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The Role of Familial Risk, Parental Psychopathology, and Stress for First-Onset Depression During Adolescence

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Abstract

Background: Adolescence represents a critical developmental period during which the initial onset of depression emerges. Family risk for depression is a salient risk factor for the initial onset of Major Depressive Disorder (MDD). We examined the effects of familial risk, stress, and behavior on the risk of developing first-onset depression.

Methods: Adolescents aged 12 to 15 with high ($n = 166$) or low ($n = 159$) familial risk for depression were assessed annually for up to five years. Stress was assessed using the Stressful Life Events Schedule and Childhood Trauma Questionnaire. The Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version was administered to the adolescents and their parents to assess lifetime psychiatric conditions and diagnose MDD onset. Survival and path analyses were used in tandem to determine the risk for first-onset depression as well as the contributions of additional direct and indirect pathways to onset.

Results: High-risk adolescents were eight times more likely to develop first-onset depression compared with low-risk adolescents. The path analyses revealed that the presence of maternal behavioral disorders and increased recent life stress directly predicted an initial onset of MDD in high-risk adolescents.

Limitations: The small samples used in this study limit the generalizability of these findings.

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Conclusions: Adolescents at high familial risk for depression had an increased risk for the emergence of first-onset depression during adolescence. Stress and maternal behavioral psychopathology directly contributed to depression onset independently of familial risk, while childhood trauma exerted an indirect effect on first-onset MDD through recent stress.

Keywords

Adolescence; Depression; Intergenerational Transmission; Stress

Introduction

Major Depressive Disorder (MDD), or depression, a mood disorder characterized by low mood, irritability, feelings of helplessness, and changes in cognitive and physical functioning, is the most common psychiatric condition (Angst et al., 2016; Avenevoli et al., 2015; Kessler et al., 2005). Depression accounts for 4.3 percent of all global disability-adjusted life years (DALY) and is the largest contributor to DALYs in middle- and high-income countries (Avenevoli et al., 2015; Lépine and Briley, 2011; Reddy, 2010). The World Health Organization estimates that 350 million people of all ages suffer from depression globally (Kessler and Üstün, 2004; Moussavi et al., 2007). Depression's effects on an individual's physical and mental health, as well as their social and economic welfare, make the disorder a global public health concern (Lépine and Briley, 2011; Moussavi et al., 2007; Reddy, 2010).

Depression can manifest at any point in the life span. It's incidence increases during adolescence, with youth between the ages of 13 to 18 years at particular risk (Avenevoli et al., 2015; Birmaher et al., 1996; Horwath et al., 1992; Weissman et al., 1999; Williamson et al., 2004). Developing MDD early in life is predictive of a grim prognosis --- individuals with depressive symptoms during middle childhood and adolescence are twice as likely to suffer from a full depression and are at significant risk for other psychiatric ailments, such as substance use and abuse, suicidal behaviors, and premature death due to suicide (Avenevoli et al., 2015; Briggs-Gowan et al., 2001; McLeod et al., 2016; Moussavi et al., 2007; Reddy, 2010; Rutter et al., 2006; Thapar et al., 2012; Weissman et al., 1999, 1987). Furthermore, individuals who experience adolescent-onset MDD are two to seven times more likely than their peers to experience another episode of depression even after controlling for various confounding factors, such as early life adversity, neuroticism, and comorbid psychiatric diagnoses (Fergusson and Woodward, 2002; Rueter et al., 1999; Rutter et al., 2006).

Given the protracted prognosis of adolescent-onset MDD, it is imperative to understand the associated risks, the most poignant of which is familial risk for depression (Avenevoli et al., 2015; Kessler et al., 2005; Rice et al., 2002; Rueter et al., 1999; Weissman et al., 1999, 1987; Williamson et al., 2004). A familial history of depression increases the risk of lifetime MDD onset by three to four times, with the risk being cumulative across generations such that individuals who have both a parent and grandparent with MDD are at the highest risk for disorder onset (Kessler et al., 2005; Rice et al., 2002; Weissman et al., 2016a, 1987; Williamson et al., 2004). Further exacerbating the risks associated with a family history of depression is the finding that the negative effects of a familial risk of depression are twofold

- having a high familial risk (HR) for depression corresponds to a higher risk for a lifetime diagnosis and earlier MDD onset and, thus, a more deleterious prognosis (Weissman et al., 2016a).

