DO GENETIC PREDISPOSITIONS MODULATE EXPRESSION OF MAJOR DEPRESSIVE DISORDER (MDD) SYMPTOMS IN ADOPTED ADOLESCENTS RAISED IN THE ABSENCE OF PARENTAL MDD? A LONGITUDINAL COMPARATIVE ANALYSIS USING THE EARLY GROWTH AND DEVELOPMENT STUDY

by

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Title: Do Genetic Predispositions Modulate Expression of Major Depressive Disorder (MDD) Symptoms in Adopted Adolescents Raised in the Absence of Parental MDD? A Longitudinal Comparative Analysis Using the Early Growth and Development Study

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Rates of major depressive disorder (MDD) have increased in the United States over recent years, with children and adolescents particularly affected. MDD is a multifactorial condition influenced by both genetic and environmental factors and is among the most prevalent mental disorders. Adoption studies offer unique insights into the interplay between genetic and environmental influences by isolating genetic predispositions from environmental factors. Using data from the Early Growth and Development Study (EGDS), this study investigates the role of genetic predisposition to MDD among adopted adolescents raised in environments without parental MDD. Adoptees' scores on the Patient-Reported Outcomes Measurement Information System (PROMIS) depression measures were compared at ages 15 and 18 across two groups based on their biological parents' responses to the Beck Depression Inventory-II (BDI-II): adoptees with a high genetic predisposition to MDD (BDI-II score of 29 or greater) and those with a low genetic predisposition to MDD (BDI-II score of 13 or lower). Analysis of PROMIS scores using a two-way, mixed, repeated measures ANOVA revealed no significant main effect for genetic predisposition, $F(1,36) = 0.283$, $p = 0.598$, no significant main effect for age, $F(1,36) = 0.909$, $p = 0.347$, and no significant interaction between genetic predisposition and age, $F(1,36) = 0.218$, $p = 0.643$ These findings suggest that genetic predisposition alone may not be sufficient to predict adolescent depressive symptoms in the absence of parental MDD, underscoring the importance of considering both genetic and environmental factors when assessing adolescent depression risk.

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Introduction

Major depressive disorder (MDD) is an internalizing mental health condition denoted by symptoms including feeling sad or hopeless, loss of interest or pleasure in activities, and changes in appetite, sleep, or energy (American Psychiatric Association, 2022). Rates of MDD symptoms among adolescents ages 13-18 years have risen dramatically in the United States in recent years (Keyes et al., 2019). From 2005 to 2017, the rate of adolescents reporting symptoms consistent with MDD in the last 12 months increased by 52% (from 8.7% to 13.2%) (Sliwa, 2019). Among individual ages 12 and older, this upward trend in MDD was further exacerbated by the COVID-19 pandemic, with rates of MDD increasing from 8.2% in 2013-2014 to 13.1% from 2021-2023 (Brody & Hughes, 2025). MDD symptoms among children and adolescents are associated with poor scholastic performance, lower interpersonal trust, and more negative body image (Wartberg et al., 2018). Additionally, adolescent MDD is linked to significant functional impairment, including increased risk of substance misuse (Marino et al., 2024), elevated suicidal ideation and attempts (Orri et al., 2020), and long-term economic consequences through reduced educational attainment and lower future earnings (Fletcher, 2012), underscoring the need to better understand factors contributing to MDD.

MDD is widely recognized as a disorder influenced by the complex interplay between genetic predispositions and environmental influences (Heim & Binder et al., 2011; Kendler et al., 2006). For example, environmental influences on MDD risk include severe childhood trauma (Negele et al., 2015), emotional and physical neglect (Springer et al., 2007), major life stressors (Kendler et al., 1999), early parental loss (Agid et al., 1999), and, most importantly, diagnosable parental MDD (Downey & Coyne, 1990). The unique contribution of genetic and environmental

factors to the development of MDD has been explored via a variety of different methodological approaches.

Family and Twin Studies of Genetic and Environmental Influences on MDD

In a meta-analysis of family, twin, and adoption studies, Kendler et al. (2006) found substantial evidence for genetic contributions to MDD. Twin studies in Kendler and colleagues' (2006) analysis indicated that familial aggregation of MDD was primarily due to additive genetic effects, with a heritability estimate of 37% (95% CI: 31–42%). Sullivan et al. (2000) conducted a complementary meta-analysis of five large, methodologically rigorous twin studies (N = 21,807), which yielded a nearly identical heritability estimate of 37% (95% CI: 33–42%). Moreover, heritability estimates varied by severity: clinical samples with more severe MDD symptoms exhibited higher genetic influence (43–50%) compared to community samples with milder MDD symptoms (34–38%).

