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Differences between adolescent depression and healthy controls in biomarkers associated with immune or inflammatory processes: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 June 2024 and was last updated on 28 June 2024.

INTRODUCTION

Review question / Objective The primary review question of this systematic review and meta-analysis is: What are the differences in biomarkers associated with immune or inflammatory processes between adolescents diagnosed with depression and healthy control adolescents?
To address this broad question, the following specific sub-questions will be considered:

1.1. Which specific immune or inflammatory biomarkers show significant differences between adolescents with depression and healthy controls?
1.2. How do these differences in biomarkers correlate with the severity and duration of depression in adolescents?
1.3. Are there any demographic factors (e.g., age, sex) that influence the differences in biomarkers between the two groups?
1.4. What are the methodological qualities and potential biases in the studies comparing these biomarkers?
These questions will be framed and refined using the PICOS framework:
Population (P): Adolescents (aged 12-18) diagnosed with depression and healthy controls.
Intervention (I): Not applicable.
Comparison (C): Healthy control adolescents.
Outcomes (O): Levels of biomarkers associated with immune or inflammatory processes (e.g., cytokines, CRP, etc.).
Study design (S): Case-control and cross-sectional studies.

Condition being studied The condition being studied is adolescent depression, specifically focusing on the differences in biomarkers associated with immune or inflammatory processes between adolescents diagnosed with depression and healthy control adolescents. This

study aims to identify specific biomarkers that are significantly altered in depressed adolescents compared to their healthy peers, thereby contributing to a better understanding of the biological underpinnings of adolescent depression and potentially informing future diagnostic and therapeutic strategies.

METHODS

Participant or population We included studies on adolescent depression that satisfied the following conditions: (1) Participants were adolescents aged 12-24 years; (2) participants had an initial diagnosis of unipolar depression based on a diagnostic system such as the International Classification of Disease (ICD), Diagnostic and Statistical Manual of Mental Disorders (DSM), or Research Diagnostic Criteria (RDC); (3) measurable biomarkers related to inflammation or immunity in the participants' blood were collected; (4) the study included a healthy control group; (5) the study was available online in English; and (6) peer-reviewed publications in the past 20 years. We excluded manuscripts based on non-human studies, studies with inadequate evaluation methods, insufficient data, or unclear findings, and studies reported in conferences, abstracts, editorials, or letters only. When multiple manuscripts were based on a single cohort, the manuscript with the largest sample was included.

Intervention This systematic review and meta-analysis is an observational study and does not involve the implementation of any specific interventions. The focus is on analyzing existing data from studies that compare blood inflammatory and immune biomarkers in adolescents diagnosed with depression to those in healthy control groups. Therefore, no experimental or therapeutic interventions are applied to the target population within the scope of this review. The aim is to synthesize available evidence to better understand the biological differences between depressed adolescents and their healthy peers.

Comparator The comparative intervention in this systematic review and meta-analysis is the inclusion of healthy control groups. These healthy controls are adolescents without a diagnosis of depression or any other psychiatric disorder. This approach allows for a direct comparison of blood inflammatory and immune biomarkers between adolescents diagnosed with depression and their healthy peers. By using healthy control groups, the study aims to avoid confounding factors and provide a clearer baseline for understanding the specific biomarkers associated with adolescent depression. This methodological choice enhances the accuracy and reliability of the findings by ensuring that observed differences in biomarkers are attributable to depression rather than other variables.

Study designs to be included The review will include cross-sectional studies and case-control studies that compare biomarkers associated with immune or inflammatory processes between adolescents diagnosed with depression and healthy controls.

Eligibility criteria We included studies on adolescent depression that satisfied the following conditions: (1) Participants were adolescents aged 12-24 years; (2) participants had an initial diagnosis of unipolar depression based on a diagnostic system such as the International Classification of Disease (ICD), Diagnostic and Statistical Manual of Mental Disorders (DSM), or Research Diagnostic Criteria (RDC); (3) measurable biomarkers related to inflammation or immunity in the participants' blood were collected; (4) the study included a healthy control group; (5) the study was available online in English; and (6) peer-reviewed publications in the past 20 years. We excluded manuscripts based on non-human studies, studies with inadequate evaluation methods, insufficient data, or unclear findings, and studies reported in conferences, abstracts, editorials, or letters only. When multiple manuscripts were based on a single cohort, the manuscript with the largest sample was included.

