

Genetic and Environmental Influences on Major Depressive Disorder

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Introduction

Major Depressive Disorder (MDD) is a complex mental health disorder influenced by biological and environmental factors. Adolescence and young adulthood are important periods because depressive symptoms and first episodes can emerge during these years. Research suggests that MDD is polygenic, meaning many genetic variants contribute to susceptibility rather than one single “depression gene.” Large genome-wide studies have identified hundreds of genetic signals associated with depression. Childhood adversity, including abuse, neglect, family conflict, and other stressful experiences, is also associated with increased depression risk. A 2024 systematic review and meta-analysis of 87 studies and 213,006 participants found that early-life adversity was associated with greater odds of youth depression (OR = 2.14), with emotional abuse showing an even stronger association (OR = 4.25). However, an important question remains: Do genetic differences change how strongly childhood adversity is related to depression? This possible relationship is known as a gene x environment (GxE) interaction.

Objectives

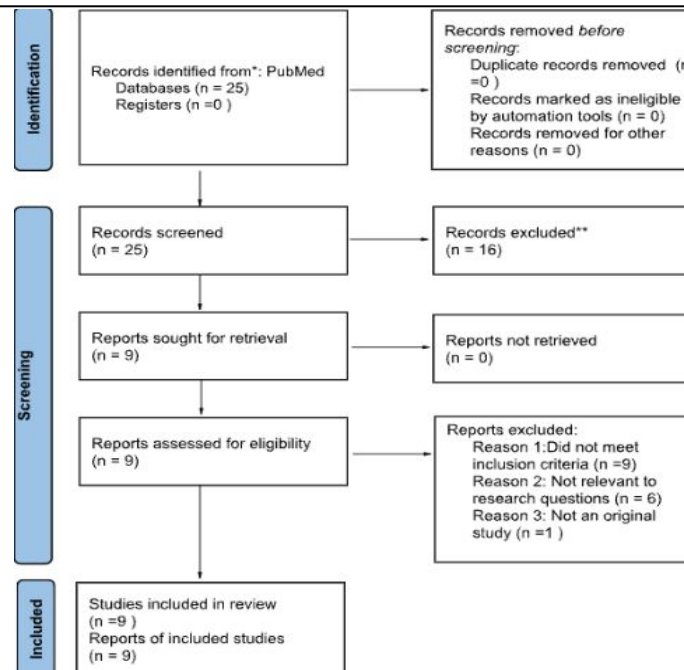
This systematic review aims to examine how genetic predisposition and childhood adversity are associated with depression in adolescents and young adults ages 15–25. It also aims to determine whether genetic risk changes the relationship between childhood adversity and depression, known as a gene x environment (GxE) interaction.

Methods

A systematic review was conducted using PubMed as the primary database. Searches used combinations of terms related to depression, genetics, polygenic risk, childhood adversity, adolescents, young adults, and gene x environment interactions. Studies were screened by reviewing their titles and abstracts, followed by the full text when they appeared relevant to the research question. Studies were included if they examined depression or depressive symptoms, genetic risk or genetic factors, and childhood adversity or other relevant environmental factors in adolescents and/or young adults. Studies that did not address these factors or were not original research studies were excluded. For each included study, information such as sample size, population, genetic measure, adversity measure, depression measure, main findings, GxE results, and limitations was recorded and compared to identify patterns across the research.

Results

Across the studies reviewed, both genetic factors and childhood adversity were associated with depression. A large genetic study of 807,553 participants identified 102 independent genetic variants, 269 genes, and 15 gene sets associated with depression (Howard et al., 2019). A 2024 meta-analysis of 87 studies and 213,006 participants found that early-life adversity was associated with greater odds of youth depression (OR = 2.14), while emotional abuse showed an even stronger association (OR = 4.25) (Yu et al., 2024). A review of 20 youth studies found that 16 (80%) reported at least one significant gene x environment interaction (Dunn et al., 2011). However, a later meta-analysis of 5,765 participants across 9 cohorts found no significant interaction between polygenic risk and childhood trauma (Peyrot et al., 2018). Overall, the findings show that genetic risk and childhood adversity are both associated with depression, but evidence for their interaction is mixed.



Discussion

The literature supports both genetic susceptibility and childhood adversity as important contributors to depression. However, evidence for a consistent gene x environment interaction is mixed. The 80% finding from the earlier youth GxE review suggests that interactions have frequently been reported. However, later genome-wide research has produced conflicting results. The 2014 study by Peyrot et al. found evidence that childhood trauma strengthened the effect of polygenic risk, while the larger 2018 meta-analysis did not find a significant genome-wide interaction. One possible explanation is methodological heterogeneity. Studies differ in the genetic measures they use, the type and timing of adversity measured, how depression is defined, and whether adversity is measured prospectively or retrospectively. The newer longitudinal evidence is especially useful because it suggests that how childhood adversity is measured may influence whether a GxE relationship is detected.

Conclusion

This systematic review found that both genetic predisposition and childhood adversity are associated with depression in adolescents and young adults, but the evidence for a consistent gene x environment interaction is mixed. Differences in genetic measures, childhood adversity measures, populations, and study designs made the results difficult to compare. Future research should use larger, more diverse, and long-term studies with consistent measures to better understand how genetic risk and childhood adversity work together. Understanding this relationship could help public health systems identify young people at higher risk and support earlier prevention, screening, and access to mental health care.

References

