with a physician-confirmed diagnosis of MDD. The exclusion criteria for both groups included chronic diseases affecting immune function, acute infection or inflammatory conditions

within the preceding two weeks, abnormal WBC counts ($<4,000$ or $>10,000$ cells/ μL), and current use of antibiotics or immunosuppressive medications. WBC count was used as a preliminary screening parameter for overt hematological abnormalities or acute inflammatory conditions. The initial target sample size was 221 participants. This estimate was based on a 17.5% prevalence of depression in a Thai population, with a 95% confidence level and a 5% margin of error. However, due to recruitment limitations, 135 participants were ultimately enrolled, including 22 with MDD and 113 HC.

2.2 Blood Collection

Peripheral venous blood samples were collected from all participants and divided into EDTA and clot activator tubes. Blood samples collected in EDTA tubes were used for complete blood count (CBC) analysis, whereas serum samples obtained from clot activator tubes were stored at -80°C until cytokine analysis.

2.3 Cytokine Measurement

Serum IL-6, IFN- γ , and IL-10 concentrations were quantified using BD OptEIA™ ELISA Sets (Cat. Nos. 555220, 555142, and 555157, respectively; BD Biosciences, San Diego, CA, USA). The manufacturer-specified standard ranges were 4.7–300 pg/mL for IL-6 and IFN- γ and 7.8–500 pg/mL for IL-10. To improve quantification at low concentrations, additional calibrators below the manufacturer-specified range were prepared for each assay from the reconstituted lyophilised standard, giving a lowest calibrator of 2.34 pg/mL for all three cytokines. The extended standard curves demonstrated acceptable linearity, with R^2 values ranging from 0.9945 to 0.9987. All serum samples were analyzed in duplicate, and patient control sample was balanced across assay plates to minimize potential inter-plate variation.

2.4 Statistical Analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median (interquartile range), as appropriate. Statistical analysis was performed using tests appropriate to the dataset, as specified in the figure legends, using GraphPad Prism 10 software (GraphPad Software, Boston, MA, USA). The p values <0.05 were considered statistically significant.

3. Results

3.1 Demographic Characteristics

A total of 135 participants were included in this study, comprising 22 patients with MDD and 113 HC. The mean age of the MDD group was higher than that of the HC group. Within the MDD cohort, males were slightly older than females. Body mass index (BMI) was slightly higher in patients with MDD than in healthy controls. However, the difference was not statistically significant. White blood cell (WBC) counts remained within the normal range across all groups (Table 1).

3.2 Comparison of Inflammatory Biomarkers Between HC and MDD Groups

To further characterize circulating cytokine alterations in MDD, serum levels and detectability of IL-6, IFN- γ , and IL-10 were compared between patients with MDD and healthy controls (HC) (Table 1). Distinct differences in cytokine detectability and circulating concentrations were observed between the two groups.

IL-6 was detectable in 13 of 22 patients with MDD (59.1%), compared with 12 of 113 HC (10.6%; $p < 0.0001$) (Table 1). However, among participants with detectable IL-6, serum concentrations did not differ significantly between the MDD and HC groups (Figure 1A, $p = 0.5033$). These findings indicate that the

difference in IL-6 between the groups was primarily attributable to a higher proportion of participants with detectable IL-6 in the MDD group rather than higher IL-6 concentrations among those with detectable levels.

Similarly, IFN- γ was detectable in 18 of 22 patients with MDD (81.8%) and 65 of 113 HC (57.5%; $p = 0.0339$), while IL-10 was detectable in all patients with MDD (22/22, 100%) compared with 94 of 113 HC (83.2%; $p = 0.0422$) (Table 1). Among participants with detectable cytokine levels, serum IFN- γ concentrations were significantly higher in the MDD group than in the HC group (Figure 1B,

$p = 0.0002$), as were IL-10 concentrations (Figure 1C, $p = 0.0048$).

Overall, these findings indicate a differential alteration of the circulating cytokine profile in MDD. IL-6 differed between groups primarily in detectability, with no significant difference in concentration among participants with detectable IL-6, whereas IFN- γ and IL-10 differed in both detectability and concentration. This pattern suggests that immune alterations in MDD involve changes in both cytokine detectability and circulating concentrations rather than a uniform increase across all cytokines.