Kendler and colleagues' (2006) meta-analysis found that environmental effects shared by siblings (e.g., emotional climate created by parents, socioeconomic status, and local environment qualities) had negligible effect on liability to MDD (0%; 95% CI: 0–5%), while nonshared (i.e., individual-specific) environmental factors (e.g., stressful life events, unique peer groups) and measurement error accounted for the remaining variance in liability to MDD (63%; 95% CI: 58–67%). Sullivan and colleagues' (2000) analysis similarly concluded that individual-specific environmental influences, rather than shared family environment, accounted for the majority of the variance in liability to MDD.

Collectively, these findings underscore the importance of an integrative model that considers both genetic predispositions and individual-specific environmental exposures in the etiology of MDD. Notably, interpretations of biological family studies are constrained by passive

gene–environment correlation, wherein genetic inheritance and environmental context are confounded, complicating efforts to disentangle their independent effects (Plomin et al., 1977; Rutter et al., 2001).

Adoption Studies Disentangling Genetic and Environmental Influences on MDD

Adoption studies, which examine children raised in non-biological environments, offer a valuable framework for disentangling genetic and environmental influences on MDD, allowing researchers to isolate genetic risk factors from environmental risk factors (D'Onofrio, 2008). These studies mitigate the limitations of biological family studies, offering a clearer view of both genetic and environmental influences (Rutter et al., 2001). Early work by Cadoret et al. (1985) demonstrated that individuals adopted away at birth whose biological parents had been diagnosed with one or more affective disorders (a broader category of mood disorders that includes MDD as well as bipolar disorders and other mood disturbances; Sekhon & Gupta, 2023) were more likely to exhibit depressive symptoms—based on adoptive parent and adoptee reports—than adoptees whose biological parents had no such diagnosis, providing evidence for genetic transmission of MDD. Specifically, as described by Sullivan et al. (2000), Cadoret et al. (1985) reported an odds ratio (OR) of 2.54 (95% CI: 1.00–6.47) for the genetic heritability of MDD, meaning that the odds of exhibiting depressive symptoms were 2.54 times higher for adoptees whose biological parents had an affective disorder than for adoptees whose biological parents did not have an affective disorder. However, in three more recent adoption studies examining MDD-related phenotypes in children (Eley et al., 1998; Tully et al., 2008; Van den Oord et al., 1994), researchers found limited evidence for strictly genetic transmission of risk for MDD.

For instance, Van den Oord et al. (1994) conducted an adoption study examining problem behaviors in internationally adopted children using the Child Behavior Checklist. Their findings revealed minimal evidence for genetic influence on internalizing problems, with correlations between siblings on the anxious/depressed subscale showing no advantage for biological siblings (r = 0.08 for girl pairs) compared to unrelated adopted siblings (r = 0.20 for girl pairs). Statistical modeling confirmed that genetic influences were negligible for internalizing behaviors, with individual-specific environmental factors accounting for the majority of variance. This pattern differed notably from externalizing behaviors, which showed substantial genetic influence (accounting for 65% of variance).

Similarly, Eley et al. (1998) conducted an adoption study examining MDD symptoms in middle childhood using data from the Colorado Adoption Project. Their findings revealed negligible evidence for genetic influence on childhood symptoms of MDD, with small correlations in MDD symptoms between biologically related siblings (r = 0.01) and unrelated adopted siblings (r = 0.21) based on self-report measures. Parent-offspring correlations in symptoms of MDD were similarly low between biological mothers and their adopted-away children (r = 0.04), providing no evidence for genetic transmission. Instead, results suggested that environmental factors, particularly individual-specific environmental influences, substantially accounted for variance in MDD symptoms during middle childhood, with shared environment playing only a modest role. These findings contrast with twin studies showing moderate heritability for MDD symptoms, suggesting that genetic influences on childhood MDD may be more limited than previously estimated. Notably, Eley and colleagues speculated that stronger genetic effects might emerge later in development, during adolescence and adulthood, highlighting the potential developmental specificity of genetic influences on MDD.

