International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Physiological outcomes associated with major depressive disorder in adolescents across multiple organ systems: a systematic review protocol

INPLASY202650072
doi: 10.37766/inplasy2026.5.0072
Received: 12 May 2026
Published: 13 May 2026

Kandakudy, L; Vergara, A; Van Voorhees, B.

Corresponding author:
Benjamin Van Voorhees

bvanvoor@uic.edu

Author Affiliation:
University of Illinois Chicago.

ADMINISTRATIVE INFORMATION

Support - This research was supported by the George R. Honig, MD, PhD, Endowed Professorship Fund.

Review Stage at time of this submission - Data extraction.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202650072

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 May 2026 and was last updated on 13 May 2026.

INTRODUCTION

Review question / Objective The aim of this systematic review is to identify the physiological outcomes associated with adolescent depression across multiple organ systems compared to healthy control adolescents. The PICOS framework was utilized to define and frame our primary research question:

P (Population): Adolescents aged 10–19 formally diagnosed with Major Depressive Disorder based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD).

I (Intervention): Not applicable.

C (Comparison): Healthy control adolescents.

O (Outcome): Physiological or biochemical changes associated with the following organ systems: Immune, Nervous, Cardiovascular, and Digestive.

S (Study Design): Peer-reviewed observational studies.'

Condition being studied Major Depressive Disorder (MDD), a leading cause of disability globally, is characterized by feelings of guilt or hopelessness, anhedonia, and other emotional disturbances. MDD is also associated with substance abuse, suicidal behaviors, and poor educational achievement. While the physiological effects of MDD in adults are well established, its physiological and biochemical effects in adolescents remain less well understood. This systematic review aims to synthesize findings from the existing literature on the physiological and biochemical outcomes associated with adolescent MDD, compared with those of healthy peers, from a multi-organ perspective.

METHODS

Participant or population The participants in all included studies were adolescents (aged 10-19

years) with a confirmed diagnosis of MDD based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD). Studies in which depression-specific physiological outcomes could not be separated from comorbid psychiatric or physical disorders were excluded. Studies with a mixed age population were included if adolescent-specific data were extractable. No restrictions on gender or ethnicity were applied.

Intervention This systematic review did not describe or evaluate the dissemination or implementation of a specific intervention. Instead, the authors focused on the physiological alterations associated with adolescent MDD across the immune, nervous, cardiovascular, and digestive systems. Differences in inflammatory biomarkers, sympathetic and parasympathetic activity, heart rate variability, gut microbiome diversity, and other physiological measures were analyzed in adolescents with MDD compared with healthy peers.

Comparator To identify the physiological consequences of MDD in adolescents, this review included studies that used healthy control groups. The authors defined a healthy control group as adolescents without a diagnosis of any psychiatric or physical disorders. Inclusion of this comparator allowed for direct comparisons of physiological measures (e.g. inflammatory biomarkers, sympathetic and parasympathetic activity, heart rate variability, gut microbiome diversity) between adolescent with MDD and their healthy counterparts. By using a healthy control group, exhibited differences in physiological measures could be more directly linked with MDD rather than underlying confounding variables.

Study designs to be included This review included peer-reviewed observational studies.

Eligibility criteria The authors deemed a study eligible for the review if the following conditions were met: (1) participants were adolescents aged 10–19 years with a formal diagnosis of MDD; (2) diagnosis of MDD was based on the latest criteria from the DSM or ICD; (3) participants did not have comorbid psychiatric or physical disorders; (4) the comparator met the definition described above; (5) the study reported a primary outcome consisting of a specific physiological disturbance associated with adolescent MDD; (6) studies that only measured depressive symptoms in participants without a formal diagnosis of MDD were excluded; (7) the study was published in English on or after 2010, aligning with modern diagnostic practices for depression as outlined in the DSM-5; (8) studies with insufficient data or unclear results were excluded; and (8) case reports, reviews, conference abstracts, and meta-analyses were excluded.

Information sources Literature on adolescent MDD was obtained from four electronic databases: Cochrane Library, PubMed, PsycINFO, and SCOPUS. Dissertations and theses databases, grey literature databases, and other non-bibliographic databases were not used.

Main outcome(s) The differences in the following physiological measures were analyzed for each organ system in this systematic review between adolescents with MDD and healthy counterparts:
Immune system: serum and plasma cytokine levels (e.g., TNF-α, IL-1β, IFN-γ, IL-2, IL-4, IL-6, and IL-8)
Nervous system: sympathetic and parasympathetic activity, gray and white matter volume
Cardiovascular system: heart rate variability and cardiac autonomic control
Digestive system: gut microbiome diversity.

Quality assessment / Risk of bias analysis The quality and risk of bias of all studies included in this systematic review will be analyzed via the Newcastle-Ottawa Scale for observational studies. Two reviewers will independently assess the included studies. Disagreements will be resolved by the principal investigator.

Strategy of data synthesis Due to the expected heterogeneity in outcomes and methods across studies involving different organ systems, a quantitative analysis will not be conducted. Data synthesis will involve qualitative analysis only. The authors plan to organize studies into 4 different groups based on the primary organ system being evaluated, including the Immune, Nervous, Cardiovascular, and Digestive systems. Within each organ system group, physiological and biochemical outcomes will be summarized and compared between adolescents with MDD and healthy control participants. The main results and outcomes of each included study will be summarized in structured comparative tables. Within the tables, reported physiological or biochemical disruptions (e.g., inflammatory biomarkers, nervous system activity, heart rate variability, neurological measures, gut microbiome diversity, and more) will be outlined and synthesized descriptively.

Subgroup analysis The authors do not plan to conduct any formal subgroup analyses in this systematic review.

Sensitivity analysis The authors do not plan to conduct formal quantitative sensitivity analyses due to the expected heterogeneity in outcomes and methods across studies involving different organ systems. However, data analysis of the included studies will be conducted through a qualitative narrative lens, thoroughly examining study quality, risk of bias, sample size, and population characteristics.

Country(ies) involved United States of America.

Keywords Major depressive disorder; Adolescent depression; Immune system; Nervous system; Cardiovascular system; Digestive system; Physiological measures.

Contributions of each author

Author 1 - Lestin Kandakudy.
Email: lkand3@uic.edu
Author 2 - Alaina Vergara.
Email: alainajvergara@gmail.com
Author 3 - Benjamin Van Voorhees.
Email: bvanvoor@uic.edu