Table 1. Demographic characteristics and cytokine detection rates in patients with major depressive disorder (MDD) and healthy controls (HC).

Group/Variable	Age (years)	BMI (kg/m ²)	WBC (x10 ³ / μ L)	Detectable cytokine, n (%)		
				IL-6	IFN- γ	IL-10
MDD (n = 22)	24.48 $\pm$ 4.96	25.19 $\pm$ 6.46	6.93 $\pm$ 1.60	13 (59.1)	18 (81.8)	22 (100)
Male (n = 5)	27.25 $\pm$ 6.40	24.14 $\pm$ 9.27	7.69 $\pm$ 1.36	2 (40.0)	4 (80.0)	5 (100)
Female (n = 17)	23.82 $\pm$ 4.54	25.66 $\pm$ 5.43	6.55 $\pm$ 1.69	11 (64.7)	14 (82.4)	17 (100)
HC (n = 113)	20.04 $\pm$ 1.48	21.85 $\pm$ 4.30	7.42 $\pm$ 1.42	12 (10.6)	65 (57.5)	94 (83.2)
Male (n = 24)	19.75 $\pm$ 1.22	22.47 $\pm$ 4.40	7.23 $\pm$ 1.23	1 (4.2)	11 (45.8)	19 (79.2)
Female (n = 89)	20.11 $\pm$ 1.54	21.68 $\pm$ 4.28	7.47 $\pm$ 1.46	11 (12.4)	54 (60.7)	75 (84.3)
p (MDD vs HC)	<0.0001	0.0956	0.3634	<0.0001	0.0339	0.0422

Note: Data are presented as mean $\pm$ standard deviation or n (%). Percentages are calculated within each row's denominator. Detectable cytokine was defined as a concentration at or above 2.34 pg/mL. Continuous variables were compared between the MDD and HC groups using the Mann–Whitney U test, and cytokine detection rates using the two-sided Fisher's exact test.

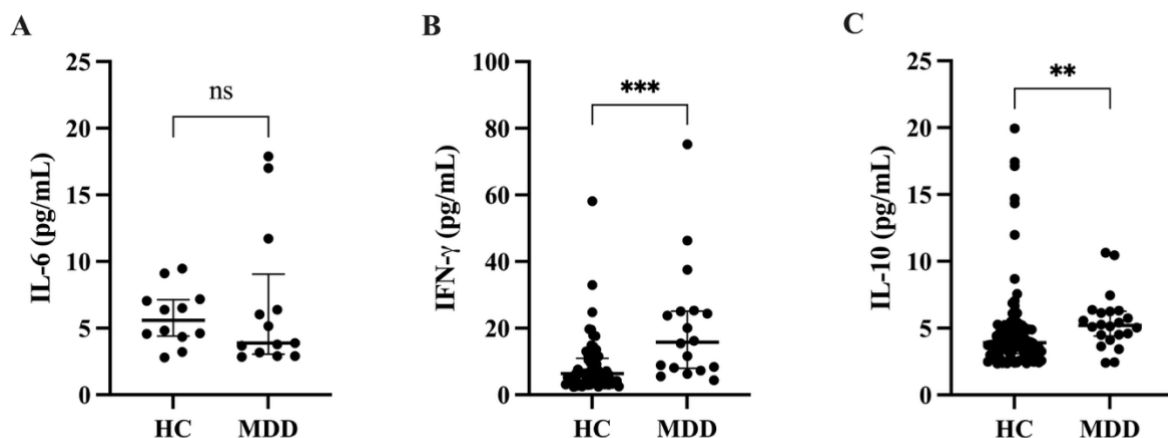


Figure 1. Serum inflammatory cytokine concentrations in healthy controls (HC) and patients with major depressive disorder (MDD). (A) Interleukin-6 (IL-6) (B) Interferon-gamma (IFN- γ) and (C) Interleukin-10 (IL-10). Data are

presented as scatter plots showing individual values with median with interquartile range. Statistical significance was determined between groups using the Mann–Whitney U test; ** $p < 0.01$, *** $p < 0.001$; ns, not significant.