Finally, Tully et al. (2008) compared rates of lifetime MDD in (a) non-adopted adolescents whose biological parents had been diagnosed with MDD to (b) adopted adolescents whose adoptive (non-biological) parents had been diagnosed with MDD, which were, in turn, compared to (c) adopted adolescents whose adoptive parents did not have MDD. The odds for having MDD were highest among non-adopted adolescents with a depressed biological parent (OR = 2.96), which supports the role of genetic transmission in MDD. However, Tully et al. also found that adopted adolescents whose adoptive parents had MDD had significantly greater odds of developing MDD themselves (OR = 2.19) compared to adopted adolescents whose adoptive parents did not have MDD. This suggests that environmental exposure to parental depression, independent of genetics, contributes meaningfully to adolescent risk for MDD. More recent studies examining birth mother internalizing disorders and young children in adoptive families (Kerr et al., 2013), genetic risk for antisocial behavior in adoptive families (O'Connor et al., 1998), and gene-environment interactions regarding MDD symptoms (Dunn et al., 2011), have found that diagnosed parental MDD is a critical environmental risk factor for depression in children (Natsuaki et al., 2014).

Collectively, these findings suggest that diagnosed parental MDD, or the presence of MDD symptoms in parents, may contribute to the environmental transmission of risk for MDD to children. This may occur through increased exposure to depressogenic behaviors (e.g., social withdrawal, irritability, negative self-talk), emotional dynamics (e.g., emotional unavailability, inconsistent responsiveness, expressed hopelessness), or related stressors (e.g., family conflict, disrupted routines, economic instability). Conversely, supportive environments may buffer against MDD. For instance, Leve et al. (2009) found that children with genetic risk for MDD (as indicated by birth parent self-report using the 21-item Beck Depression Inventory) who were

raised in supportive adoptive homes showed fewer behavioral problems than would be predicted by genetic risk alone. Although Leve et al. (2009) stands as an exception, few studies have specifically assessed how MDD-related genetic vulnerability might be expressed in environments systematically free from parental MDD.

Current Study

The current study extends this line of inquiry by employing a comparative analysis that specifically isolates genetic predisposition from the environmental influence of parental MDD. My use of the Early Growth and Development Study (EGDS) dataset, with its prospective longitudinal design and standardized assessment protocols, provides methodological advantages over adoption studies that have typically relied on medical records or retrospective reporting of MDD symptoms (Rice, 2010). The EGDS's assessment of both birth and adoptive parents, coupled with measurement of adoptee outcomes at developmentally significant ages (ages 15 and 18 years), allows for more nuanced analysis of how genetic vulnerability might manifest across adolescence—a critical period for MDD onset (Thapar et al., 2012). My approach also extends beyond traditional adoption studies by employing standardized, contemporary measures of MDD from the Patient-Reported Outcomes Measurement Information System (PROMIS; Cella et al., 2010). Specifically, this study compares adopted children with a genetic predisposition to MDD to those without a genetic predisposition to MDD, all of whom were raised by adoptive parents who did not report significant MDD symptoms when the adoptee was age 9 months. By assessing how genetic vulnerability to MDD manifests when children are raised in adoptive environments free from significant parental MDD symptoms, this study will further our understanding of how genetic and environmental factors uniquely contribute to mental health outcomes in adopted children.

Method

Participants and Procedures

Data for the current study were drawn from the EGDS (Leve et al., 2007; Leve et al., 2019). The EGDS dataset contains 361 cases representing adopted children and their adoptive and birth parents (Leve et al., 2019). Adoptive and birth parents were recruited between January 2003 and January 2006 following the birth of a child through 33 adoption agencies across 10 states in the Mid-Atlantic, West/Southwest, Midwest, and Pacific Northwest regions of the United States, representing diverse agency types including public, private, religious, secular, and those with varying adoption philosophy approaches. Once recruited, participants were asked to complete longitudinal assessments of social competence, externalizing behaviors, and internalizing behaviors, including symptoms of MDD (see Table 3 of Leve et al., 2007, for a complete list of measures). Participants were included in the EGDS study based on five criteria: (a) completion of a domestic adoption placement, (b) placement of the infant within 3 months postpartum, (c) placement with a nonrelative adoptive family, (d) absence of major medical conditions in the infant (e.g., extreme prematurity or extensive medical surgeries), and (e) birth and adoptive parents' ability to read or understand English at the eighth-grade level. All families meeting these criteria during the recruitment period were considered for enrollment. Birth parents completed self-report MDD assessments at 5, 10, and 20 months postpartum. Adoptive parents completed self-report MDD assessments every 9 months until their adoptee reached 27 months of age. Adoptees were screened for MDD using self-report measures at ages 15 and 18 years.