In addition to a familial history of depression, other forms of parental psychopathology have been implicated in adolescent-onset depression. In 2004, we reported that maternal lifetime anxiety disorders significantly added to the risk of the development of first-onset MDD (Williamson et al., 2004). Additionally, studies examining the relationship between child and parent psychopathology have found that, compared to their non-depressed peers, youth with depression are more likely to have mothers with anxiety disorders, substance use disorders, and suicide attempts (Mitchell et al., 1989). Taken together, these results suggest that, in addition to a familial history of depression, it is important to consider other lifetime psychiatric disorders as they may increase one's risk for developing first-episode depression.

The multi-risk factor model of depression transmission in high-risk families posits considerable overlap among environmental stressors associated with a heightened risk for depression and parental depression (Hammen et al., 2004). To this point, research has suggested that high-risk subjects are exposed to significantly more adverse conditions, which are created by their families and which in turn increase their risk for developing MDD independently of their familial risk for depression. High-risk families are more likely to exhibit familial conflict and marital discord and experience a greater number of stressful life events. One report noted that, for youth at high risk for depression (especially those with mothers and grandmothers with the disorder), maternal depression predicted lower perceived parenting quality by the youth and increased youth stress, and each of these independently predicted depression with their interaction predicting more severe depression (Hammen et al., 2004).

In addition to the environmental factors that disproportionally confer risk for depression on youth with HR, genetic factors have been shown to contribute additional risk. Recently, Feurer et al. reported that depressive symptoms were highest amongst the offspring of depressed mothers with higher hypothalamic-pituitary-adrenocortical (HPA) axis multilocus genetic profile scores who experienced the highest levels of interpersonal stress compared to their peers with lower depressive symptomology scores (Feurer et al., 2017). Furthermore, higher HPA axis multilocus scores are related to disturbed regulation of the HPA system, which is reflected by pathologically increased adrenocorticotropin and cortisol release in response to stress and which in turn increases risk for affective pathology (Modell et al., 1998). Together, these findings underscore that both genetic and environmental factors confer risk for depression amongst the youth of depressed parents, but certain factors, such as stress and parenting, may represent modifiable risk (Feurer et al., 2017).

Research on the children of depressed parents has made it clear that high-risk youth are more likely to be exposed to higher levels of stress than the children of non-depressed parents are (Williamson et al., 1998). However, stressful life events, both distal (i.e., early childhood adversity) and proximal (i.e., recent life stress), increase the risk of MDD onset amongst high- and low-risk youth. In terms of early life stress, epidemiological research has found that early life adversity accounts for as much as 54% of the population attributable

risk for depression (Andersen and Teicher, 2008). Specifically, adolescents with a history of childhood maltreatment are three times more likely to become depressed (Brown et al., 1999), and childhood maltreatment doubles the risk for recurrent and persistent depressive episodes (Nanni et al., 2012). In addition to distal life stressors, relationships among proximal life stressors and the onset of MDD in adolescence have been widely described (Williamson et al., 1998). In a study of 541 adolescents, Goodyer et al. reported that recent stressful events occurring within one month of assessment were associated with MDD onset and that 53% of MDD onsets in a 12-month period were preceded by a disappointing event or a loss event amongst the youth (Goodyer et al., 2000). Additionally, in a study of 103 depressed and non-depressed adolescents, those with a history of early life stress in the form of childhood abuse and/or neglect had a lower threat level (i.e., less objective stress) prior to onset of their first depressive episode than did those with no history of early life stress (Harkness et al., 2006). Hence, early life stress may sensitize one to the effects of later life stress, such that lower levels of proximal stress are necessary to precipitate MDD onset in youth with distal life stress.

Here, we report on a cohort of 325 adolescents with either HR or low familial risk (LR) for depression who were followed over a five-year period. Using survival and path analyses, we evaluated the direct and indirect effects of a familial risk for depression, distal and proximal stressors, and parental psychopathology on the onset of adolescent MDD. Extending from prior research, we hypothesized that (a) high-risk status and distal and proximal stress would directly affect MDD onset, (b) high-risk status and early life stress would both moderate the relationship between recent life stress and MDD onset, and (c) parental psychopathology would have indirect effects on MDD onset above and beyond those of high-risk status.