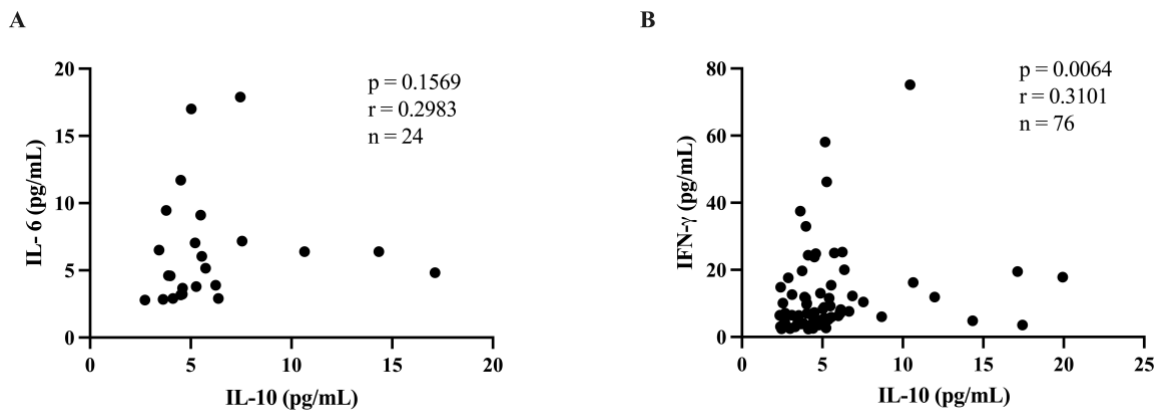


Figure 2. Correlation between serum IL-10 and pro-inflammatory cytokine concentrations. (A) IL-6 and (B) IFN- γ . Each point represents one participant; only participants in whom both cytokines were detectable are shown. Patients with MDD and healthy controls are pooled. Correlation coefficients (r) are Spearman rank correlation coefficients with two-sided p values.

3.3 Relationship between IL-10 and pro-inflammatory cytokines

To examine the relationship between IL-10 and pro-inflammatory cytokine levels, Spearman rank correlation analyses were performed. The study included participants with measurable levels of both cytokines (Figure 2). IL-10 was positively correlated with IFN- γ ($r = 0.3101$, $p = 0.0064$, $n = 76$), whereas no significant correlation was observed with IL-6 ($r = 0.2983$, $p = 0.1569$, $n = 24$). Within-group correlations were positive but did not reach significance for either cytokine pair (IL-6: MDD $r = 0.4780$, $p = 0.0985$, $n = 13$; HC $r = 0.2455$, $p = 0.4669$, $n = 11$; IFN- γ : MDD $r = 0.2982$, $p = 0.2293$, $n = 18$; HC $r = 0.2087$, $p = 0.1160$, $n = 58$), consistent with the limited number of participants with detectable cytokine in each group.

4. Discussion

The present study investigated circulating inflammatory cytokine profiles in young adults with MDD. Overall, the findings demonstrated a differential pattern of cytokine alterations in MDD. IL-6 was detectable in a significantly higher proportion of patients with MDD than in healthy controls, although IL-6 concentrations among participants with detectable levels did not differ significantly between groups. In contrast, serum IFN- γ and IL-10 concentrations

were significantly higher in patients with MDD. These findings support an association between MDD and systemic immune dysregulation involving both pro-inflammatory and anti-inflammatory responses (Miller and Raison 2008; Tubbs et al. 2020; Wessa et al. 2025; Sălcudean et al. 2025; Hole et al. 2025; Ren et al. 2026).

Among the cytokines evaluated, IL-6 showed a distinct pattern of alteration. IL-6 was detectable in 59.1% of patients with MDD compared with only 10.6% of healthy controls. However, among participants with detectable IL-6, serum concentrations did not differ significantly between groups. Thus, the difference in IL-6 in the present study was primarily related to its detectability rather than its concentration. This finding is consistent with previous evidence implicating IL-6 in MDD, although previous studies have generally reported elevated circulating IL-6 concentrations and associations with symptom severity and treatment resistance (Rethorst et al. 2012; Strawbridge et al. 2015; Roohi et al. 2021). The different pattern observed in our study may reflect heterogeneity in inflammatory responses among individuals with MDD and differences in clinical characteristics, assay methods, or other biological factors. IL-6 may influence depression through peripheral–central immune signaling, including effects on microglial activation and neuroinflammatory

processes (Garner et al. 2018; Kennedy and Silver 2022). These processes may be associated with alterations in neuroplasticity, neurogenesis, and synaptic function in brain regions involved in mood regulation (Zhao et al. 2025; Sălcudean et al. 2025; Blossom et al. 2025). However, the relatively small MDD group and cross-sectional design limit definitive interpretation. Larger longitudinal studies are warranted to determine whether IL-6 detectability or concentration is associated with symptom severity, disease progression, or treatment response.

