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The role of inflammatory biomarkers in adolescent major depressive disorder: a systematic review

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Abstract

Purpose: Major Depressive Disorder (MDD) in adolescents is an escalating mental health problem with underlying biological pathways. Increasing evidence highlights the role of inflammatory response and immune dysregulation in its development and progression. This study aims to explore the role of inflammatory biomarkers in Major Depressive Disorder (MDD) among adolescent populations, elucidating their potential utility for more effective treatment strategies. **Methods:** A systematic review was conducted using Ebsco, PubMed, Scopus, Web of Science, and Google Scholar databases. Studies published between 2019 and 2025 that focused on adolescent MDD (aged 10-19 years) and inflammation were included. Study quality was evaluated using the Joanna Briggs Institute (JBI) tool, and narrative analyses were conducted for data synthesis. The PICOS (Population, Intervention, Comparison, Outcome, and Study Design) framework is used to ensure clarity in defining the research question and inclusion criteria. The systematic review was registered in PROSPERO (CRD420251129403). **Results:** A total of 29 articles met the inclusion criteria for this study. Across the included studies, elevated levels of pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α), were consistently associated with MDD in adolescents. Dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis and alterations in anti-inflammatory cytokines such as IL-10 were also observed. These biomarkers were linked to changes in stress hormone regulation. **Conclusion:** Inflammatory biomarkers play a significant role in the pathophysiology of MDD among adolescents, offering promising avenues for early detection and personalised intervention. Integrating biomarker assessment into clinical practice may improve diagnosis and guide targeted treatments.

Keywords: adolescents; cytokines; HPA axis; inflammatory biomarkers; major depressive disorder

INTRODUCTION

Adolescence represents a distinct period of human growth and holds significant importance for establishing a foundation of good health [1]. Adolescence is a critical period of brain development, making individuals vulnerable to mental health disorders, including MDD [2]. Adolescents undergo significant and rapid changes across the interplay of physical health, cognitive abilities, and social functioning. This dynamic growth affects their feelings, thinking patterns, ability to make choices, and their relationship with the world [3]. While it is considered a healthy stage of life, it is also fraught with challenges that can trigger mental health disorders, such as MDD [4].

The World Health Organisation (WHO) states that more than 280 million individuals are currently affected by MDD, representing 3.8% of the global population [5]. The prevalence of depression in Indonesia in 2023 is 1.4%. The prevalence of depression is highest among young people (15-24 years), at 2% [6]. MDD constitutes a primary driver of the global burden associated with mental health disorders, affecting various aspects of life and increasing the risk of premature death. MDD in adolescents often goes undiagnosed and untreated, which can negatively impact their future development. MDD can have a substantial effect on adolescents' lives, including academic outcomes, social relationships, and physical health [3].

In recent years, research has highlighted the role of biological mechanisms, especially inflammation and immune dysregulation, in the pathophysiology of MDD. Elevated pro-inflammatory cytokines, including IL-6 and TNF-α, have been associated with neurotransmitter imbalance, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and impaired neuroplasticity. These changes may serve as measurable inflammatory biomarkers that can aid in detecting depression, monitoring its progression, and guiding targeted interventions for adolescents [7].

Adolescents experiencing MDD may experience difficulty concentrating, decreased motivation, and social isolation. In severe cases, MDD can lead to suicidal thoughts or behaviour [8]. Although the biological basis of depression has been widely researched, the relationship of MDD with inflammatory events and Hypothalamic-Pituitary-Adrenal (HPA) dysregulation is still not fully understood. Chronic stress can disrupt the HPA axis, triggering inflammatory responses and imbalances in glucocorticoid and gonadal hormone secretion that contribute to declines in physical health and behavioural changes as adolescents become adults. Neuroinflammation, characterised by the activation and release of cytokines, is positively correlated with the severity of depressive symptomatology [9].

MDD is not only a mental burden, but also has a substantial effect on physical health. MDD sufferers have a higher risk of developing a range of serious physical health problems. This relationship between MDD and physical health problems is bidirectional. That is, MDD can trigger or worsen physical health, and conversely, chronic or debilitating physical conditions can increase the risk of MDD. Immune-metabolic pathways, involving various chemical messengers such as cytokines, insulin, and leptin, are critically implicated in the development and progression of MDD. These pathways, which link the immune system and the body's metabolic processes, may be dysregulated in individuals with MDD [7]. Research by Liu et al. indicates that cytokines can influence brain function and contribute to MDD symptoms [10].

Inflammation is critically involved in the underlying mechanisms of MDD through various mechanisms, notably the dysregulation of the HPA axis [11], microglial activation [12], disruption of neurotransmitter balance [13], and alterations in the kynurenine metabolic pathway [14]. Pro-inflammatory cytokines can trigger systemic inflammatory and neuroinflammatory responses, which contribute to depressive symptoms. In addition, immune dysregulation can impair neuroplasticity and disrupt brain function. The inflammatory process is significantly implicated in the pathological mechanisms underlying MDD.