Methods

Study procedure

The participants in this study were recruited as part of the Teen Alcohol Outcomes Study (TAOS), the sampling and recruitment procedures for which have been previously described (Bogdan et al., 2012; Ramage et al., 2015; Swartz et al., 2017, 2015; White et al., 2012). Briefly, using commercially available information, families with an adolescent living within a 30-mile radius of the University of Texas Health Center at San Antonio were randomly contacted and phone-screened for participation in the TAOS study. Following screening for interest in the study and age eligibility, 1,089 youth between the ages of 12 years 0 months and 14 years 11 months were evaluated in person and classified as being at HR or LR for depression. Consistent with our prior research (Williamson et al., 2004), adolescents were determined to be at HR for depression if they had at least one first-degree and one second-degree relative with a lifetime history of major depression. Adolescents were identified as being at LR for depression if they had no first-degree and minimal second-degree relatives (<20%) with lifetime histories of depression (Williamson et al., 2004) (See Supplementary Table 1 for data on the prevalence of lifetime psychopathology amongst the first- and second-degree relatives of the HR and LR youth).

Of the 1,089 adolescents screened, 325 and their parents were selected from the randomly screened sample; 166 were in the HR group, and 159 were included in the LR group. In

addition to meeting the criteria for familial risk, adolescents were excluded if they met the criteria for any psychiatric diagnoses at the baseline assessment (with the exception of anxiety in the HR group), including externalizing disorder (e.g., Conduct Disorder and/or Attention-Deficit/Hyperactivity Disorder) (National Institute on Alcohol Abuse and Alcoholism, 2004). HR youth were not excluded on the basis of an anxiety disorder diagnosis given the large body of evidence demonstrating a link between anxiety and depression and our desire to enrich this sample for depression amongst HR youth (Williamson et al., 2005). Lifetime psychiatric disorders were assessed via interviews with both the adolescent and their parent(s) using the Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). The participants were reassessed annually for new-onset disorders and the persistence of existing conditions. In addition to the K-SADS-PL, the participants completed self-report measures of mood, anxiety, stress, and substance use, as described in more detail below. The study was reviewed and approved by the Institutional Review Board at the University of Texas Health Sciences Center at San Antonio.

Materials

Childhood Trauma Questionnaire (CTQ)

Twenty-five items of the 28-item CTQ short form (Cronbach's $\alpha = 0.81$) were used to assess exposure to five different types of childhood trauma: emotional, physical, and sexual abuse as well as emotional and physical neglect (Bernstein and Fink, 1998). Three items were excluded because they measured minimization and denial and did not assess childhood trauma. Higher scores on any of the subscales suggested greater exposure to different types of childhood trauma. The CTQ total score, which reflects a variety of forms of maltreatment and early neglect, has good reliability (Scher et al., 2001).

Stressful Life Events Schedule (SLES)

The SLES was used to assess the occurrence of stressful life events during the previous year (Williamson et al., 2003). The use of the SLES and the scoring used in this study have been described previously (Bogdan et al., 2012; Ramage et al., 2015; Swartz et al., 2017). Briefly, the SLES assesses the presence and occurrence of age-appropriate stressors in children and adolescents across several domains (e.g., family, friends, and school). For example, the SLES investigates the adolescent's relationship difficulties and health concerns, deaths of relatives or friends, and domestic issues amongst the adolescent's parents. Each stressor was given subjective and objective stress ratings by a consensus panel, and the total subjective and objective stress scores were each calculated by summing the squares of all individually reported stressors. This procedure produces an overall measure of stress that is more heavily weighted by the occurrence of severe events and not unduly influenced by larger numbers of minimally stressful events (Swartz et al., 2017).

K-SADS-PL

The lifetime psychiatric disorders of the participants were assessed according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth edition, Text Revision; DSM-IV-TR) (American Psychiatric Association, 2000) using the K-SADS-PL (Kaufman et al.,

1997). The child and parent/guardian served as informants, and summary symptom assessments were made by the clinical interviewer based on each informant. At follow-up, the KSADS-PL was used to assess the onset of MDD.

Family History Screen

A modified version of the Family History Screen (Weissman et al., 2000) was used to collect information on lifetime psychiatric disorders according to the DSM-IV-TR and suicidal behaviors in all first-degree relatives. For these analyses, parental psychopathology was defined as the presence of lifetime anxiety, affective, behavioral (e.g., conduct disorder, oppositional defiant disorder), thought (e.g., psychosis, schizophrenia), and/or substance disorders and/or alcohol or drug abuse.

