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Associations between Depression-Relevant Genetic Risk and Youth Stress Exposure: Evidence of Gene-Environment Correlations

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Abstract

Familial risk for depression is associated with youth exposure to self-generated dependent stressful life events and independent events that are out of youth's control. Familial risk includes both genetic and environmental influences, raising the question of whether genetic influences, specifically, are associated with youth exposure to both dependent and independent stressful life events. To address this question, this study examined the relation between a genome-wide association study (GWAS)-derived depression-based polygenic risk score (DEP-PRS) and youth experiences of dependent and independent stress. Participants were 180 youth (ages 8–14, 52.2% female) of European ancestry and their biological mothers recruited based on the presence versus absence of a history of major depressive disorder (MDD) in the mothers. Youth and mothers were interviewed every 6 months for 2 years regarding the occurrence of stressful life events, which were coded as independent or dependent (self-generated). Results indicated that youth's DEP-PRS and maternal history of MDD were uniquely associated with increased exposure to both dependent and independent events. Similar results were observed when examining major versus minor events separately, with the additional finding of a DEP-PRS × mother MDD interaction for major dependent events such that levels of moderate to severe dependent life stressors were highest among youth with high DEP-PRSs who also had mothers with MDD. These results not only support the presence of depression-relevant gene-environment correlations (rGEs), but also highlight the possibility that rather than only capturing depression-specific genetic liability, GWAS-derived polygenic risk scores may also capture genetic variance contributing to stress exposure.

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General Scientific Summary:

The current study highlights the potential presence of depression-relevant gene-environment correlations and suggests that GWAS-derived depression polygenic risk scores are associated with greater exposure to both dependent and independent stressors. However, the findings also raise questions regarding the extent to which GWAS-derived PRSs may capture rGEs in addition to genetic liability for depression.

Keywords

polygenic risk score; rGE; depression; stress exposure

Introduction

A robust body of literature highlights the role of stressful life events in the etiology of depression (Brown & Harris, 1978; Kessler, 1997). However, stress exposure does not occur completely at random, and youth with a maternal history of major depressive disorder (MDD) are more likely to be exposed, which may be one mechanism of risk for the intergenerational transmission of depression. The stress generation hypothesis emphasizes the active role that people play in shaping their environments and posits that individuals at risk for depression possess vulnerabilities that contribute to the generation of additional stressors that are dependent on one's actions (Hammen, 1991; Hammen, 2006). Supporting this hypothesis, offspring of depressed mothers, who are at risk for depression themselves (Goodman, 2020), experience elevated levels of dependent stressful life events compared to offspring of never-depressed mothers (Adrian & Hammen, 1993; Feurer et al., 2016). Importantly, these at-risk youth are also exposed to elevated levels of independent stressful life events that are out of their control (Adrian & Hammen, 1993), suggesting that even "fateful" stressful life events may not be random for youth with a familial history of depression. However, despite these established links with both dependent and independent life events, questions remain regarding how familial depression risk contributes to stress exposure in youth.

Genetic influences may explain the link between familial depression risk and increased stress exposure given that maternal depression contributes to offspring risk, at least in part, via genetic mechanisms (Goodman, 2020) and given evidence for the heritability of environmental exposures (i.e., gene-environment correlations; rGEs) (e.g., Jaffee & Price, 2007; Kendler & Baker, 2007; Knafo & Jaffee, 2013). Genetic factors are proposed to influence the environment through multiple pathways (i.e., passive, active, and evocative rGEs) (Plomin et al., 1977). Passive rGE refers to a correlation between genetic influences and characteristics of the environment that are accounted for by shared genetic variance with a family member. For example, in passive rGE, parental genotype contributes to the environment they create for their offspring and is also passed on to their offspring. Active rGE refers to the process by which an individual's genetically-mediated traits contribute to their self-selection into certain environments. Finally, evocative rGE refers to the process by which an individual's genetically-mediated traits shape their environment by evoking responses from it.