Studies investigating the role of inflammatory markers in MDD have predominantly focused on adults, despite the growing prevalence of this condition among adolescents [15]. Although evidence linking inflammation and MDD is well-established in adults, there is limited understanding of how inflammatory biomarkers manifest in adolescents, particularly those who are drug-naïve. This gap restricts the development of biomarker-based screening and intervention strategies for this vulnerable group. Therefore, this systematic review aims to synthesize current evidence on inflammatory responses and immune system dysregulation in adolescent MDD and to identify potential biomarkers to inform personalized treatment approaches.

METHODS

Search strategy

A systematic review approach was used in this study, and data were collected from several databases: EBSCO (5), PubMed (91), Scopus (64), Web of Science (2), WHO (2), and Google Scholar (92). Searches were conducted both directly and using the Publish or Perish database search tool. The search was limited to publications from the last six years (2019-2025) to ensure inclusion of current data and research. The following keywords were used: ('Major Depressive Disorder' OR 'Depression') AND ('Inflammation' OR 'Cytokine') AND ('Cortisol in MDD' OR 'Cortisol and inflammation') AND ('DHEA in MDD' OR 'Dehydroepiandrosterone') AND ('HPA in MDD' OR 'Hypothalamic- pituitary-adrenal ') AND (' Microglia in MDD'OR "Microglia activity") AND (' Brain-derived neurotrophic factor'OR "BDNF") AND (' Kynurenine in MDD' OR "KA in MDD").

Framework

This review was structured according to the PICOS (Population, Intervention, Comparison, Outcome, and Study Design) framework to ensure clarity in defining the research question and inclusion criteria. The population was adolescents aged 10-19 years diagnosed with MDD. The exposure focused on the presence and measurement of inflammatory biomarkers, including cytokines, cortisol, DHEA, microglial activity, Brain-Derived Neurotrophic Factor (BDNF), and kynurenine pathway metabolites. This review lacks a comparator or control. The outcome was Major Depressive Disorder (MDD), defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) diagnostic criteria. The presence and severity of MDD were identified through standardized detection methods reported in the included studies, such as structured clinical interviews or validated psychometric scales (e.g., HAM-D, BDI, PHQ-9). The study design encompassed observational studies (cross-sectional, case-control, and cohort) and experimental designs that met the inclusion criteria.

Eligibility criteria and screening process

Inclusion and exclusion criteria were summarised in Table 1. Criteria were defined based on the PICOS framework and the WHO age classification for adolescents. After excluding articles, the authors (CPK, MPS, and SH) independently reviewed the search results and screened the full texts for inclusion.

The initial screening process followed the PRISMA flowchart (Figure 1). This figure illustrates the sequential stages of article selection: initial identification, title and abstract screening, and full-text assessment. To ensure objectivity and minimize bias, the screening process was performed independently by three reviewers (CPK, MPS, and SH). Initially, the titles and abstracts were screened against the inclusion criteria, followed by a rigorous full-text assessment of potentially relevant articles. Any discrepancies or disagreements regarding study eligibility were resolved by consensus or, if necessary, consultation with a fourth senior reviewer. Furthermore, the PRISMA checklist [16] was used to evaluate the reporting quality of the selected articles. The systematic and transparent application of the flowchart and PRISMA checklist ensured the validity and reliability of the resulting literature review. Ultimately, 29 studies based on the inclusion criteria were selected for more detailed assessment.

Table 1. Eligibility criteria for included studies

Criteria type	Description
Inclusion	a. Original research with primary data from observational and experimental designs (cohort, cross-sectional, case-control, or experimental studies) b. Adolescents aged 10-19 years (WHO definition) c. Article measuring inflammatory biomarkers (cytokine, cortisol, DHEA, BDNF, microglia activity, kynurenine) d. Studies reporting biomarker levels before treatment e. No gender restriction
Exclusion	a. Articles addressing depression without MDD b. MDD with comorbid physical or mental illnesses c. Duplicate publications

Note: DHEA (Dehydroepiandrosteron), BDNF (Brain-Derived Neurotrophic Factor), and MDD (Major Depressive Disorder)

Selection process

Extracting insights from data involved reviewing the title, year of publication, author information, study design, study data, significance of results, and discussion. Each author (CPK, MPS, and SH) independently collected and extracted data, and then met to resolve any discrepancies. Three researchers worked independently to perform blinded data extraction, ensuring unbiased data capture. The extraction process included collecting information regarding (1) title, (2) year of publication, (3) study design, (4) study data, (5) significance of results, (6) age range of samples, (7) MDD and healthy control groups, (8) names of biomarkers analysed, (9) biomarker analysis methods.

Analysis data

Due to heterogeneous data from various study designs, meta-analysis was not feasible. The authors (CPK, MPS, and SH) conducted a narrative analysis, creating tables and categorising the data based on examination parameters, units used, and association with MDD. Results and discussion were presented by sub-section. Given the limited number of studies remaining after screening, data identification was performed individually.

Study risk of bias assessment

The thorough examination of these sub-themes provides a basis for the overall quality assessment, highlighting both the strengths and limitations of the included studies. To evaluate the quality of the articles included in this systematic review, the Joanna Briggs Institute (JBI) Critical Appraisal tool was used [17]. Rather than using a single tool, design-specific JBI checklists were applied: the 8-item checklist for cross-sectional studies, the 11-item checklist for cohort studies, and the 13-item checklist for experimental (randomized controlled) studies. Each criterion within the JBI tool was coded as "No" (0), "Yes" (1), or "Not Applicable" (NA). A proportional quality assessment score was calculated for each research project, and full appraisal results are presented in Table 3.