To be included in the current study, *adoptive* parents had to report the absence or minimal presence of MDD symptoms when their adoptee was 9 months postpartum; a total of 7 cases

were removed due to missing data on the MDD symptom measure (n = 354). To create more distinct comparison groups (i.e., high vs. low genetic risk), participants were excluded if one or both *birth* parents' responses to the assessment of MDD symptoms at 5 months postpartum suggested they may have moderate MDD (n = 50) or were missing data on this variable (n = 137). That is, only data from the 167 participants whose birth parents reported no or only mild MDD symptoms (n = 127) or severe MDD (n = 40) at 5 months postpartum were included. Further cases were removed due to missing MDD symptom data among adoptees at ages 15 years (n = 47), 18 years (n = 49), and both 15 and 18 years (n = 33), as both measurements were required for our longitudinal analysis.

The final analytical sample included 38 adopted children (20 males, 18 females) and their adoptive families (35 families with one mother and one father, two families with two fathers, and one family with two mothers), as well as their biological parents. Of these, 19 were categorized as having a higher genetic predisposition to MDD (9 female, 10 male), and 19 were categorized as having a lower genetic predisposition to MDD (9 female, 10 male).

Measures

Demographics

The EGDS collected detailed demographic information from adoptive parents, birth mothers, and birth fathers using several versions of a Demographic Recruitment Form created for the study. This form included structured questions addressing household composition, child status, socioeconomic variables, and personal background. For adoptive parents, the form asked about the number of biological and adopted children in the home, with response options ranging from *0* to *4 or more*. Family composition was documented, distinguishing between heterosexual couples, same-sex couples, and single-parent households. Marital status was categorized with

options such as married, remarried, separated, divorced, single (never married), widowed, or living with a romantic partner.

Occupational information was collected through open-ended questions. Religious affiliation was assessed with multiple-choice options including Catholic, Protestant, Baptist, Methodist, Jewish, Muslim/Islamic, Buddhist, None, and Other, with space to specify if "Other" was selected. Annual gross household income was captured using predefined ranges (e.g., less than $20,000; $20,000–$39,000; up to $100,000 or more). Age was recorded as a numerical value in years. Ethnicity was coded based on U.S. Census definitions as Hispanic or Latino or Not Hispanic or Latino, and race was categorized as American Indian/Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, more than one race, Hispanic/Latino descent, or unknown/not reported. Educational attainment was captured through a 12-point scale, ranging from having completed less than 8th grade to having completed professional or graduate school, with an additional "Other" category that allowed for further specification.

Birth parents were asked many of the same demographic questions as adoptive parents, with slight adaptations. These included assessments of number of children, marital status, occupation, income, religion, ethnicity, race, and education. For birth mothers, additional questions included relationship status with the birth father and knowledge of the birth father's identity. The structure and phrasing of the questions were standardized to allow consistent coding across the sample.

MDD Symptoms

The Beck Depression Inventory-II (Beck et al., 1996) was employed to assess symptoms and presumptive presence of MDD in both birth and adoptive parents. The BDI-II comprises 21

items; however, item 9 (assessing suicidal ideation) was excluded, resulting in a 20-item assessment. Participants were instructed to select one of four statements per item that best characterized their emotional state during the preceding 7 days. For example, the sadness item presents the following response options: *I do not feel sad* (0), *I feel sad* (1), *I am sad all the time and I can't snap out of it* (2), and *I am so sad or unhappy that I can't stand it* (3). Items are summed to yield a total score ranging from 0 to 60. Higher scores indicate greater severity of MDD symptomatology. Following established clinical cutoffs (Smarr & Keefer, 2011), adoptees were categorized on the basis of their birth parents' scores as having a higher genetic predisposition to MDD (i.e., birth parent BDI-II score was between 29 and 60, indicating moderate-to-severe MDD symptoms) or a lower genetic predisposition to MDD (i.e., birth parent's BDI-II score was 13 or lower, indicating the presence of no or only mild MDD symptoms). Adoptees whose birth parents' scores on the BDI-II were between 17 and 28 were excluded to create more distinct comparison groups.

Measures from the PROMIS (Cella et al, 2010) were used to assess the likely presence of MDD in adoptees. The PROMIS depression measures have demonstrated strong convergent validity with other widely used self-report measures of MDD (Milette et al., 2010; Pilkonis et al., 2014), including the Center for Epidemiological Studies Depression Scale for adults (CES-D; Radloff, 1977) and the Patient Health Questionnaire (PHQ-9; Spitzer et al., 1999). At age 15 years, all adoptees were assessed using the PROMIS Pediatric Bank v2.0 Depressive Symptoms (Cella et al., 2010), which measures MDD symptoms in adolescents ages 11 to 17. This measure includes 14 items asking participants to report how often they experienced specific symptoms related to MDD (e.g., "I felt sad") over the past 7 days, with response options of never (1), almost never (2), sometimes (3), often (4), and almost always (5). Items are summed to form a