These established rGEs may help to clarify the link between familial depression risk and increased stress exposure in youth. For example, Hammen's (1991) stress generation hypothesis suggests that depressogenic vulnerabilities may contribute to stress generation through self-selection into stressful environments or generation of stressful contexts by eliciting negative responses from others, therefore incorporating the concepts of active and evocative rGEs. Additionally, increased exposure to independent stress observed in youth at familial risk for depression could be due to stressful life events that are under their parents' influence, reflecting passive rGE. Of note, individuals with a history of MDD typically exhibit greater exposure to dependent, but not independent, stressful life events (Liu & Alloy, 2010), whereas youth at familial risk for depression exhibit increased exposure to both forms of stress (Adrian & Hammen, 1993). Therefore, passive rGEs may be particularly relevant for at-risk youth whose parents have direct influence over the environment in which they live.

Supporting the role of rGEs, behavioral geneticists have highlighted genetic influences on stress exposure, though these studies largely suggest that the heritability of dependent life events (31–45%) is stronger than that of independent life events (7–17%) (Bemmels et al., 2008; Boardman et al., 2011; Kendler & Baker, 2007). Although behavioral genetics studies cannot delineate which genes contribute to rGEs, molecular genetic studies can provide insight regarding whether genetic liability for depression, more specifically, contributes to rGEs. Mirroring behavioral genetics research, there is emerging evidence that genetic variants associated with depression risk may be associated with increased risk for the generation of dependent life events (for review, see Bahji et al., 2021). Specifically, possessing one or two copies of the short allele of the serotonin transporter gene (5-HTTLPR) predicts increased generation of dependent stressful life events for adolescents with a history childhood maltreatment (Harkness et al., 2015), depression symptoms (Starr et al., 2012), or ADHD symptoms (Brinksma et al., 2018). Similarly, a polygenetic risk score (PRS) associated with hypothalamic-pituitary-adrenal (HPA) axis dysfunction predicted more dependent interpersonal stress among adolescents exposed to childhood adversity (Huang & Starr, 2019). Notably, these studies did not observe evidence for genetic influences on exposure to independent stressors.

Although these studies provide preliminary evidence for potential depression-relevant rGEs, one major limitation is that prior studies only captured risk conveyed by a single or a few candidate genes. Given increasing concern regarding the replicability of findings based on single candidate genes (Bosker et al., 2011; Duncan & Keller, 2011) coupled with evidence that risk for depression is distributed across the genome (Duncan et al., 2019a; Howard et al., 2019), genetic predictors circumscribed to a few genes likely only capture a small amount of variance in genetic liability for depression. Alternatively, markers of MDD risk derived from genome wide association studies (GWASs), which utilize large datasets to identify genetic markers across the entire genome, may allow for a more nuanced and reliable examination of the relation between genetic liability for depression and stress exposure.

Recent GWASs of depression have successfully identified PRSs indicative of MDD risk (Howard et al., 2018; Hyde et al., 2016; Wray et al., 2018). Further, a recent highly-

powered meta-analysis, combining the samples from these three studies conducted in adults, identified a depression PRS (DEP-PRS) that replicated in independent samples to explain 1.5% to 3.2% of the variance in depression (Howard et al., 2019) and prospectively predicted depression symptoms within the context of elevated stress exposure (Fang et al., 2020). Importantly, there is evidence this PRS also predicts depression risk in youth, despite being derived from an adult sample. Specifically, this DEP-PRS predicted prospective increases in depressive symptoms and accounted for 0.37% to 2.21% of the variance in youth depression symptoms, with the relation between youth PRS and depression symptoms increasing with age from pre-adolescence to early adulthood (Kwong et al., 2021). Therefore, the DEP-PRS also appears relevant for youth depression risk, and thereby may be leveraged to explore depression-relevant rGEs in youth.