In contrast to IL-6, serum IFN- γ concentrations were significantly higher in patients with MDD than in HC. IFN- γ is a key Th1-associated cytokine involved in cell-mediated immune responses and inflammatory signaling. Increased IFN- γ may contribute to depressive symptoms through activation of indoleamine 2,3-dioxygenase (IDO), which diverts tryptophan metabolism from serotonin synthesis toward the kynurenine pathway (Wichers and Maes 2004; Yu et al. 2023; Cui et al. 2024; O'Regan et al. 2026). Increased kynurenine pathway activity and the production of neuroactive metabolites may affect serotonin availability and contribute to mood disturbances and cognitive dysfunction. IFN- γ may also stimulate microglial activation and amplify neuroinflammatory processes within the central nervous system (Kwon and Koh 2020; Chen et al. 2024; Zong et al. 2026). These mechanisms provide a possible biological context for the elevated IFN- γ observed in the present study. However, the cross-sectional design does not allow a causal relationship between IFN- γ and MDD to be established.

Serum IL-10 concentrations were also significantly higher in patients with MDD. IL-10 is generally considered an anti-inflammatory cytokine that suppresses excessive immune activation and limits tissue damage. The increased IL-10 observed in this study may therefore represent a counter-regulatory response to inflammatory activation rather than an isolated anti-inflammatory process (Hiles et al. 2012; Taraz et al. 2012). Previous studies have similarly suggested that both pro-inflammatory

and anti-inflammatory pathways may be activated simultaneously in MDD, reflecting a complex and dysregulated immune response (O'Brien et al. 2006; Dhabhar et al. 2009; Hiles et al. 2012; Taraz et al. 2012).

Among participants with detectable levels of both cytokines, higher IL-10 levels were associated with higher IFN- γ levels. This association suggests coordinated alterations in pro-inflammatory and regulatory cytokine responses. Recent evidence has also reported elevated IFN- γ and IL-10 in individuals with MDD, further supporting alterations in inflammatory and regulatory pathways (Gędek et al. 2025). In contrast, IL-10 was not significantly correlated with IL-6, which may reflect differences in the regulation of individual cytokines. However, the correlation analyses were limited to participants with detectable cytokine levels, particularly for IL-6 ($n = 24$), and the within-group analyses had limited statistical power. Therefore, these findings should be interpreted cautiously and considered associative rather than mechanistic. Larger studies are warranted to clarify the coordinated regulation of pro- and anti-inflammatory cytokines in MDD.

Although white blood cell counts remained within normal ranges in all groups, significant differences in cytokine concentrations were observed between patients with MDD and healthy controls. This finding suggests that conventional hematological parameters may not adequately reflect subtle immune alterations associated with depression. Cytokine measurements may therefore provide greater sensitivity for detecting immune dysregulation in psychiatric disorders (Jeon and Kim 2016; Foley et al. 2022; Dong et al. 2025).

The biological relationship between immune dysregulation and depression is likely multifactorial. Inflammatory signaling may influence neurotransmitter metabolism, neuroendocrine function, and neuronal plasticity. Pro-inflammatory cytokines can activate the hypothalamic–pituitary–adrenal (HPA) axis, potentially resulting in sustained cortisol secretion and stress-response dysregulation.

Inflammatory mediators may also reduce brain-derived neurotrophic factor (BDNF) expression, impair neurogenesis, and affect neural circuits involved in emotional regulation (Kennedy and Silver 2022; Cui et al. 2024; Lei et al. 2025). These mechanisms provide a biological framework for understanding the association between altered cytokine profiles and depression, although the present study cannot determine whether these pathways directly mediate MDD.