Statistical analyses

To compare the demographic characteristics and follow-up periods between the high- and low- risk adolescents, χ^2 statistics and *t*-tests were used as appropriate. Subsequently, independent survival analyses were used to examine the adjusted survival functions across the follow-up examinations according to the effects of demographics, early childhood trauma, recent life stress, and lifetime parental psychopathology on the cumulative probability of MDD onset. Factors emerging from the univariate survival analyses as contributors to MDD onset were included in the final survival analysis. The identified risk factors were then allowed to forward-step into the Cox Proportional Hazards model in SPSS (version 24; IBM Corporation, Armonk, NY, USA).

Path analyses were then used to identify the direct and indirect paths among the factors identified as contributing to MDD onset. The model fits of the path analyses were evaluated using the root mean square error of approximation (RMSEA), comparative fit index (CFI), and standardized root mean square residual (SRMR). RMSEA values less than 0.07, CFI values over 0.95, and SRMR values less than 0.05 indicate good model fit (Hooper et al., 2008; Hu and Bentler, 1999; MacCallum et al., 1996). The path analyses were conducted with Mplus (version 8; Muthén and Muthén, 2010) using the maximum likelihood estimator. All values are presented as mean $\pm$ standard error of the mean.

Results

Sample characteristics and follow-up

At interview one, the participants were 13.48 ± 0.05 years old (Table 1). The participants completed 3.85 ± 0.08 interviews and were followed for 3.51 ± 0.31 years. The participants were 16.54 ± 0.10 years old at their last interview. Twenty-six adolescents were interviewed only once, while post-baseline, 299 were re-interviewed at least once. The LR group had 4.03 ± 0.11 follow-up assessments, while the HR group had 3.67 ± 0.11 $p = 0.02$).

The sample was evenly split by sex (50.5% female). The majority of the cohort was white (56.3%), and this cohort had a large percentage of Hispanic participants (29.8%). The HR and LR groups did not differ with respect to sex and race percentages or age at first and last interviews (see Table 1). The LR youth had more interviews and higher standardized

socioeconomic status (SES) scores (see Table 1). The effects of the follow-up periods and various demographic characteristics on the risk for developing MDD are examined below.

Demographic and follow-up predictors of first-onset MDD

The Cox Proportional Hazards analyses demonstrated that age at initial assessment [$\chi^2 = 1.50$, degrees of freedom (df) = 1, $p = 0.221$; Exp(B) = 0.769, 95% confidence interval (95% CI) = 0.504–1.173, $p = 0.223$], number of assessments ($\chi^2 = 2.760$, df = 5, $p = 0.737$; Exp(B) = 0.719, 95% CI = 0.484–1.069, $p = 0.104$], Tanner stage [$\chi^2 = 0.53$, df = 1, $p = 0.467$; Exp(B) = 1.198, 95% CI = 0.736–1.948, $p = 0.467$], sex [$\chi^2 = 1.42$, df = 1, $p = 0.234$; Exp(B) = 0.622, 95% CI = 0.282–1.37, $p = 0.238$], race ($\chi^2 = 2.854$, df = 1, $p = 0.09$), and parental marital status assessment [$\chi^2 = 3.22$, df = 1, $p = 0.072$; Exp(B) = 0.416, 95% CI = 0.143–1.207, $p = 0.106$] were not related to the cumulative probability for first-onset MDD. SES was associated with the cumulative probability of developing MDD [$\chi^2 = 4.804$, df = 1, $p = 0.05$; Exp(B) = 0.752, 95% CI = 0.583–0.971, $p = 0.05$] with lower SES conferring greater risk.

Rates of first-onset MDD in HR and LR youth

After the study baseline, 26 (8.0%) of the 325 adolescents examined in the study were diagnosed with MDD (Figure 1). Twenty-three (13.8%) of the HR adolescents developed MDD compared to only three (1.89%) of the LR adolescents. The cumulative probability of developing MDD in the HR adolescents compared with the LR adolescents was statistically significant ($\chi^2 = 17.24$, df = 1, $p = 0.01$). Similarly, the Cox Proportional Hazards regression showed that HR adolescents were 8.24 times more likely to develop MDD (95% CI = 2.47–27.47, $p = 0.01$). The corresponding cumulative survival rates during the entire follow-up period were 0.87 ± 0.1 for the HR subjects and 0.98 ± 0.00 for the LR subjects. Of the children who developed first-onset MDD, the age of onset was 14.75 ± 0.24 years (range, 12.50–17.5 years). The initial ages at the time of onset of the first episode of MDD did not differ between the HR (14.82 ± 0.25) and LR (14.16 ± 0.67) groups [$F(1, 25) = 0.78$, $p = 0.38$].