In the current study, we sought to build upon the existing literature on rGEs by examining whether genetic liability for depression, indexed by an established GWAS-derived DEP-PRS, was associated with stress exposure in a risk-enhanced sample of youth with and without a maternal history of MDD. Consistent with converging evidence from behavioral (Bemmels et al., 2008; Boardman et al., 2011; Kendler & Baker, 2007) and molecular (Bahji et al., 2021) genetic studies, we hypothesized that youth at increased genetic risk for depression would exhibit greater exposure to dependent, but not independent, life events. In doing so, we sought to determine whether relations between the DEP-PRS and stress exposure would be at least partially independent of mothers' histories of MDD, a known risk factor for both dependent and independent life stress (Adrian & Hammen, 1993; Feurer et al., 2016), which also contributes to offspring risk via environmental pathways (Goodman, 2020). Based on evidence that the heritability of dependent life events is stronger than that of independent life events (Bemmels et al., 2008; Boardman et al., 2011; Kendler & Baker, 2007), we hypothesized that the relation between youth DEP-PRS and dependent stress would be at least partially independent of the influence of maternal history of MDD.

In addition to examining the unique influence of youth DEP-PRS statistically controlling for the potential influence of mothers' own depression risk, exploratory analyses were also conducted to examine the combined influence of youth's DEP-PRS and mothers' MDD history on stress exposure. Depression in mothers is hypothesized to contribute to offspring depression risk through both genetic and non-genetic influences (Goodman, 2020). Despite evidence that independent stressful life events may not be as heritable as dependent life events, the fact that offspring of mothers with a history of MDD are exposed to greater independent stress suggests that mothers' depression may also contribute to increased stress exposure via non-genetic pathways. Therefore, we examined whether the highest levels of stress exposure would be observed for youth with higher DEP-PRS scores who also had a mother with MDD.

Finally, given evidence that major life events are stronger predictors of depression risk than minor life events (Vrshek-Schallhorn et al., 2015), researchers have sought to identify predictors of major life events specifically (Safford et al., 2007; Uliaszek et al., 2012). However, this has not been tested within the context of genetic liability for depression and research to date has only examined prediction of dependent major life events but not independent major life events. Therefore, exploratory analyses examined major and minor

life events separately to determine whether any observed rGEs were driven by levels of major versus minor life events.

Method

Participants

Participants were a subset of mothers and their biological children between the ages of 8 and 14 recruited from the community for a 2-year longitudinal study on the intergenerational transmission of depression risk. The original sample from which the current participant subset was drawn included 255 mother-child dyads (Feurer et al., 2016). However, 7 dyads were excluded due to missing genetic data for the child, 3 dyads were excluded as the mothers originally had no lifetime history of MDD at study entry but experienced an onset of MDD during the course of the study, 60 dyads were excluded as genetic samples indicated that children were not of European ancestry, and 5 dyads were excluded due to children's genetic data not passing post-imputation quality control measures (see genotyping information below and Supplementary Table 1). Therefore, a total of 180 mother-child dyads were retained for analysis. To be included in the study, mothers were required to either have a history of MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition* (DSM–IV; American Psychiatric Association, 1994) during their child's lifetime (n = 81) or have no lifetime history of any DSM-IV mood disorders (n = 99). Exclusion criteria for mothers were a history of schizophrenia or bipolar disorder, or a diagnosis of alcohol or substance dependence within the last 6 months. If participating mothers had more than one child eligible for the study, a single child was chosen at random for participation. For youth, the average age was 11.40 (SD = 1.90) and 52.2% were female. In the current sample, participants were limited to European ancestry for two reasons. First, this was done to match the ancestry of the original sample from which the PRS was derived (Howard et al., 2019) as PRS scores from European samples perform poorly when applied to non-European samples (Duncan et al., 2019b). Second, this was the largest homogenous group available for genetic imputation, as described below, and the remaining homogenous ancestral groups were too small to allow for meaningful comparison across groups.

Measures

Maternal and Youth Depression Diagnoses—Maternal and youth histories of MDD and other DSM-IV Axis I Disorders were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1995) and the Schedule for Affective Disorders and Schizophrenia for School Age Children–Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997), respectively. As noted above, 81 mothers had at least one episode of MDD during their child's life, and 99 mothers had no lifetime history of any Axis I mood disorders. Ten youth met criteria for a lifetime history of MDD at the baseline assessment. A subset of 20 SCIDs and K-SADS-PL were coded by a separate interviewer to assess inter-rater reliability for diagnoses of MDD, yielding excellent kappa coefficients (all κs = 1.00).