Several limitations should be considered when interpreting these findings. First, although the initial target sample size was 221 participants, recruitment limitations resulted in a final sample of 135 participants, including only 22 patients with MDD and 113 HC. The small and unequal group sizes may have reduced statistical power and generalizability; therefore, the findings should be considered exploratory. In addition, the cross-sectional design precludes conclusions regarding temporal or causal relationships between cytokine alterations and MDD. Although BMI did not differ significantly between the MDD and HC groups, other factors that may influence cytokine levels, including medication use, stress, sleep, physical activity, and dietary habits, were not fully controlled. Differences in age distribution between groups may also have contributed to variation in cytokine levels. Second, inflammatory status was assessed primarily using clinical history, recent infection or inflammatory conditions, and WBC counts. Although WBC count was used as a preliminary screening parameter, normal WBC counts do not exclude mild or subclinical inflammation. Because CRP and other systemic inflammatory markers were not measured, some participants with low-grade inflammation may have been included. Future studies should include larger, balanced cohorts with longitudinal follow-up and comprehensive assessment of potential confounders and inflammatory markers, including CRP, to further clarify the relationship between cytokine alterations and MDD.

5. Conclusion

Patients with MDD demonstrated a higher proportion of detectable IL-6, as well as significantly elevated circulating levels of IFN- γ and IL-10, compared with healthy controls. Among participants with detectable cytokine levels, IL-6 concentrations did not differ significantly between groups. The simultaneous alteration of pro-inflammatory and anti-inflammatory cytokines is consistent with systemic immune dysregulation in MDD, even in the absence of abnormal peripheral WBC counts. The positive correlation between IL-10 and IFN- γ further suggests a coordinated alteration of pro-inflammatory and regulatory immune responses. However, the cross-sectional design does not allow causal relationships to be established, and these cytokine alterations cannot be considered established biomarkers of MDD or disease activity. Further studies with larger and more balanced cohorts, longitudinal follow-up, and assessment of disease severity and treatment response are warranted to determine their clinical relevance and potential biomarker utility in MDD.

Acknowledgement

The research team would like to thank all volunteers who participated in this study. We also thank the Faculty of Allied Health Sciences, Burapha University, for providing facilities and equipment for this research. In addition, we thank the Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, for providing facilities and equipment to support this study.

Funding

This work was financially supported by the Faculty of Allied Health Sciences, Burapha University (Grant no. AHS04/2567) and the Faculty of Pharmaceutical Sciences, Ubon Ratchathani University (Phar. UBU.0604.11-4/2569, and UBU.0604.11-2/2568), the Research, Innovation and Academic Service Fund of Ubon Ratchathani University.