total score, ranging from 14 to 70. At age 18 years, the same adoptees were re-assessed using the PROMIS Adult Item Bank v.1.0 – Emotional Distress – Depression - Short Form (Cella et al., 2010). This measure includes 8 items asking participants to report how often they experienced specific symptoms related to MDD (e.g., "I felt sad") over the past 7 days, with response options of never (1), rarely (2), sometimes (3), often (4), and always (5). Items are summed to form a total score, ranging from 8 to 40. The adult version includes items focused on feelings of worthlessness, helplessness, and hopelessness that are not present in the child version, and the child version includes items about loneliness, stress, and social functioning that are not present in the adult version. For both the pediatric and adult PROMIS depression measures, higher raw scores are indicative of greater severity of MDD. To allow comparison across measures, raw scores were converted to T-scores, which have a mean of 50 and a standard deviation of 10 in the reference population, using conversion tables created by the measures' developers. T-scores were calculated by matching each participant's raw score to its equivalent T-score value on the age-appropriate PROMIS scoring table. T-scores were then interpreted as follows: scores below 55.0 indicated the absence or minimal presence of MDD (i.e., none to slight); scores of 55.0-59.9 indicated mild MDD; scores of 60.0-69.9 indicated moderate MDD; and scores of 70 and over indicated severe MDD.

Data Analysis

Data were organized by genetic risk (high vs. low) and measurement time point (adoptee age 15 vs. 18). I conducted a mixed two-way repeated measures analysis of variance (ANOVA) using the Real Statistics Resource Pack add-in for Microsoft Excel to assess the effect of genetic predisposition (high vs. low) as a between-subjects factor and age (15 vs. 18) as a repeated, within-subjects factor on MDD symptoms, as well as their interaction. I considered effects

statistically significant if they demonstrated a *p*-value below 0.05. Cell means were calculated as descriptive statistics and used to interpret the nature of effects. I created bar graphs to visualize individual PROMIS T-scores and level of MDD symptoms based on those T-scores by genetic risk group and age. To visualize the distribution of depression severity levels across groups, I created a frequency table that categorized participants by depression level based on PROMIS T-scores (i.e., none to slight, mild, moderate, severe), genetic risk for MDD (high vs. low), and age (15 vs. 18). I entered the raw counts for each severity category and time point into a structured table in Microsoft Excel. This table served as the basis for a clustered bar chart that illustrates changes in depression severity by genetic risk group across the two ages.

Results

Descriptives

As shown in Figure 1, PROMIS depression T-scores at ages 15 and 18 for participants *without* a genetic risk for MDD display there is variation across individuals, with some differences observed between the two time points. Figure 2 shows a similar pattern among participants *with* a genetic risk for MDD, with individual scores varying at both ages 15 and 18. At age 15, participants without a genetic predisposition to MDD had a mean PROMIS score of 51.95 ± 14.38, while those with a genetic predisposition to MDD had a mean PROMIS score of 52.96 ± 10.48, $d = 0.08$. Similarly, at age 18, participants without a genetic predisposition to MDD had a mean PROMIS score of 52.75 ± 10.47, while those with a genetic predisposition to MDD had a mean PROMIS score of 55.30 ± 10.09, $d = 0.25$. To visually contextualize symptom severity, Figure 3 provides a categorical breakdown of PROMIS depression T-scores illustrating how participants were distributed across severity levels—none to slight, mild, moderate, and severe—by genetic risk status and age.

Figure 1

PROMIS Depression T-Scores for Participants without Genetic Risk for Major Depressive Disorder (MDD)