Youth Symptoms—Youth symptoms of depression and anxiety were assessed using the Children's Depression Inventory (CDI; Kovacs, 1981) and the Multidimensional

Anxiety Scale for Children (MASC; March, Parker, Sullivan, Stallings, & Conners, 1997), respectively. Both measures have demonstrated excellent psychometric properties in previous research (Kovacs, 1981; March et al., 1997).

Youth Episodic Stress—Youth experiences of dependent and independent episodic life stressors were assessed using the UCLA Life Stress Interview for Children (LSI-C; Adrian & Hammen, 1993). This semi-structured interview is modeled after contextual threat interviews (Brown & Harris, 1978) and was used to probe for the occurrence of negative life events. At the initial assessment, youth and their mothers were interviewed separately about any stressful life events that may have occurred in the youth's life during the 6 months prior to the assessment. For each follow-up assessment, youth and mothers were asked about any stressful events since the date of their last assessment. The average length of time between assessments was 6.52 months ($SD = 2.06$). If the dyad missed an assessment, the LSI-C focused on stress experienced during the entire time between assessments instead of just the most recent 6-month interval. In these cases, any events reported before the date of their missed appointment were summed separately from the rest of the events reported at that time period in order to back-date the events to the appropriate time point.

Interviewers asked about the occurrence of any life stressors within a variety of domains (e.g., peer, family, academic) and probed any reported events for further objective information about the timing, duration, content, and context in which the stressor occurred. Each reported life event was then presented to a team of 4–7 coders, devoid of any subjective information. The team assigned a negative impact stress score between 1 and 5 to each event. A score of "1" indicates no stress, whereas a score of "5" indicates severe stress and significant impact. Coders also assigned a dependence score to each event to signify the extent to which the occurrence of an event was due to the actions of the participant. A dependence score of "1" indicated that the event was entirely independent of and not directly caused by the youth, a score of "3" indicated mixed or indeterminate dependence, and a score of "5" indicated that the event was completely dependent on and caused by the actions of the youth. Consistent with previous studies, an event was classified as "dependent" (versus "independent") if the event received a dependence score of 3 or higher (e.g., Feurer et al., 2016; Hammen, 1991; Vrshek-Schallhorn et al., 2015). Additionally, consistent with previous research (e.g., Uliaszek et al., 2012), stressors with a negative impact score of 2.5 or higher were categorized as "major life events" (versus "minor life events"). An example of a major life event would be having a fight that resulted in the end of a friendship with one's only friend, whereas an example of a minor life event would be having a minor argument with a peer that lasted one day. To create stress scores, negative impact scores were summed separately for dependent and independent episodic stress reported by either the youth or their mothers. For the exploratory analyses of major versus minor life events, dependent and independent episodic stress were also summed separately based on severity category (i.e., minor life events, major life events). Before summing the total amount of episodic stress for each category, the objective impact scores were recoded from 1–5 to 0–4 to avoid inflation of the total stress scores (i.e., due to participants reporting events that ended up being coded as having no objective impact). Finally, to assess inter-rater reliability, a subset of 50 life stress events were coded by an independent team of coders. Inter-rater

reliability was excellent for assigned negative impact stress scores (ICC = .91), as well as for classification of life stressors as dependent or independent (κ = .80).

Genotyping, Quality Control, and Genetic Imputation—Youth DNA was collected and isolated from buccal cells using established methods (Freeman et al., 1997; Lench et al., 1988). Participants were genotyped using OmniExpressExome arrays (Illumina, Inc.) that were run on an Illumina HiScan system following the manufacturer's protocols and were genetically imputed using the Michigan Imputation Server. See supplementary materials for details regarding genetic imputation.