References

- Blossom V, Ullal SD, D'Souza MM, Ranade A V., Kumar NA, Rai R (2025) Implicating neuroinflammation in hippocampus, prefrontal cortex and amygdala with cognitive deficit: a narrative review. *3 Biotech* 15(9):320. <https://doi.org/10.1007/S13205-025-04468-2>
- Charoensakulchai S, Usawachoke S, Kongbangpor W, Thanavirun P, Mitsiriswat A, Pinijnai O, Kaensingh S, Chaiyakham N, Chamnanmont C, Ninnakala N, Hiri-o-Tappa P, Ponginsee V, Atichatpongsuk V, Asawathepmetha EO, Thongprayoon C, Mao MA, Cheungpasitporn W, Varothai N, Kaewput W (2019) Prevalence and associated factors influencing depression in older adults living in rural Thailand: A cross-sectional study. *Geriatr Gerontol Int* 19(12):1248–1253. <https://doi.org/10.1111/GGI.13804>
- Chen MH, Bai YM, Hsu JW, Huang KL, Tsai SJ (2024) Proinflammatory cytokine levels, cognitive function, and suicidal symptoms of adolescents and young adults with major depressive disorder. *Eur Arch Psychiatry Clin Neurosci* 274(7):1681. <https://doi.org/10.1007/S00406-024-01780-5>
- Cortes-Altamirano JL, Alfaro-Rodríguez A, González-Maciél A, Pérez-Guillén B, Soriano-Rosales RE, Bonilla-Jaime H, Ávila-Luna A, Bueno-Nava A, Sánchez-Aparicio P, Dotor-Llerena AL (2026) Neuroimmune Dysregulation and the Role of IL-10 in Depression: A Systematic Review. *Brain Sciences* 2026, Vol 16, Page 548 16(6):548. <https://doi.org/10.3390/BRAINS16060548>
- Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, Wang Y, Tang Y, Xia M, Li B (2024) Major depressive disorder: hypothesis, mechanism, prevention and treatment. *Signal Transduction and Targeted Therapy* 2024 9:1 9(1):30-. <https://doi.org/10.1038/s41392-024-01738-y>
- Dhabhar FS, Burke HM, Epel ES, Mellon SH, Rosser R, Reus VI, Wolkowitz OM (2009) Low serum IL-10 concentrations and loss of regulatory association between IL-6 and IL-10 in adults with major depression. *J Psychiatr Res* 43(11):962–969. <https://doi.org/10.1016/J.JPSYCHIRE.2009.05.010>
- Dong Z, Bi B, Li R, Wang X, Liu H, Wu G, Sun Z, Pu E, He C, Zhang Y, Wang X, Tian B, Tan Y, Chen S (2025) Circulating inflammatory proteins associated with risks of schizophrenia, bipolar disorder, and major depressive disorder: a mendelian randomization study. *Translational Psychiatry* 2025 16:1 16(1):3-. <https://doi.org/10.1038/s41398-025-03738-0>
- Elgellaie Asmahan, Thomas Susan, Kaelle Jacqueline, Bartschi Jessica, Larkin Theresa (2022) Pro-inflammatory cytokines IL-1 α , IL-6 and TNF- α in major depressive disorder: Sex-specific associations with psychological symptoms. <https://doi.org/10.22541/AU.167061324.47723227/V1>
- Felger JC, Lotrich FE (2013) Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications. *Neuroscience* 246:199–229. <https://doi.org/10.1016/J.NEUROSCIENCE.2013.04.060>
- Foley ÉM, Parkinson JT, Mitchell RE, Turner L, Khandaker GM (2022) Peripheral blood cellular immunophenotype in depression: a systematic review and meta-analysis. *Molecular Psychiatry* 2022 28:3 28(3):1004–1019. <https://doi.org/10.1038/s41380-022-01919-7>
- Garner KM, Amin R, Johnson RW, Scarlett EJ, Burton MD (2018) Microglia priming by interleukin-6 signaling is enhanced in aged mice. *J Neuroimmunol* 324:90. <https://doi.org/10.1016/J.JNEUROIM.2018.09.002>