Parental predictors of first-onset MDD

The parental risk factors significantly related to an increased cumulative probability of developing first-onset MDD included maternal lifetime affective disorders [$\chi^2 = 8.616$, df = 1, $p = 0.003$; Exp(B) = 3.080, 95% CI = 1.396–6.795, $p = 0.005$], paternal lifetime affective disorders [$\chi^2 = 14.692$, df = 1, $p = 0.001$; Exp(B) = 4.017, 95% CI = 1.861–8.677, $p < 0.01$], maternal lifetime anxiety disorders [$\chi^2 = 13.817$, df = 1, $p = 0.001$; Exp(B) = 4.003, 95% CI = 1.815–8.828, $p = 0.001$], paternal lifetime anxiety disorders [$\chi^2 = 18.775$, df = 1, $p = 0.001$; Exp(B) = 4.696, 95% CI = 2.171–10.156, $p = 0.001$], maternal lifetime behavioral disorders [$\chi^2 = 7.87$, df = 1, $p = 0.005$; Exp(B) = 3.086, 95% CI = 1.340–7.103, $p = 0.001$], maternal lifetime thought disorders [$\chi^2 = 4.267$, df = 1, $p = 0.039$; Exp(B) = 4.082, 95% CI = 0.960–17.36, $p = 0.057$], maternal alcohol use disorders [$\chi^2 = 4.621$, df = 1, $p = 0.030$; Exp(B) = 0.622, 95% CI = 0.282–1.37, $p = 0.238$], and paternal alcohol use disorders ($\chi^2 = 7.259$, df = 1, $p = 0.001$; Exp(B) = 2.765, 95% CI = 1.27–5.92, $p = 0.010$). Paternal behavioral [$\chi^2 = 1.156$, df = 1, $p = 0.282$; Exp(B) = 1.602, 95% CI = 0.673–3.813, $p =$

0.287] and thought ($\chi^2 = 2.066$, $df = 1$, $p = 0.151$; $\text{Exp}(B) = 0.257$, 95% CI = 0.035–1.898, $p = 0.183$) disorders did not significantly contribute to the prediction of first-onset MDD.

Stress predictors of first-onset MDD

The youth in this study reported experiencing 5.64 ± 0.19 stressful events in the previous year; the HR and LR groups experienced comparable numbers of stressors. The most commonly experienced stressors were trouble with school (10.87%), having a hospitalized friend or family member (5.92%), having a pet die or run away (4.95%), and breaking up with a girlfriend/boyfriend (4.72%). A comparison of the amounts of recent life stress between the HR and LR youth exhibited a trend for significance at baseline, with the HR youth reporting more recent life stress (See Supplementary Table 2). Additionally, the HR youth reported significantly more early life trauma than the LR youth did (See Supplementary Table 2).

The cumulative probability of developing first-onset MDD was greater in adolescents with more stressful life events in the previous year [$\chi^2 = 32.405$, $df = 1$, $p = 0.001$; $\text{Exp}(B) = 95\%$ CI = 1.03–1.07, $p = 0.001$] and more early childhood trauma [$\chi^2 = 9.527$, $df = 1$, $p = 0.002$; $\text{Exp}(B) = 1.06$, 95% CI = 1.02–1.10, $p = 0.002$].

Modeling cumulative risk for first-onset MDD

Based on the above analyses, the variables that significantly predicted first-onset MDD ($p = 0.05$) were allowed to forward-step into the model with the grouping variable of risk status (HR vs. LR) and SES variable. Over and above familial risk status [$\text{Exp}(B) = 4.50$, 95% CI = 1.26–16.5, $p = 0.021$], only recent stressful life events [$\text{Exp}(B) = 1.06$, 95% CI = 1.03–1.08, $p = 0.001$] and maternal behavioral disorders [$\text{Exp}(B) = 2.86$, 95% CI = 1.09–7.54, $p = 0.034$] predicted cumulative risk for MDD.