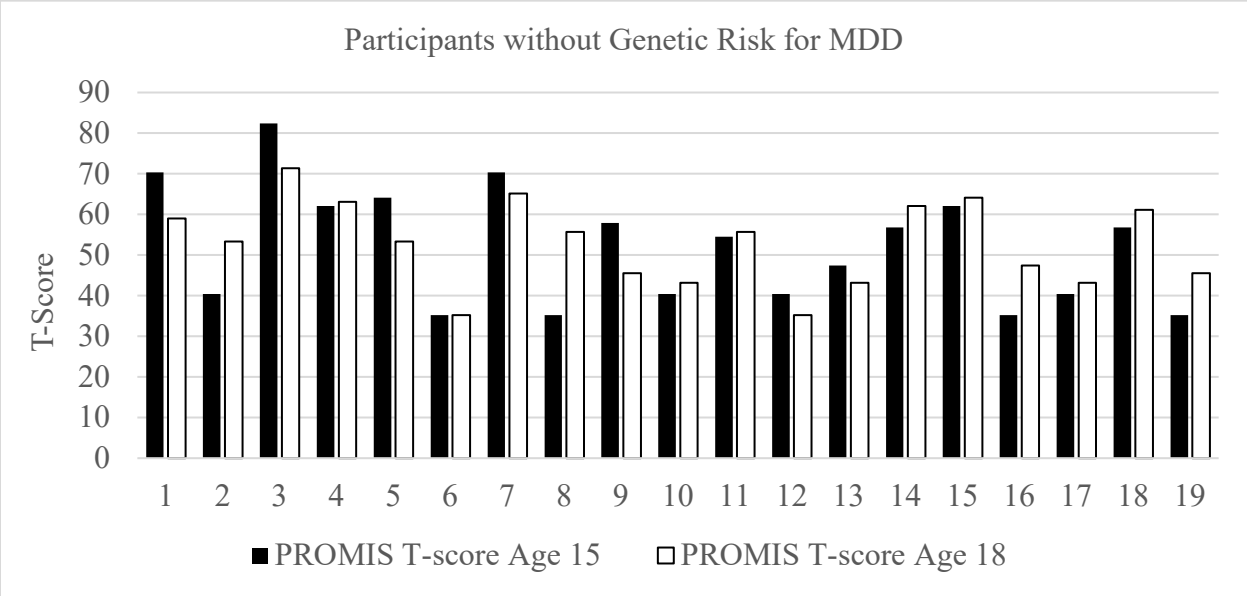


Figure 2

PROMIS Depression T-Scores for Participants with Genetic Risk for Major Depressive Disorder (MDD)

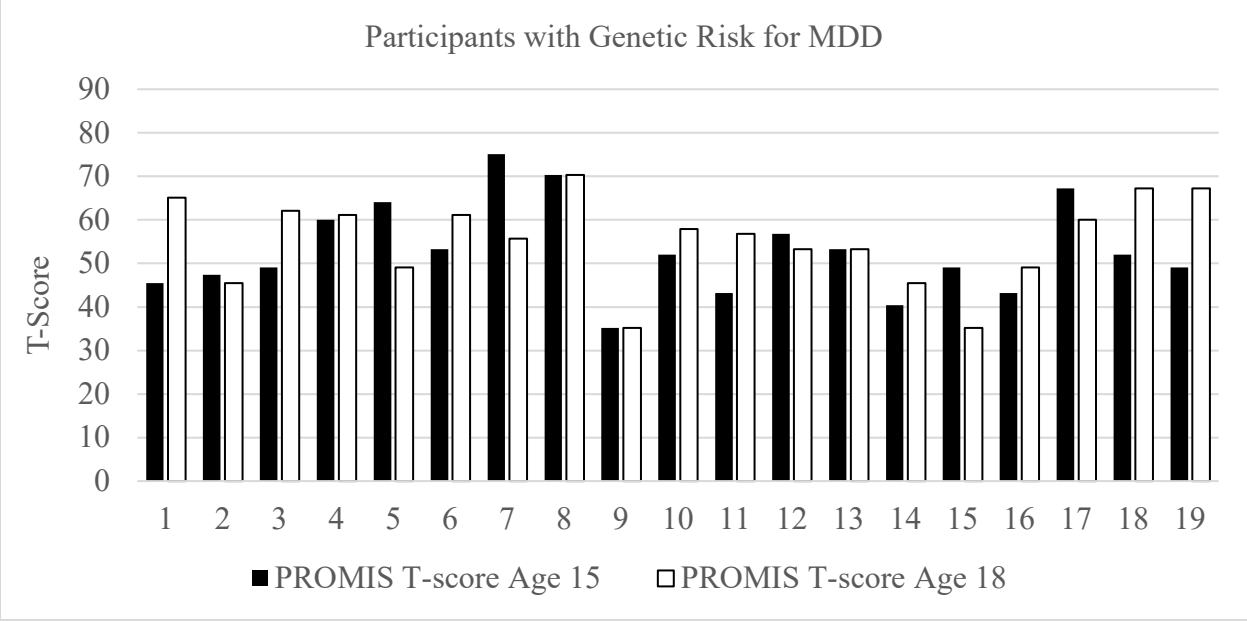
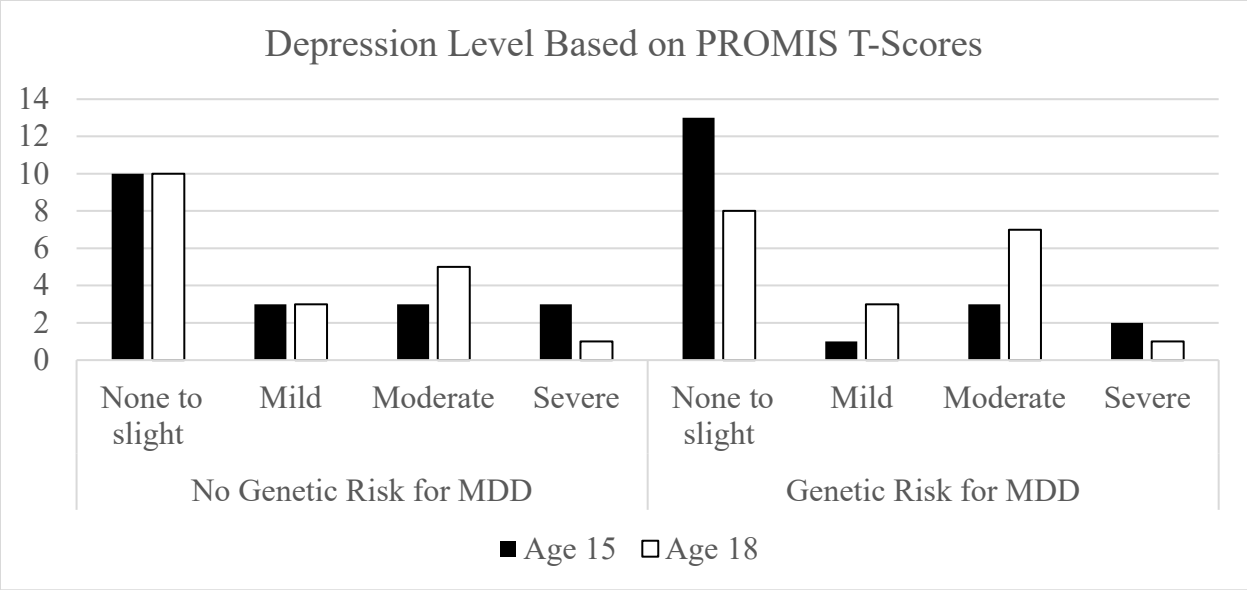