- Gędek A, Modrzejewski S, Materna M, Iwański M, Wichniak A, Dominiak M (2025) Altered Cytokine Levels in the First Episode of Major Depression and in Antidepressant-Naïve Patients: A Systematic Review and Meta-Analysis. *Int J Mol Sci* 26(21). <https://doi.org/10.3390/IJMS262110362>
- Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimäki M (2015) Cumulative meta-analysis of interleukins 6 and 1 β , tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain Behav Immun* 49:206. <https://doi.org/10.1016/J.BBI.2015.06.001>
- Hassamal S (2023) Chronic stress, neuroinflammation, and depression: an overview of pathophysiological mechanisms and emerging anti-inflammatories. *Front Psychiatry* 14:1130989. <https://doi.org/10.3389/FPSYT.2023.1130989/XML>
- Hiles SA, Baker AL, de Malmanche T, Attia J (2012) A meta-analysis of differences in IL-6 and IL-10 between people with and without depression: Exploring the causes of heterogeneity. *Brain Behav Immun* 26(7):1180–1188. <https://doi.org/10.1016/j.bbi.2012.06.001>
- Hole C, Dhamsania A, Brown C, Ryznar R (2025) Immune Dysregulation in Depression and Anxiety: A Review of the Immune Response in Disease and Treatment. *Cells* 14(8):607. <https://doi.org/10.3390/CELLS14080607>
- <https://www.who.int/news-room/fact-sheets/detail/depression> Depressive disorder (depression). <https://www.who.int/news-room/fact-sheets/detail/depression>. Accessed 17 Aug 2026
- Jeon SW, Kim YK (2016) Neuroinflammation and cytokine abnormality in major depression: Cause or consequence in that illness? *World J Psychiatry* 6(3):283. <https://doi.org/10.5498/WJP.V6.I3.283>
- Jiao W, Lin J, Deng Y, Ji Y, Liang C, Wei S, Jing X, Yan F (2025) The immunological perspective of major depressive disorder: unveiling the interactions between central and peripheral immune mechanisms. *Journal of Neuroinflammation* 2024 22:1 22(1):10-. <https://doi.org/10.1186/S12974-024-03312-3>
- Kennedy RH, Silver R (2022) Neuroimmune Signaling: Cytokines and the Central Nervous System. *Neuroscience in the 21st Century: From Basic to Clinical: Third Edition* :883–922. https://doi.org/10.1007/978-3-030-88832-9_174/SAVE-RESEARCH
- Kwon HS, Koh SH (2020) Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Transl Neurodegener* 9(1):42. <https://doi.org/10.1186/s40035-020-00221-2>
- Lei AA, Phang VWX, Lee YZ, Kow ASF, Tham CL, Ho YC, Lee MT (2025) Chronic Stress-Associated Depressive Disorders: The Impact of HPA Axis Dysregulation and Neuroinflammation on the Hippocampus—A Mini Review. *Int J Mol Sci* 26(7):2940. <https://doi.org/10.3390/IJMS26072940>
- Liangruenrom N, Joshanloo M, Hutaphat W, Kittisuksathit S (2025) Prevalence and correlates of depression among Thai university students: nationwide study. *BJPsych Open* 11(2). <https://doi.org/10.1192/BJO.2025.21>
- Miller AH, Raison CL (2008) Immune System Contributions to the Pathophysiology of Depression. *Focus (Madison)* 6(1):36–45. <https://doi.org/10.1176/FOC.6.1.FOC36>
- O'Brien SM, Scully P, Scott L V., Dinan TG (2006) Cytokine profiles in bipolar affective disorder: Focus on acutely ill patients. *J Affect Disord* 90(2–3):263–267.

- <https://doi.org/10.1016/j.jad.2005.11.015>
- O'Regan G, Plummer Z, Christie BR, Shultz SR, Allen J (2026) Kynurenine pathway dysregulation in major depressive disorder: the convergence of excitotoxicity, neuroinflammation, and oxidative stress. *Journal of Neuroinflammation* 2026 23:1 23(1):179-.
<https://doi.org/10.1186/S12974-026-03717-2>
- Pengpid S, Peltzer K, Anantanasuwong D (2023) Prevalence and determinants of incident and persistent depressive symptoms among middle-aged and older adults in Thailand: prospective cohort study. *BJPsych Open* 9(3).
<https://doi.org/10.1192/BJO.2023.72>
- Petralia MC, Mazzon E, Fagone P, Basile MS, Lenzo V, Quattropani MC, Di Nuovo S, Bendtzen K, Nicoletti F (2020) The cytokine network in the pathogenesis of major depressive disorder. Close to translation? *Autoimmun Rev* 19(5):102504.
<https://doi.org/10.1016/J.AUTREV.2020.102504>
- Poletti S, Mazza MG, Benedetti F (2024) Inflammatory mediators in major depression and bipolar disorder. *Translational Psychiatry* 2024 14:1 14(1):247-.
<https://doi.org/10.1038/s41398-024-02921-z>
- Ren N, Zhang XN, Yu Z, Che Y, Zhang YJ, Song M, Mao H (2026) Inflammatory Cytokines as a Shared Pathophysiological Pathway in Depression and Chronic Insomnia: A Narrative Review of Mechanisms and Clinical Implications. *Neuropsychiatr Dis Treat* 22:1–20.
<https://doi.org/10.2147/NDT.S585611>
- Rethorst CD, Toups MS, Greer TL, Nakonezny PA, Carmody TJ, Grannemann BD, Huebinger RM, Barber RC, Trivedi MH (2012) Pro-Inflammatory Cytokines as Predictors of Antidepressant Effects of Exercise in Major Depressive Disorder. *Mol Psychiatry* 18(10):1119.
<https://doi.org/10.1038/MP.2012.125>
- Roohi E, Jaafari N, Hashemian F (2021) On inflammatory hypothesis of depression: what is the role of IL-6 in the middle of the chaos? *J Neuroinflammation* 18(1):45.
<https://doi.org/10.1186/S12974-021-02100-7>
- Sălcudean A, Bodo CR, Popovici RA, Cozma MM, Păcurar M, Crăciun RE, Crisan AI, Enătescu VR, Marinescu I, Cimpian DM, Nan AG, Sasu AB, Anculia RC, Strete EG (2025) Neuroinflammation—A Crucial Factor in the Pathophysiology of Depression—A Comprehensive Review. *Biomolecules* 2025, Vol 15, Page 502 15(4):502.
<https://doi.org/10.3390/BIOM15040502>
- Singkhorn O, Apidechkul T, Pitchalard K, Moonpanane K, Hamtanon P, Sunsern R, Leaungsomnapa Y, Thepsaw J (2021) Prevalence of and factors associated with depression in the hill tribe population aged 40 years and older in northern Thailand. *Int J Ment Health Syst* 15(1):1–9.
<https://doi.org/10.1186/S13033-021-00487-7/TABLES/2>
- Strawbridge R, Arnone D, Danese A, Papadopoulos A, Vives AH, Cleare AJ (2015) Inflammation and clinical response to treatment in depression: A meta-analysis. *European Neuropsychopharmacology* 25:1532–1543.
<https://doi.org/10.1016/j.euroneuro.2015.06.007>
- Strawbridge R, Young AH, Cleare AJ (2017) Biomarkers for depression: recent insights, current challenges and future prospects. *Neuropsychiatr Dis Treat* 13:1245–1262.
<https://doi.org/10.2147/NDT.S114542>
- Taraz M, Khatami MR, Gharekhani A, Abdollahi A, Khalili H, Dashti-Khavidaki S (2012) Relationship between a pro- and anti-inflammatory cytokine imbalance and depression in