Information sources
1) Electronic Databases: PubMed, Web of Science, Elsevier ScienceDirect
2) Manual Searches:Reference lists of relevant articles and previous reviews.
3)Grey Literature:Unpublished studies identified through trial registers.Conference abstracts and proceedings.
4)Direct Contact:Correspondence with authors of included studies for additional data or clarification.

Main outcome(s) The primary outcome of this systematic review and meta-analysis is to identify and quantify differences in biomarkers associated with immune or inflammatory processes between adolescents diagnosed with depression and healthy control adolescents. These biomarkers, which are measured in peripheral blood, include:Platelet to Lymphocyte Ratio (PLR), White Blood Cells (WBC), Neutrophil to Lymphocyte Ratio (NLR), Platelets, Tumor Necrosis Factor-α

(TNF-α), Interleukin-1β (IL-1β), Neutrophils, Mean Platelet Volume (MPV), Mean Corpuscular Volume (MCV), Interleukin-8 (IL-8), Procalcitonin (PCT)etc. These outcomes are defined by the levels of these biomarkers in the blood, measured at the time of diagnosis or during the course of the included studies. The primary outcome will be assessed using standardized mean differences (SMDs) between the biomarker levels in depressed adolescents and healthy controls, where available.

Additional outcome(s) Correlation between Biomarkers and Depression Severity:
Definition: The relationship between the levels of immune or inflammatory biomarkers and the severity of depression in adolescents, as measured by standardized depression rating scales such as the Hamilton Depression Scale (HAM-D).Measurement: Correlation coefficients (e.g., Pearson or Spearman) between biomarker levels and depression severity scores reported in the included studies.

Quality assessment / Risk of bias analysis The risk of bias and quality of the included studies will be assessed using the Newcastle-Ottawa Scale (NOS).

Strategy of data synthesis
1. Data Aggregation:
We will aggregate the extracted data on biomarkers associated with immune or inflammatory processes in adolescents diagnosed with depression and healthy controls. The data will include mean levels and standard deviations of biomarkers measured in peripheral blood.
2. Meta-Analysis:
Model: We will use a random-effects model for the meta-analysis to account for variability among studies. This choice is based on the expectation of heterogeneity in study populations, diagnostic criteria, and biomarker assessment methods.
Standardized Mean Differences (SMDs): The primary effect size will be calculated using standardized mean differences (SMDs) to compare the levels of biomarkers between depressed adolescents and healthy controls. This approach allows for the combination of results from studies using different scales or units of measurement.
Software: Review Manager (RevMan) software will be used for conducting the meta-analysis.
3. Heterogeneity Assessment:
Statistical Tests: Heterogeneity among studies will be assessed using the I^2 statistic and χ^2 (χ^2) tests. An I^2 value greater than 25% will be considered indicative of significant heterogeneity.

Subgroup analysis We do not plan any specific subgroup analyses for this review. The primary focus is on comparing biomarkers associated with immune or inflammatory processes between adolescents diagnosed with depression and healthy controls. Heterogeneity among studies will be assessed using the I^2 statistic and χ^2 (χ^2) tests. Where significant heterogeneity is detected, it will be addressed through sensitivity analyses rather than predefined subgroup analyses.

Sensitivity analysis
1)Excluding Studies with High Risk of Bias:Sensitivity analysis was performed by excluding studies that received low scores on the Newcastle-Ottawa Scale (NOS) for quality assessment. This helped determine if the overall results were influenced by the inclusion of lower-quality studies.
2)Influence of Individual Studies:An influence analysis was conducted by systematically excluding one study at a time and observing the effect on the overall meta-analysis results. This helped identify if any single study disproportionately affected the findings.
3)Using Alternative Statistical Approaches:Although our primary analysis used a random-effects model, we also recalculated the results using alternative statistical approaches where appropriate to ensure the robustness of our conclusions.

Country(ies) involved China.

Keywords adolescent depression, biomarkers, immune, inflammation, literature review, meta-analysis.

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