Figure 3

Depression Severity Levels based on PROMIS T-Scores by Age and Genetic Risk for Major Depressive Disorder (MDD)



Primary Analysis

The mixed, repeated measures two-way ANOVA did not reveal a statistically significant difference between the genetic predisposition group (MDD Risk) and the non-genetic predisposition group (No Risk), $F(1, 36) = 0.283$, $p = 0.598$. Similarly, there was no significant main effect for age, $F(1, 36) = 0.909$, $p = 0.347$, and no significant interaction between genetic predisposition and age, $F(1, 36) = 0.218$, $p = 0.643$. These findings indicate that MDD symptoms, as assessed by the PROMIS, did not significantly differ on the basis of genetic predisposition to MDD in our adolescent population at either age 15 or age 18, leaving open the possibility that genetics may not have been influential in these cases.

Discussion

This study investigated the relationship between genetic predisposition to MDD and MDD symptoms as assessed with PROMIS scores in adopted adolescents living in an adoptive environment without parental MDD at two developmental time points: age 15 and 18 years. MDD is widely recognized as a complex, polygenic disorder with both genetic and environmental determinants (Dunn et al., 2015). Numerous twin and adoption studies have established a clear genetic basis for MDD (Lau & Eley, 2009 & Sullivan et al., 2000); however, contrary to this past research and my hypotheses, no statistically significant differences were observed in MDD symptoms between groups with and without a genetic predisposition to MDD. However, as the null cannot be proven, my findings should not be interpreted as evidence against genetic influences on MDD.

One potential explanation for the discrepancy between research demonstrating strong heritability of MDD and the current findings lies in the fact that many genetic heritability estimates are derived from studies that do not adequately account for environmental influence. This is particularly relevant regarding the presence of parental MDD, a well-established environmental risk factor, especially in the context of maternal MDD (Natsuaki et al., 2014). The importance of considering environmental factors in the development of psychopathology in adolescents is supported by research showing the potency of environmental influences, with adoptive parents' psychopathology being more strongly correlated with adolescent psychopathology than birth parents' psychopathology (Marceau et al., 2024). Thus, failing to account for environmental factors, such as parental psychopathology, may lead to an overestimation of genetic contributions in studies of MDD. In contrast, our study specifically

examined adolescents raised in environments where parental MDD was ostensibly not a factor, a condition that may have attenuated the expression of genetic risk.