Modeling direct and indirect pathways to first-onset MDD

To examine how familial risk status, recent life stress, early childhood trauma, and maternal behavioral disorders directly and indirectly predicted first-onset MDD, path analyses were conducted. Prior to conducting the path analyses, we examined and confirmed the correlations between the variables of interest (See Supplementary Table 3). Given the extensive literature describing early childhood trauma as a predictor for MDD onset, we hypothesized that it would indirectly contribute to MDD onset. We therefore included it in the model even though it did not emerge as a contributor to the cumulative risk model for MDD in the Cox survival hazard analysis. The specified model examined the direct effects of group status, recent life stress, distal life stress, and maternal behavioral disorders on MDD onset while accounting for follow-up time. We also specified the effects of early life stress and maternal behavioral disorders on recent life stress. Finally, we examined the indirect effects of all predictor variables on MDD onset. As shown in Figure 2, the specified model fit the data well [CFI = 0.974, RMSEA = 0.068 (range, 0.000–0.0145), and SRMR = 0.021].

The final model showed that familial risk group ($\beta = 0.206$, $p = 0.001$), recent life stress ($\beta = 0.312$, $p = 0.001$), early childhood trauma ($\beta = 0.161$, $p = 0.006$), and maternal behavioral

disorders ($\beta = 0.142, p = 0.012$) had total effects on MDD onset. As shown in Figure 2, the path analyses revealed that only risk group ($\beta = 0.120, p = 0.025$), recent life stress ($\beta = 0.312, p = 0.001$), and maternal behavioral disorders ($\beta = 0.149, p = 0.005$) had direct effects on MDD, while childhood trauma did not ($\beta = 0.105, p = 0.065$). The model revealed that early childhood trauma had indirect effects on MDD through recent life stress ($\beta = 0.056, p = 0.004$) and that, in addition to having direct effects on MDD onset, risk group had indirect effects on MDD onset through maternal behavioral disorders ($\beta = 0.044, p = 0.012$). The total model had a R^2 value of 0.179 in predicting MDD onset ($p = 0.001$) (See Table 2).

Discussion

In this report, we examined the relative contributions of factors known to confer risk for adolescent-onset MDD and found that familial risk was the most significant risk factor for new-onset depression. Seminal studies by Weissman (Weissman et al., 1987) and our group (Williamson et al., 2004) have previously established that the offspring of depressed parents and/or relatives are four times more likely to develop an episode of depression. Here, we extend these findings to show that, for those who are HR, experiencing recent stressful life events and/or having a mother with a behavioral disorder increases their risk for developing an initial episode of depression during adolescence. Modeling these predictors in path analyses further revealed that familial risk, recent stressful life events, and maternal behavioral disorders exerted direct effects on the first onset of MDD, while early childhood trauma had an indirect effect on first-onset MDD through recent life stress. Our findings only partially supported our proposed hypotheses. In accordance with hypothesis (a), we report that HR status and proximal stress directly affected MDD onset. We did not find evidence supporting hypothesis (b) that high-risk status and early life stress would both moderate the relationship between recent life stress and MDD onset. Our findings that maternal behavioral disorders directly predicted MDD onset provided partial support for our hypothesis (c) that parental psychopathology would affect MDD onset above and beyond the effects of HR status. The results of this study add to prior literature confirming the importance of a family history of depression on the risk of an initial onset of depression in adolescence and begin to parse out aspects of the additive genetic and shared environmental factors reflected in familial risk.

Our findings were consistent with prior research establishing the importance of the familial aggregation of affective disorders in juvenile-onset MDD (Milne et al., 2009; Rice et al., 2017; Williamson et al., 2004). Interestingly, the magnitude of the increased risk in our cohort was consistent with previous longitudinal reports on various risk criteria in individuals with familial histories of MDD (Lieb et al., 2002; Weissman et al., 2016b; Williamson et al., 2004). Here, with our requirement that the first- and second-degree relatives of the subjects had depression, we report an eight-fold increased risk for MDD, which was slightly higher than the risk we previously reported (Williamson et al., 2005). This difference might have been related to the subsequent inclusion of HR adolescents with a history of anxiety disorders in the current study.

Our finding that recent life stress significantly increased one's risk for developing depression over and above familial risk was consistent with the large body of literature supporting

recent life stress as one of the most salient risk factors for adolescent-onset MDD (Espejo et al., 2007; Kendler et al., 1995; Nima et al., 2013; Rueter et al., 1999; Williamson et al., 1995a). In our previous study, we observed increased amygdala reactivity in HR adolescents and adolescents exposed to recent stressful life events (Swartz et al., 2017). Furthermore, we previously reported that threat-related amygdala activity increased with age in HR adolescents and LR adolescents exposed to higher levels of recent life stress (Swartz et al., 2015). Thus, familial risk and recent stress may exert differential effects on heightened fear responses during adolescence, and these heightened fear responses may in turn increase the risk for depression. Taken together, these results suggest a potential mechanism underlying the increased risk of an initial onset for depression in HR adolescents. Future studies are needed to elucidate if heightened threat responses, such as amygdala activity, predict initial episodes of depression as HR adolescents develop due to shared genetic factors.