RESULTS

The initial systematic search across six databases (Ebsco, PubMed, Scopus, Web of Science, WHO, and Google Scholar) using predefined strategic keywords yielded 256 unique articles. Following the initial identification and removal of duplicates, the title and abstract screening phase was conducted according to the established PICOS inclusion criteria, specifically targeting adolescents (aged 10–19 years) diagnosed with MDD and measuring relevant biomarkers. A subsequent full-text assessment was independently conducted by three authors (CPK, MPS, and SH), with any discrepancies resolved through joint discussion. This rigorous process ensured that only primary data from observational or experimental studies that met all eligibility criteria, such as reporting biomarker levels before treatment, were retained.

Figure 1 shows the PRISMA screening results for MDD-related studies. The initial total of articles on MDD was 256, and 29 met the inclusion criteria for this study. This selection aims to maintain consistency in comparisons across studies: only studies that report biomarkers with clear age ranges and measurement methods are included in the main table, ensuring that statistical summaries, narrative syntheses, and comparisons between studies are valid. Thus, although 29 publications were identified in the review, Table 2 highlights the primary studies that provide direct empirical evidence of the relationship between inflammatory indicators and depressive symptoms in adolescents.

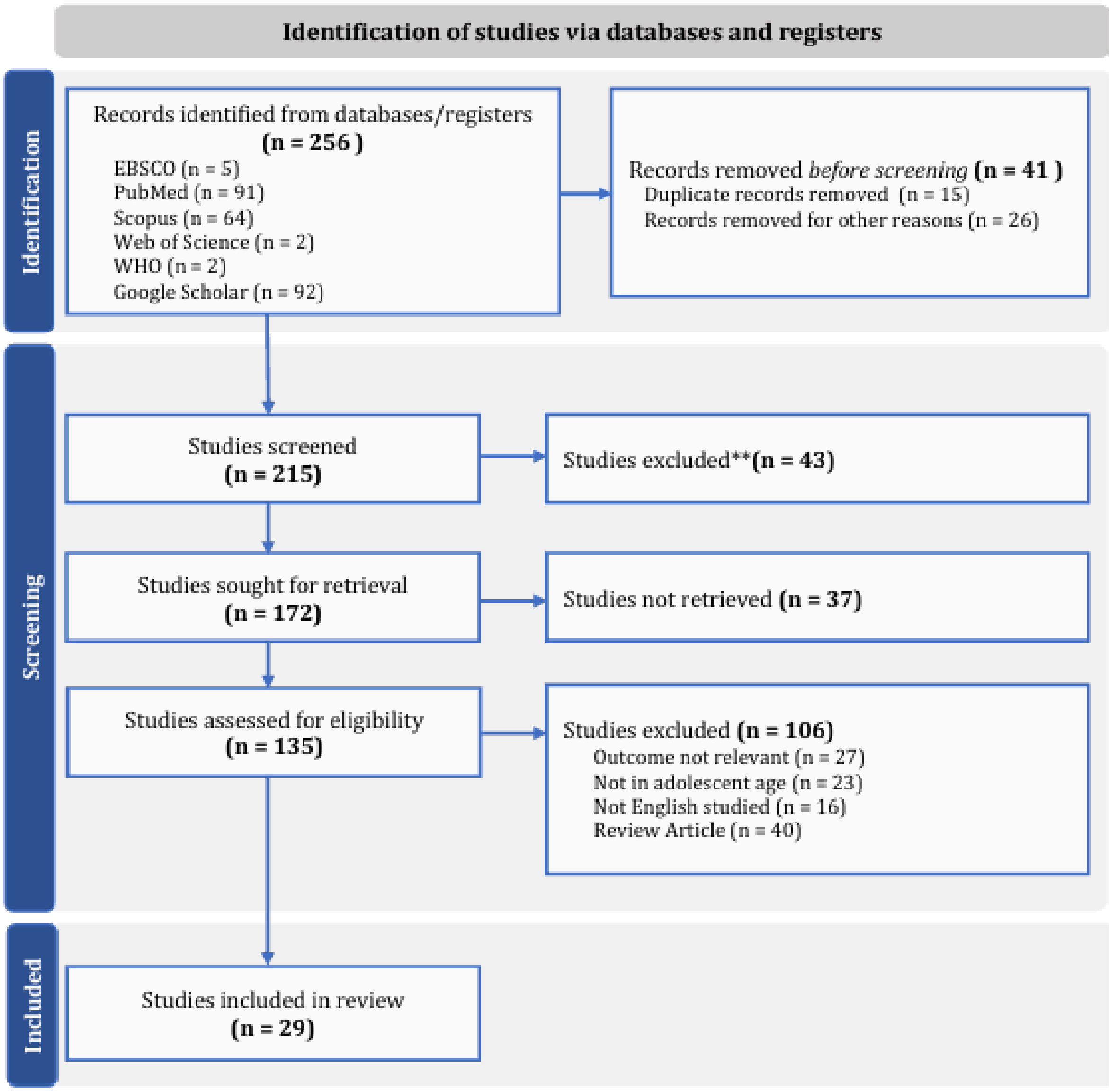

Figure 1. PRISMA flow diagram of the study selection process

Table 2. Characteristics of included primary studies on inflammatory biomarkers and depression