- haemodialysis patients. *Eur Cytokine Netw* 23(4):179–186.
<https://doi.org/10.1684/ecn.2013.0326>
- Tubbs JD, Ding J, Baum L, Sham PC (2020) Immune dysregulation in depression: Evidence from genome-wide association. *Brain Behav Immun Health* 7:100108.
<https://doi.org/10.1016/J.BBIH.2020.100108>
- Wangtongkum S, Sucharitakul P, Wongjaroen S, Maneechompoo S (2008) Prevalence of depression among a population aged over 45 years in Chiang Mai, Thailand. *Journal of the Medical Association of Thailand* 91(12):1812–1817
- Wessa C, Simon MS, De Picker L (2025) Current evidence on immune-driven depression. *Curr Opin Psychiatry* 39(1):8.
<https://doi.org/10.1097/YCO.00000000000001047>
- Wichers MC, Maes M (2004) The role of indoleamine 2,3-dioxygenase (IDO) in the pathophysiology of interferon- α -induced depression. *Journal of Psychiatry and Neuroscience* 29(1):11.
<https://doi.org/10.1139/jpn.0402>
- Yu X, Wang S, Wu W, Chang H, Shan P, Yang L, Zhang W, Wang X (2023) Exploring New Mechanism of Depression from the Effects of Virus on Nerve Cells. *Cells* 12(13):1767.
<https://doi.org/10.3390/CELLS12131767>
- Zhan Y, Zhou Y, Zheng W, Liu W, Wang C, Lan X, Deng X, Xu Y, Zhang B, Ning Y (2020) Alterations of multiple peripheral inflammatory cytokine levels after repeated ketamine infusions in major depressive disorder. *Translational Psychiatry* 2020 10:10(1):246-.
<https://doi.org/10.1038/s41398-020-00933-z>
- Zhao K, Zhang Y, Yang S, Xiang L, Wu S, Dong J, Li H, Yu H, Hu W (2025) Neuroinflammation and stress-induced pathophysiology in major depressive disorder: mechanisms and therapeutic implications. *Front Cell Neurosci* 19:1538026.
<https://doi.org/10.3389/FNCEL.2025.1538026>
- Zong S, Cui X, Wu S, Lu Z (2026) Microglia and neuroinflammation: function, heterogeneity, and crosstalk. *Cellular & Molecular Immunology* 2026 :1–19.
<https://doi.org/10.1038/s41423-026-01438-3>