Genome-wide association study (GWAS) summary statistics were obtained for 8,483,301 markers from a large GWAS of MDD (Howard et al., 2019). Of these markers, 4,301,263 (representing 82% of sample data) were available in the imputed data that passed QC. After clumping, 1,222,666 markers remained. PRSice version 2 (Choi & O'Reilly, 2019) was used to derive polygenic risk scores (PRS) for sample data at a p-threshold of .005. These PRSs, which included 7,022 SNPs, were extracted, multiplied by a constant of 1000 to help with model convergence, and used for subsequent linear mixed models. Of note, research utilizing this PRS in youth shows that although the optimized p-threshold for the PRS ranges from 0.005 to 1.0 depending on the age at which depression symptoms were examined, prospective trajectories of depression symptoms across adolescence were best predicted by the PRS thresholded at p = .005 (Kwong et al., 2021).[1]

Procedure

Participants were recruited through a variety of means (e.g., newspaper and bus ads, flyers) and were screened over the telephone to determine their eligibility. After obtaining informed consent and assent, the SCID-I and the K-SADS-PL were administered to assess for diagnoses of MDD and other DSM-IV Axis I disorders in mothers and youth, respectively. The CDI and MASC were administered to youth to assess for current depression and anxiety symptoms. Additionally, the LSI-C was administered separately to mothers and youth to assess youth experience of dependent and independent stress in the preceding 6 months. Finally, youth buccal cells were obtained for genotyping.

Participants returned to the laboratory for 6-, 12-, 18-, and 24-month follow-up assessments. At each follow-up assessment, youth and their mothers were re-administered the LSI-C to assess for youth's experience of life stress in the interim between assessments. Youth were also administered the CDI and MASC at each follow-up assessment. Finally, youth were re-administered the depression supplement of the K-SADS-PL to assess whether youth experienced any depressive episodes since their last assessment. All study procedures were approved by Binghamton University (SUNY)'s Institutional Review Board (protocol number 2013–09) and participants were compensated for their time.

[1]We also re-conducted primary analyses with PRSs with p-thresholds of p = 1.0, 0.5, 0.1, 0.05, 0.01, and 0.001 in tests of sensitivity (See Supplementary Table 2). The pattern of results regarding the impact of youth PRS on stress generation was largely maintained across PRSs, though the strength of the relation varied.

Analytic Plan

Linear mixed modeling was used to test our hypotheses due to the nested nature of the data and repeated assessment of episodic stress (i.e., five time points nested within participant). This statistical approach allows for the examination of the impact of Level 2 variables (i.e., youth PRS, mother history of MDD) on a Level 1 outcome (i.e., episodic stress) as well as the inclusion of time-varying covariates in tests of robustness, as described below. Given the relatively low base rate of participants who reported at least one dependent stressful life event at each time point (*Range* = 44.7 – 60.0%), analyses focused on the main and interactive effects of youth's DEP-PRS and mother MDD on overall levels of episodic stress across all assessments. Consistent with the current study's focus on examining depression relevant rGEs, rather than changes in stress exposure over time, the current study did not examine longitudinal trajectories of change in stress exposure. An autoregressive (AR1) covariance matrix was used for all models and random intercepts were included. Using episodic stress scores as the dependent variable, we entered the main effect of youth's DEP-PRS in the first step of the analysis and mothers' histories of MDD (yes versus no) in the second step as fixed effects. Analyses were conducted separately for Dependent and Independent Stress.

Additionally, a series of follow-up analyses were conducted to test the robustness of any significant findings. Given that current depression diagnoses and symptoms are associated with stress generation in youth (Krackow & Rudolph, 2008), youth MDD status (any MDD: yes versus no in the interim between assessments), CDI, and MASC at each time point were all individually entered as covariates to examine if results were maintained when statistically controlling for the influence of current symptoms and diagnoses. We also examined whether results were maintained controlling for demographic variables (i.e., youth age, sex, family income) and the first 10 ancestral principal components calculated from genetic data from the full genetic imputation sample to control for population stratification.

In exploratory analyses, analyses were conducted separately for minor and major stressful life events to determine if results were driven by minor or major life events. Finally, exploratory analyses examined whether maternal history of MDD moderated the impact of youth DEP-PRS on exposure to dependent or independent life events.