Author, year	Country	Design	Biomarker measured	Key findings
Du N et al. 2024 [2]	China	Cohort	IL-1 β, IL-6, and IL-10	ECT reduced pro-inflammatory markers and depressive symptoms
Liu M et al. 2025 [4]	China	Cross-sectional	IL-4, IFN-γ, IL-8, IL-12, and TNF-α	Elevated pro-inflammatory cytokines in adolescents with MDD vs controls
Liu et al. 2024 [10]	China	Cohort	IL-6, TNF-α, IFN-γ, IL-1β, and IL-10	Elevated cytokine levels predicted a higher risk of depression onset and severity over time, supporting inflammation as a causal factor in depression.
Xi YQ et al. 2024 [18]	China	Cross-sectional	IL-6, IFN-α, and TNF- α	TNF-α and Brain-Derived Neurotrophic Factor (BDNF) correlated with cognitive function; cytokines linked to cognition
Min X et al. 2023 [19]	China	Cross-sectional	IL-6, IL-10, and TNF- α	Associations between cytokines and depressive symptoms in adults (context for adolescents).
McLachlan C et al. 2023 [20]	United States of America	Cross-sectional	CRP, IFN-γ, TNF-α, IL-6, IL-8, and IL-10	Obesity amplifies inflammatory–depression associations in adolescents
Lee H et al. 2020 [21]	Korea	Cohort	IL-2, IFN-γ, TNF-α, and IL-10	Baseline cytokines predicted MDD onset/progression
Zeng Y et al. 2023 [22]	China	Cross-sectional	IL-1β and IL-4	IL-6 & TNF-α central nodes in MDD inflammatory network
Liu et al. 2024 [23]	China	Cohort	IL-1β and TNF-α	Higher inflammatory cytokine levels predicted the onset and persistence of depressive symptoms, supporting a causal role of inflammation in depression.
Elgellaie A et al. 2023 [24]	Australia	Cross-sectional	IL-1α, IL-6, and TNF-α	Sex-specific associations between pro-inflammatory cytokines and psychological symptoms
Zajkowska et al. 2023 [25]	UK	Cross-sectional	IL-6, IL-8, IL-10, IL-12, TNF-α, and IFN-γ	The study identified distinct inflammatory profiles for adolescent depression based on biological sex
Tsang et al. 2025 [26]	UK	Cohort	C-reactive protein (CRP)	Elevated CRP predicts a trajectory of increasing depressive symptoms.
Ji Y et al. 2024 [27]	China	Cross-sectional	C-reactive protein (CRP)	Higher hs-CRP is associated with increased prevalence of depressive symptoms.
Saadat SH et al. 2024 [28]	Iran	Case-control	BDNF; C-reactive protein (CRP)	BDNF is lower in MDD with suicide attempts; CRP results are mixed.
Batail et al. 2025 [29]	France	Cohort	C-reactive protein (CRP)	Baseline CRP was identified as a significant positive predictor of depression severity.
Poletti et al. 2019 [14]	Italy	Cross-sectional	Tryptophan–kynurenine pathway metabolites	Structural brain alterations correlated with activation of the kynurenine pathway, suggesting immune–metabolic links in mood disorders.
de Azeredo LA et al. 2020 [30]	Brazil	Case-control	Hair cortisol	Victimized youth had higher hair cortisol linked to mental health problems
Bendezú JJ et al. 2022 [31]	United States of America	Cohort	HPA, Cortisol	Joint HPA–inflammatory profiles predicted depressive symptoms
Hadjicharalambous et al. 2024 [32]	Greece	Cohort	Serum cortisol	The pubertal stage influenced immune-inflammatory responses
Chronister BN et al. 2021 [33]	United States of America	Cross-sectional	Testosterone, estradiol, DHEA, cortisol (saliva)	Sex hormones & cortisol related to anxiety/depression scores.
Fung MH et al. 2022 [34]	United States of America	Observational	Hair cortisol concentration, salivary cortisol	Pandemic-related cortisol changes in youth are associated with mental health changes.
Brosch K et al. 2022 [35]	Germany	Experimental	DLPFC volume	DLPFC volume as a correlate of resilience in high-risk individuals.
Zonca V et al. 2024 [36]	Brazil	Cross-sectional	Interferon	Sex-specific interferon inflammatory pathways associated with adolescent depression
Gabbay V et al. 2024 [37]	United States of America	Experiments	Chemokines	Acute social stress provokes immune and neural responses relevant to adolescent depression.
Wu Y et al. 2024 [38]	China	Observational clinical	Plasma S100B	Gender differences in plasma S100B levels among MDD patients.
Shen Z et al. 2022 [39]	China	Observational clinical	S100B	Combined S100B and cytokines showed diagnostic potential for GAD (ML model).
Dawood S et al. 2022 [40]	Pakistan	Clinical observational	Serotonin	Molecular docking of antidepressant and anti-inflammatory drugs to IDO/TDO enzymes
Kaszás A et al. 2025 [41]	Hungary	Clinical observational	Neuroinflammation	MRI markers indicate neuroinflammation in MDD with spiritual/religious concerns
Zwolińska et al. 2024 [42]	Poland	Case-Control	BDNF	Depressed adolescents showed significantly lower serum BDNF levels and higher methylation at specific *BDNF* gene promoters compared to healthy peers.