Our observation that childhood maltreatment indirectly affected MDD onset appears at first to diverge from the well-supported body of research suggesting early childhood trauma predicts juvenile onset of MDD. Our study excluded individuals who had already experienced first-onset depression; thus, maltreated individuals with childhood-onset depression might have been excluded. We believe this divergence may highlight an important distinction between juvenile-onset MDD that emerges in childhood and juvenile-onset MDD that emerges during adolescence (Kaufman et al., 2001). Although prior studies have suggested that childhood-onset depression is strongly related to childhood maltreatment, the relationship between childhood maltreatment and the emergence of depression during adolescence remains less clear (Bernet and Stein, 1999; Luby et al., 2006; Lumley and Harkness, 2007). The results of the present study suggesting a time-limited influence of childhood maltreatment on depression may help elucidate the relationship between childhood maltreatment and depression. With the exclusion of adolescents with childhood-onset depression, we did not find a direct relationship between childhood maltreatment and depression, suggesting that those who do not develop MDD before adolescence and/or have a low stress load during adolescence are at lower risk for developing depression related to childhood maltreatment. Our findings should be considered with the literature outlining the relationship between childhood maltreatment/neglect and adolescent-onset MDD, which suggests that individuals exposed to certain types of maltreatment (i.e., sexual abuse) are at heightened risk for first-onset depressive episodes during adolescence (Brown et al., 1999; Lumley and Harkness, 2007). The divergence of our results from the literature suggests that adolescent- and childhood-onset MDD are etiologically heterogeneous and underscores the need to examine the risks for these two subtypes of depression separately (Wickramaratne and Weissman, 1998).

Our study results also diverge from the literature suggesting sex differences in the risk for first-onset MDD. We believe that family history better accounts for differences in MDD onset and that the effect of sex is attenuated after familial risk has been considered. Similarly, we observed no sex differences in MDD onset in our previous study (Williamson et al., 2004).

We also observed that maternal behavioral disorders had both direct and indirect paths to MDD onset, with the latter acting through familial risk. Numerous studies have established

shared genetic and environmental risks for depression and externalizing disorders (King et al., 2004; Williamson et al., 2004). Although our study excluded youth with externalizing disorders, an underlying shared genetic risk for behavioral and depressive disorders may manifest in relatives, particularly mothers with histories of behavioral disorders with or without depression. Our study did not find that parental psychopathology other than maternal behavioral disorders contributed to MDD onset in adolescence. However, this diverges from previous results, including those of our study showing that maternal anxiety predicted adolescent-onset MDD (Williamson et al., 2004) and another showing that paternal substance abuse disorders interacted with maternal depression to predict adolescent-onset MDD (Brennan et al., 2002). The effects of maternal anxiety and/or depression onset in this cohort may have been masked by the inclusion of childhood anxiety disorders in the HR group but not in the LR group. Because we included only HR youth with anxiety disorders and maternal anxiety disorders strongly predict childhood anxiety disorders (Orvaschel et al., 1988), we might have subsumed the potential contribution of maternal anxiety as a predictor of depression in HR adolescents and/or precluded our ability to examine its contribution in the absence of familial risk.

Our study was not without limitations. First, our study identified potential study participants with a commercially available phone list of households with adolescents. Thus, we might not have screened all possible eligible adolescents and systematic differences may have existed between youth with and without commercially available phone numbers. Second, we excluded only LR youth with a history of anxiety. While this design was intended to enrich the sample for depression amongst HR youth, it limited our ability to specify the risk for first-onset depression among anxious adolescents in the absence of a familial history of depression. Third, this study design might have contributed to the relatively low level of MDD diagnoses made during the study follow-up period; future research is needed to examine if the rates of MDD diagnoses increase as adolescents develop. Given the relatively low number of participants who developed first-onset depression during follow-up, these results should be interpreted with caution, and follow-up studies are needed to confirm these findings. As with all longitudinal studies, there were issues with attrition in our sample, and this might have influenced our ability to fully understand the development of depression across adolescence. Finally, we only used one measure of childhood trauma and recent life stress, and these results are susceptible to self-report and mono-informant bias. Despite these limitations, this study had many strengths. In addition to this study conducting a unique longitudinal assessment of depression in adolescence, it is one of the first to offer precise estimates of the incidence rates of first-onset MDD during adolescence through the exclusion of subjects with depression at intake and to chart the relationships among numerous well-established risk factors and the development of MDD and, specifically, adolescent-onset MDD.