Results

Preliminary Analyses

An initial inspection of the data revealed that several variables (i.e., CDI, MASC, Stress) exhibited significant skew ($z > 3.29$; cf. Tabachnick & Fidell, 2007). These variables were square root or inverse transformed prior to analysis to meet the assumptions of normality.[2] Additionally, given the presence of missing data (T2-T5 Stress: 10.6–28.3%;

[2]Although major independent stress and major dependent stress did not reach our criteria for normality ($z < 3.29$) following transformation, the inverse transformation resulted in the lowest skew statistic, and was therefore used for these variables. Additionally, Bernoulli analyses were conducted to examine whether results for major and minor stressful life events were maintained when examining whether a stressful life event was reported for each time point (dichotomized as yes versus no), rather than focusing on the summation of negative impact scores. Results for these Bernoulli analyses were identical to the results presented below for major and minor dependent and independent stress. Summary of analyses are available upon request from the corresponding author.

Child MDD Status T2-T5: 9.4–29.4 %; CDI T1-T5: 2.2–31.1%; MASC T1-T5: 3.9–32.8%), we examined whether the data were missing at random. Little's missing completely at random (MCAR) test (Little and Rublin, 1987) was non-significant, $\chi^2(2415) = 2368.39$, $p = .75$, supporting the imputation of missing values (Schafer & Graham, 2002). Therefore, maximum likelihood estimates of missing data were created and used for all analyses.

Descriptive statistics for all study variables are presented in Table 1. To facilitate comparisons with other studies, values presented in the table are based on untransformed data. As seen in Table 1, family income was lower for offspring of depressed mothers compared to never-depressed mothers. No other demographic differences were observed between the two groups. In addition, youth's DEP-PRS did not differ between youth of depressed and never-depressed mothers.

Preliminary correlation analyses were conducted to examine whether youth DEP-PRS was associated with youth depression symptoms assessed using the CDI at any point. Results indicated that greater youth PRS was associated with greater depression symptoms at Time 5, $r = .16$, $p = .036$, but not any other time point, rs $\leq .06$, ps $\geq .43$.

Primary Analyses

First, we examined the impact of youth's DEP-PRS on youth dependent and independent episodic stress. The results of these analyses are presented in Table 2. As noted above, the main effect of youth DEP-PRS was entered in the first step of these analyses and mother MDD was entered in the second step. As can be seen in the table, there was a significant main effect of youth's DEP-PRS on both forms of youth episodic stress, such that higher levels of genetic risk were associated with higher levels of dependent and independent stress. This effect was maintained even after statistically controlling for the role of mothers' MDD history. Additionally, mother history of MDD was also uniquely related to higher levels of both dependent and independent stress even after accounting for the variance explained by youths' DEP-PRS.

A series of analyses was then conducted to test the robustness of our findings. The significant main effects for both youth's DEP-PRS and mother MDD were maintained even after statistically controlling for the influence of demographic variables (i.e., youth age, sex, family income), the first 10 principal components identified for ancestral background, youth MDD status (MDD: yes versus no) at each time point, and depression (CDI) and anxiety (MASC) symptom levels at each time point (all DEP-PRS and mother MDD main effect ps $\leq .04$ and $r_{effect\ sizes} \geq .15$). Given similar findings for dependent and independent stress, we also examined whether results for each form of stress were maintained after statistically controlling for the influence of the other form of stress to determine whether youth DEP-PRS and MDD in mothers uniquely predict both the generation of dependent events and exposure to independent events. The main effects of youth DEP-PRS and mother MDD were maintained for dependent stress when statistically controlling for independent stress and vice versa (all main effect ps $\leq .017$ and $r_{effect\ sizes} \geq .18$). Full details regarding individual tests of robustness are presented in Supplementary Table 3.

Minor and Major Life Events

Next, we examined whether the results were maintained when separately examining youth experiences of minor and major stress. As can be seen in Table 3, the main effect of youth's DEP-PRS was significant for minor and major dependent stress and minor independent stress, but not major independent stress. Additionally, the main effect of mother history of MDD on youth episodic stress was significant for minor and major dependent stress and major independent stress, but not minor independent stress.