Table 3. JBI critical appraisal result

Author, year	Design	Assesment (Yes/Total)	Results (%)	Remarks
Du N et al. 2024 [2]	Cohort	10/11	91	High quality
Liu M et al. 2025 [4]	Cross-sectional	7/8	87.5	High quality
Liu et al. 2024 [10]	Cohort	10/11	91	High quality
Xi YQ et al. 2024 [18]	Cross-sectional	7/8	87.5	High quality
Min X et al. 2023 [19]	Cross-sectional	7/8	87.5	High quality
McLachlan C et al. 2023 [20]	Cross-sectional	7/8	87.5	High quality
Lee H et al. 2020 [21]	Cohort	10/11	91	High quality
Zeng Y et al. 2023 [22]	Cross-sectional	7/8	87.5	High quality
Liu et al. 2024 [23]	Cohort	9/11	82	Moderate
Elgellaie A et al. 2023 [24]	Cross-sectional	7/8	91	High quality
Zajkowska et al. 2023 [25]	Cross-sectional	10/11	91	High quality
Tsang et al. 2025 [26]	Cohort	10/11	91	High quality
Ji Y et al. 2024 [27]	Cross-sectional	7/8	91	High quality
Saadat SH et al. 2024 [28]	Case-control	9/10	90	High quality
Batail et al. 2025 [29]	Cohort	10/11	91	High quality
Poletti et al. 2019 [14]	Cross-sectional	7/8	91	High quality
de Azeredo LA et al. 2020 [30]	Case-control	9/10	90	High quality
Bendezú JJ et al. 2022 [31]	Cohort	10/11	91	High quality
Hadjicharalambous et al. 2024 [32]	Cohort	9/11	82	Moderate
Chronister BN et al. 2021 [33]	Cross-sectional	7/8	91	High quality
Fung MH et al. 2022 [34]	Observational	9/11	82	Moderate
Brosch K et al. 2022 [35]	Experimental	12/13	92	High quality
Zonca V et al. 2024 [36]	Cross-sectional	10/11	91	High quality
Gabbay V et al. 2024 [37]	Experiments	12/13	92	High quality
Wu Y et al. 2024 [38]	Observational	10/11	91	High quality
Shen Z et al. 2022 [39]	Observational	10/11	91	High quality
Dawood S et al. 2022 [40]	Observational	10/11	91	High quality
Kaszás A et al. 2025 [41]	Observational	10/11	91	High quality
Zwolińska et al. 2024[42]	Case-Control	9/10	91	High quality

Note: JBI: Assessment from the ratio of yes to total

Table 4. Systematic characteristics of proinflammatory and antiinflammatory cytokine reviews

Author (year)	MDD sample	Design	Country	Proinflammatory cytokines							Antiinflammatory cytokines	
				IL-6 (pg/mL)	IL-8 (pg/mL)	IL-12 (pg/mL)	IFN-α (pg/mL)	IFN-γ (pg/mL)	IL-1β (pg/ml)	TNF-α (pg/mL)	IL-4 (pg/mL)	IL-10 (pg/mL)
Du N et al. 2024 [2]	38	Cohort	China	55.85 ± 32.07	NA	NA	NA	NA	83.92 ± 16.49	NA	NA	447.82 ± 107.81
Liu M et al. 2025 [4]	58	Cross-sectional	China	NA	2.39 ± 2.89	20.54 ± 21.07	NA	18.34 ± 21.75	NA	8.41 ± 4.17	14.71 ± 6.83	NA
Liu et al. 2024 [10]	111	Cohort	China	0.53 ± 0.34	NA	NA	NA	7.51 ± 3.42	0.05 ± 0.01	1.70 ± 1.28	NA	0.18 ± 0.11
Xi YQ et al. 2024 [18]	22	Cross-sectional	China	2.18 ± 0.41	NA	NA	4.05 ± 3.13	NA	NA	13.29 ± 12.98	NA	NA
Min X et al. 2023 [19]	113	Cross-sectional	China	2.494	NA	NA	NA	NA	NA	13.403 ± 0.429	NA	3.160
McLachlan C et al. 2023 [20]	47	Cross-sectional	USA	0.86 ± 0.11	8.24 ± 0.53	NA	NA	5.01 ± 0.79	NA	2.35 ± 0.11	NA	0.44 ± 0.06
Lee H et al. 2020 [21]	25	Cohort	China	NA	NA	NA	NA	6.07 ± 1.59	NA	10.25 ± 3.88	32.51 ± 42.38	7.39 ± 1.64
Zeng Y et al. 2023 [22]	280	Cohort	China	3.44 ± 5.85	NA	NA	NA	18.85 ± 14.42	2.73 ± 2.16	6.63 ± 3.80	82.14 ± 89.49	NA
Liu et al. 2024 [23]	82	Cohort	China	NA	NA	NA	NA	NA	3.63 ± 2.56	3.7 ± 1.6	NA	NA
Elgellaie A et al. 2023 [24]	60	Cross-sectional	Australia	9.49 ± 7.75	NA	NA	NA	NA	NA	1.95 ± 1.79	NA	NA
Zajkowska et al. 2023 [25]	50	Cross-sectional	UK	NA	10.46 ± 0.99	0.11 ± 0.02	NA	10.31 ± 2.81	NA	3.1 ± 0.12	NA	0.61 ± 0.12