The PROMIS depression measures are validated and widely used tools for assessing MDD symptoms. Yet, despite their psychometric strengths, self-report measures inherently rely on subjective interpretations of emotional distress and may not fully capture underlying biological or neurophysiological factors associated with genetic risk. It is possible that structured clinical interviews or neurobiological assessments of MDD symptoms (e.g., functional MRI [fMRI], cortisol measurements, and event-related potentials [ERPs]), used alongside self-report measures, could have offered a more comprehensive picture of MDD symptomatology.

Beyond measurement considerations, several additional factors may have influenced the lack of significant differences. One key consideration is the role of resilience mechanisms in mitigating genetic risk. Research has found that social support (Southwick et al., 2005; Stice et al., 2004), positive coping strategies (Fortea et al., 2025, and stable early-life environments (Wade et al., 2015) may buffer against vulnerability for MDD. Given that all participants in the current study were raised in adoptive families without parental MDD, their environments may have provided protective effects that reduced the likelihood of MDD-symptom expression, even among those with a genetic predisposition to MDD.

Additionally, MDD is known to follow variable trajectories, with some individuals experiencing episodic symptoms while others show persistent distress (Heath & Camarena, 2002; Holsen et al., 2000). Participants were queried at ages 15 and 18 years about symptoms they experienced in the past 7 days; thus, if a person was not actively (or recently) experiencing MDD symptoms, the assessment would not have detected it. Previous longitudinal studies on adolescent psychiatric assessments have demonstrated the effectiveness of more frequent

measurement, implementing protocols that assessed subjects every 3-6 months throughout adolescence (Costello et al., 2003; Long et al., 2020). This approach may be more likely to detect MDD episodes, especially if the assessment asked about symptoms experienced since the last assessment (e.g., over the past 3 or 6 months vs. only the past 7 days).

Limitations

Limitations of the study offer important insights for future research. First, the sample size limited statistical power to detect small effects of genetics on MDD symptoms (Suresh & Chandrashekara, 2012), and Cohen's *d* estimates in this study were small (Cohen, 1988). Notably, one possible interpretation of the observed increase in effect size from age 15 ($d = 0.08$) to age 18 ($d = 0.25$) is that genetic influences on MDD may become more pronounced in later adolescence. Alternatively, adolescents may have greater self-awareness of MDD symptoms in later adolescence, leading to greater reporting. This pattern warrants further investigation to confirm and better understand the developmental trajectory of genetic risk.

Second, and related to the point above, the study relied on self-report measures, which do not capture biological markers associated with MDD, such as inflammatory biomarkers (Haapakoski et al., 2015), neuroendocrine indicators (Horowitz & Zunszain, 2015), or neurotransmitters like 5-HT1A (Kaufman et al., 2016. Future research would benefit from integrating objective biological assessments of known MDD markers, including polygenic risk scores from genetic samples, neuroimaging to examine brain structure and function, and physiological biomarkers in blood samples. These complementary approaches could help establish clearer connections between specific genetic variants and the mechanisms through which they influence MDD symptoms (Anderson et al., 2018.

Additionally, although the study controlled for parental MDD in the adoptive environment, the limitations to self-report as noted for adolescents are true for adoptive parents as well (i.e., only reported on the past 7-days at 9-month post-partum vs. assessing MDD at routine 3- or 6-month intervals across their child's life). Additionally, the study did not account for other environmental factors that may interact with genetic risk. For example, research has demonstrated that genetic predisposition to MDD often interacts with environmental stressors, such as early-life adversity or social isolation, to influence symptom expression (Lesch, 2004). I did not directly assess environmental stability factors such as family conflict or cohesion, peer victimization or bullying, school climate and sense of belonging, traumatic experiences, and discrimination. These unmeasured variables could play a substantial role in determining whether genetic predispositions manifest as MDD symptoms. Future studies should more comprehensively account for environmental influences beyond the home to more accurately assess how genetic and contextual factors jointly shape MDD symptoms over time.

Conclusion

This study provides valuable insights into the role of genetic predisposition in the onset of adolescent MDD symptoms, particularly in the absence of parental MDD in the adoptive environment. The absence of significant differences in MDD symptoms among adoptees who differ in genetic risk for MDD is consistent with research suggesting that genetic risk alone may not fully explain the manifestation of MDD symptoms; however, the present findings cannot be viewed as confirmation of an absence of genetic influence. Future research should further investigate how genetic predisposition interacts with environmental factors to influence the manifestation of MDD symptoms. Employing larger sample sizes, objective biomarkers of MDD, and more frequent longitudinal assessments that provide full coverage of the assessment window (vs. only the past 7 days) should help clarify the complex interplay between genetic and environmental influences on adolescent mental health.

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