Given the well-established observation that a familial risk for depression is the single biggest predictor of first-onset depression (Rice et al., 2017; Weissman et al., 1987; Williamson et al., 2004, 1995b), it is surprising that familial risk-related factors that are crucial for the emergence of this debilitating disease have not been better elucidated. Although the results of this study add insights into the importance of distal and recent stress over and above familial risk, there is still much to be discovered. One intriguing area of research emerging

from preclinical models of depression is the differentiation of brain-wide oscillations of local field potentials called electomes in mice that are susceptible for depression following chronic social defeat stress (Hultman et al., 2018). Toward this end, studies incorporating a combination of magnetoencephalography and electroencephalography (e.g., Krishnaswamy et al., 2017) could extend these preclinical findings and shed light on the aspects of familial risk that contribute to the initial onset of depression. Moreover, emerging results from the Psychiatric Genetics Consortium of Depression may yield candidate genetic markers that contribute to the emergence and maintenance of this chronic condition (Howard et al., 2018).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CFI	comparative fit index
CI	confidence interval
CTQ	Childhood Trauma Questionnaire
DALY	disability-adjusted life years
df	degrees of freedom
HR	high familial risk
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version
LR	low familial risk
MDD	major depressive disorder
RMSEA	root mean square error of approximation
SE	standard error of the mean
SES	socioeconomic status
SLES	Stressful Life Events Schedule
SRMR	standardized root mean square residual

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Highlights

- Familial history of MDD is related to 8 times the risk for MDD onset
- Maternal behavioral disorders also predict first onset MDD
- Increased recent life stress directly predicts an initial onset of MDD
- Childhood-trauma exerts only an indirect effect through recent stress for first-onset depression

Figure 1.
Cumulative probability of Major Depressive Disorder (MDD) onset by the end of the study for the **Low Familial Risk (LR; in green)** and **High Familial Risk (HR; in blue)** youth

Figure 2.

Model representing the direct and indirect effects of stress, familial risk status, and maternal behavioral disorders on first-onset major depressive disorder (MDD)

* $p < 0.05$

** $p < 0.005$

The dashed lines indicate indirect paths to MDD onset.

Table 1.

Descriptive statistics of the study groups

	Range	LR n = 159 Mean (SE)	HR n = 166 Mean (SE)	t (df)	p
Age at Interview 1	11.61–15.84	13.49 (0.08)	13.47 (0.08)	0.13 (323)	0.90
Age at Final Interview	11.69–20.04	16.67 (0.14)	16.42 (0.13)	1.32 (321.86)	0.19
Number of Interviews	1–6	4.03 (0.11)	3.67 (0.11)	2.27 (322.68)	0.02
Standardized Socioeconomic Status	–5.10–3.52	0.04 (0.11)	–0.29 (.11)	2.05 (311.99)	0.04
Number of Siblings	0–6	1.40 (0.09)	1.37 (0.09)	0.27 (322.19)	0.79
Gender	N/A	M = 79 F = 80	M = 79 F = 84	$\chi^2 = 0$	0.99
Race	N/A	White = 88 White/Hispanic = 10 Hispanic = 53 African-American = 4 Asian = 2 Other = 5	White = 95 White/Hispanic = 16 Hispanic = 44 African-American = 5 Asian = 1 Other = 2		
Parental Marital Status		Divorced = 2 Married = 144 Living with partner = 6 Other = 8	Divorced = 11 Married = 140 Living with partner = 9 Other = 12		

Abbreviations: LR, low familial risk; HR, high familial risk; df, degrees of freedom; SE, standard error of the mean; M, male; F, female

Table 2.

Path analyses results: direct and indirect paths to onset of major depressive disorder

	Total β	Direct β	Indirect β
Risk Group	0.206 ^{***}	0.120 [*]	
→ Via Maternal Behavioral Disorders			0.044 [*]
Recent Life Stress	0.312 ^{***}	0.312 ^{***}	
Childhood Trauma	0.161 ^{**}	0.105	
→ Via Recent Life Stress			0.056 ^{**}
Maternal Behavioral Disorders	0.142 [*]	0.149 ^{**}	

* $p < 0.05$,** $p < 0.01$,*** $p < 0.001$