Abbreviation: MDD (Major Depressive Disorder), TNF-α (Tumor Necrosis Factor-α), IL-6 (Interleukin-6), IL-8 (Interleukin-8), IL-12 (Interleukin-12), IFN-α (Interferon-alpha), IFN-γ (Interferon-gamma), IL-1β (Interleukin-1β), IL-4 (Interleukin-4), IL-10 (Interleukin-10), and NA (Not Applicable), USA (United of America), UK (United Kingdom)

The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) checklist. Most studies n = 26; 89%) were rated as high quality (≥87.5%), Three studies (Liu et al. 2024 [23], Hadjicharalambous et al. 2024 [32], and Liu M et al. 2025 [4]) were rated as moderate quality (82%) were rated as moderate quality (82%) due to minor limitations in reporting or methodology; no study was classified as low quality (Table 3).

The results of the analysis of 11 studies on the role of proinflammatory and anti-inflammatory cytokines in the pathogenesis of MDD are summarized in Table 4, complete with terms and quantitative data. Table 4 summarizes the characteristics of the included studies and the reported concentrations of proinflammatory and anti-inflammatory cytokines in patients with Major Depressive Disorder (MDD) alone. These studies used a cross-sectional, prospective design and evaluated a broad spectrum of inflammatory biomarkers, including interleukins, interferons, and tumor necrosis factor-alpha.

These studies show that, in patients with MDD, proinflammatory cytokines are elevated relative to anti-inflammatory cytokines. Some proinflammatory cytokines reported to be increased in MDD include Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-12 (IL-12), Interferon-α (IFN-α), Interferon-γ (IFN-γ), and Tumor Necrosis Factor-alpha (TNF-α). The increase in proinflammatory cytokines in MDD indicates that inflammation is involved in its development.

The role of inflammatory biomarkers is shown in Figure 2. Increased proinflammatory cytokines, decreased anti-inflammatory cytokines, decreased growth factors such as BDNF and S100B, and increased cortisol induced by psychological and metabolic stress disrupt cortisol regulation and cause neurotransmitter imbalance, which triggers the onset of MDD.

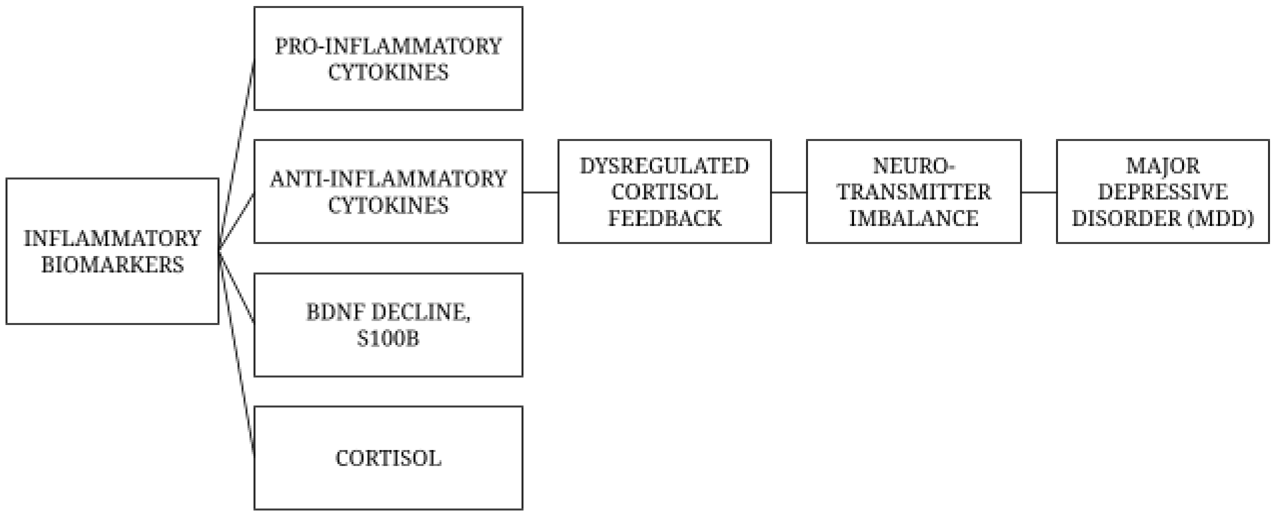

Figure 2. The role of inflammatory biomarkers in MDD

DISCUSSION

Inflammatory biomarkers and HPA axis dysregulation in adolescent MDD

MDD in adolescents is an increasingly serious mental health concern with a rising prevalence [43]. Consistent with the aims of this review, evidence was synthesised on the role of inflammatory biomarkers and HPA axis dysregulation in adolescent MDD. The findings consistently demonstrate elevated inflammatory biomarkers accompanied by abnormal cortisol patterns, indicating a biological pathway that complements psychosocial risk factors in the pathophysiology of depression during this developmental stage [15].

Globally, approximately 14% of adolescents experience mental health disturbances triggered by multiple factors [5]. Affected adolescents are vulnerable to social impairment, self-exclusion, discrimination, reduced academic performance, and poor physical health [44]. Stress-related mental health disorders are closely associated with dysregulation of hormonal, neural, and immune systems. Stress alters concentrations of cortisol and dehydroepiandrosterone (DHEA) [33]. Cortisol, a steroid hormone central to stress responses and glucose regulation, is secreted via activation of the HPA axis and follows a diurnal rhythm, peaking in the morning and declining throughout the day [31,34,45].

Chronic stress overstimulates the HPA axis and disrupts circadian cortisol secretion, affecting metabolic, immune, cardiovascular, and central nervous system functions [34], and is associated with adverse physical health outcomes [46]. Excess glucocorticoid exposure contributes to MDD pathophysiology by inhibiting neurogenesis and brain trophic support, while antidepressants may partially reverse these effects by modulating neurotransmitters, HPA activity, and BDNF expression [21,31,47].

Adolescents exposed to pubertal or chronic stress exhibit impaired 24-hour cortisol secretion, with those diagnosed with unipolar MDD showing elevated nocturnal cortisol levels [30,33,48]. Increased diurnal cortisol has been linked to reduced ventrolateral prefrontal cortex (vlPFC) volume and behavioural disturbances [35,48,49]. Elevated cortisol, particularly at night, increases the risk of MDD, metabolic disorders, and chronic immune conditions [45]. Higher hair cortisol levels have been observed in victimised adolescents, and elevated bedtime cortisol has been reported in adolescents with MDD and suicide attempts, indicating HPA axis dysregulation and sleep disturbance [34,50].

In addition to cortisol, stress in adolescents with MDD or bipolar disorder is associated with increased secretion of DHEA and testosterone, whereas estradiol levels remain largely unchanged [45,51]. Reduced concentrations of gonadal hormones and DHEA may result in delayed puberty, impaired sexual development, reduced muscle growth, lower bone density, and social difficulties [32].

Proinflammatory and anti-inflammatory cytokines in adolescent MDD

Studies in drug-naive adolescents with MDD indicate that elevated peripheral TNF-α levels are associated with the disorder. TNF-α, a key pro-inflammatory cytokine, has been linked to neurodegenerative diseases and adult MDD [36], and peripheral inflammation is associated with structural and functional brain alterations in depression [9]. Pro-inflammatory cytokines, particularly IL-6 and TNF-α, are frequently elevated in MDD and can activate indoleamine 2,3-dioxygenase (IDO), accelerating tryptophan degradation and reducing serotonin-related metabolites [19]. This process activates the kynurenine pathway, in which imbalances between kynurenic acid (KA) and quinolinic acid (QA) may contribute to MDD by modulating NMDA receptors [40].

Neuroinflammation, characterised by microglial activation and increased cytokine secretion, is increasingly recognised as a core feature of MDD, with imaging studies demonstrating heightened neuroinflammatory activity across multiple brain regions [41]. Pro-inflammatory cytokines such as TNF-α and IL-6 contribute to systemic inflammation, increased blood–brain barrier permeability, and central neuroinflammatory responses. Immune dysregulation, including Th17/Treg imbalance and abnormal activation of microglia and astrocytes, can impair neurotransmission and neuroplasticity, leading to neuropathological changes [11,52].

As summarised in Table 2, elevated IL-6 and TNF-α disrupt the neurotransmitter and hormonal systems that regulate stress responses [18]. They are associated with suicide-related behaviours, cognitive impairment, altered brain structure, treatment response, and childhood trauma in MDD [13,53]. Increased IL-1, IL-6, and TNF-α further suggest glucocorticoid resistance, heightened HPA axis activity, and impaired hippocampal neurogenesis [54]. Nevertheless, some studies report reduced levels of TNF-α, IL-2, IFN-γ, and IL-10 in adolescents with MDD, indicating heterogeneity in inflammatory responses [20,22]. Overall, an imbalance between pro- and anti-inflammatory cytokines is considered a potential contributor to depression, although cytokine changes do not consistently predict antidepressant response [22,26].

Clinically, the consistent elevation of inflammatory biomarkers supports their potential inclusion in early screening and risk stratification for adolescents with MDD, particularly among psychosocially vulnerable groups. Integrating biomarker assessment with school-based prevention programmes may facilitate earlier diagnosis, targeted interventions, and improved outcomes.

Integrating inflammatory pathways into the understanding of adolescent MDD

MDD is characterised by depressive episodes involving low mood, anhedonia, and negative thinking. In contrast, bipolar disorder is defined by episodes of mania or hypomania marked by elevated mood and increased goal-directed behaviour [54]. Both mood disorders are associated with a chronic, low-grade systemic inflammatory state, reflected by increased circulating inflammatory mediators that can affect multiple tissues, including the brain. Pro-inflammatory cytokines such as TNF-α and IL-6 can alter behaviour, emotional regulation, and cognition by modulating neurotransmitter systems and activating stress-related hormonal pathways [24]. In addition, anti-inflammatory cytokines, including IL-4 and IL-10, have been detected in individuals with MDD [13].

Numerous studies link inflammation with both MDD and bipolar disorder, supported by the high prevalence of depressive symptoms in patients with chronic and autoimmune diseases [46]. Alfian et al. reported an increased risk of cardiovascular disease in individuals with depressive symptoms, highlighting the need for targeted preventive strategies [8]. Consistently, a systematic review demonstrated significant improvement in depressive symptoms following anti-cytokine therapy in autoimmune disorders [23].

A meta-analysis showed significantly elevated levels of several inflammatory markers, including interleukins, sIL-2R, TNF-α, sTNFR2, and CCL-2, in individuals with MDD compared with healthy controls [55]. C-reactive protein (CRP), an acute-phase protein that rises in both acute and chronic inflammation, represents an early component of the immune response [27,56]. Hepatocytes synthesise CRP in response to IL-6 released by macrophages and T cells, and play a key role in innate immunity [57]. Although CRP does not normally cross the blood–brain barrier, inflammatory conditions allow its entry into the central nervous system [28,58]. Peripheral CRP, therefore, represents a potential biomarker of systemic and neuroinflammation in MDD and may help guide immunotherapies targeting TNF-α and IL-6 [27].

From inflammation to neuroendocrine dysregulation in adolescent MDD

Inflammatory processes activate pro-inflammatory cytokines, including IL-1, IL-6, TNF-α, and IFN-α, which stimulate the release of corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol [58]. Glucocorticoids normally suppress inflammation through negative feedback on the HPA axis [13]. However, chronic inflammation leads to sustained glucocorticoid elevation and reduced glucocorticoid receptor sensitivity, weakening HPA axis feedback and allowing persistent cortisol dysregulation [31,45]. Elevated cortisol with impaired regulatory control is a consistent feature of mood disorders [33].

Neuroinflammation promotes microglial activation, a process that under physiological conditions supports synaptic maintenance and neural homeostasis [41,59]. Chronic microglial activation results in increased secretion of TNF-α, IL-1β, and IL-6, along with elevated reactive oxygen and nitrogen species [65,66]. Prolonged activation contributes to neuronal apoptosis, disrupted synaptic connectivity, impaired neuroplasticity, and maladaptive behaviours [37,60]. Increased microglial activity has been associated with cognitive impairment, depression severity, and suicide risk, supported by post-mortem evidence of elevated activated microglia in mood disorder cases [61-66].

Inflammation also impairs synaptic plasticity and learning by altering levels of brain-derived neurotrophic factor (BDNF), a key regulator of neuronal survival, differentiation, and synaptic transmission [66–68]. Another neuroplasticity marker, S100B, exhibits concentration-dependent effects: nanomolar levels support neuronal growth, whereas micromolar levels induce neurotoxicity and pro-inflammatory cytokine expression [38]. Elevated circulating S100B has been observed during depressive and manic episodes, suggesting glial involvement in mood disorder pathophysiology [39].

Pro-inflammatory cytokines such as IL-2, TNF-α, and interferons activate indoleamine 2,3-dioxygenase, shifting tryptophan metabolism toward the kynurenine pathway [69,70]. This reduces serotonin synthesis and generates neuroactive metabolites, including 3-hydroxykynurenine, quinolinic acid, and kynurenic acid, which contribute to neurotoxicity and neurotransmitter imbalance in MDD [13,70,71]. The interaction between inflammation, neuroendocrine dysregulation, and neurotransmission in MDD is illustrated in Figure 2 [63,71].

This review has limitations, including the predominance of cross-sectional designs, heterogeneity in diagnostic criteria and biomarker assays, and variability in participant characteristics, which limit causal inference. Future longitudinal, multi-centre studies with standardised biomarker methodologies are needed to validate these findings and assess their predictive value for treatment response.

CONCLUSION

Psychosocial factors, such as gender, socioeconomic disadvantage, and poor sleep, and biological mechanisms, including elevated inflammatory biomarkers, influence MDD in adolescents. These alterations disrupt brain function, neurotransmitter balance, and hormonal regulation. Combining biomarker assessment with psychosocial screening can guide earlier, more targeted treatment, including psychological therapy, lifestyle modification, and, where appropriate, anti-inflammatory or hormonal regulation strategies. Families and schools should be more alert to changes in adolescent behavior in their daily lives, and immediately report to the authorities if there are indications of depression in adolescents, such as to health facilities, because the results of reviews from several studies prove that mental health significantly affects physical health.

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Conflicts of interest
The authors declare no conflicts of interest.

Use of artificial intelligence (AI)
The authors used ChatGPT -3 during manuscript preparation for brainstorming, initial drafting, and language editing to improve grammar and clarity. The authors have independently reviewed and verified all content and remain fully responsible for the accuracy and originality of the work.

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