DEP-PRS × Mother MDD Interaction

Finally, we examined whether maternal history of MDD moderated any of the relations between youth DEP-PRS and stress exposure. Results indicated the DEP-PRS × maternal MDD interaction was significant for major dependent stress, $t(175.62) = 2.47$, $p = .01$, $r_{effect\ size} = .18$, but not any other forms of dependent or independent stress exposure. Examining the form of this interaction, higher DEP-PRS was associated with higher levels of major dependent stress for offspring of mothers with a history of MDD, $t(78.75) = 2.64$, $p = .01$, $r_{effect\ size} = .29$, but not for offspring of never depressed mothers, $t(96.98) = 0.03$, $p = .98$, $r_{effect\ size} = .003$.[3]

Discussion

The goal of the current study was to examine rGEs in youth, specifically the associations between a GWAS-derived depression polygenic risk score and exposure to both dependent and independent stress in youth. Partially consistent with hypotheses, youth DEP-PRS score was associated with greater self-generated dependent life events. However, unexpectedly, this DEP-PRS was also associated with exposure to independent stressful life events. The main effect of youth DEP-PRS on youth stress exposure was maintained while statistically controlling for the influence of maternal history of MDD, suggesting that the relation between youth DEP-PRS and stress exposure was at least partially independent of influences associated with mothers' own depression phenotype. Additionally, all findings were maintained when statistically controlling for youth depression diagnoses and internalizing symptoms, suggesting that the relation between youth DEP-PRS and levels of dependent and independent stress was at least partially independent of youth current psychopathology. The findings were also maintained statistically controlling for potential demographic influences (i.e., youth age, sex, family income). Finally, exploratory analyses focusing on minor and major life events separately indicated that youth DEP-PRS was associated with exposure to both minor and major dependent life events and exposure to minor, but not major, independent life events. Although conclusions remain tentative pending replication, the current findings build upon the previous research documenting rGEs and suggest that GWAS-derived depression-relevant PRSs may be associated with increased stress exposure in youth.

[3]Information regarding additional analyses separately examining mother and youth report of episodic stress can be found in supplementary materials and Supplementary Table 4.

The current findings are partially consistent with behavioral genetic research which has highlighted the heritability of stressful life events. However, these prior studies have typically observed greater heritability of dependent life events than independent life events (Bemmels et al., 2008; Boardman et al., 2011; Kendler & Baker, 2007). In contrast, the current study found that genetic liability for depression was associated with increased risk for both dependent and independent life events, with little differences in effect size. It is possible that prior findings highlighting lower heritability for independent life events may be due to the assessment of stressful life events. Specifically, prior behavioral genetics studies have largely relied on checklist measures of life events, which circumscribes the types of assessed stressful life events to those on the questionnaire and may conflate stress response with stress exposure (Harkness & Monroe, 2016). In contrast the current study utilized an interviewer-based assessment of life events, which accounts for objective context to differentiate between stress exposure and stress response, independent versus dependent stress, and can capture individualized stressful life events.

This said, it is also important to note that molecular genetic studies have found that genetic variants associated with depression risk exacerbate risk for self-generated dependent stress, but not independent stress, despite utilizing gold-standard interview-based assessments of stressful life events (Harkness et al., 2015; Huang & Starr, 2019; Starr et al., 2012). There are a few possible reasons for these differences in findings. Whereas previous studies have taken either a single candidate gene approach (i.e., 5-HTTLPR) or have focused on a few polymorphisms within a specific biological pathway (i.e., the HPA axis), the current study utilized a GWAS-derived PRS that agnostically examined genetic variants distributed across the genome. Therefore, it is possible that genetic associations with independent stress are only observed when examining the cumulative impact of numerous SNPs associated with depression across the genome, rather than a few isolated SNPs.

It also is important to note the critical difference between previously examined genetic variants and the DEP-PRS examined in the current study. The genetic variants utilized in prior studies were theoretically chosen based on their links with certain biological pathways (i.e., serotonergic system, HPA axis) (Brinksma et al., 2018; Harkness et al., 2015; Huang & Starr, 2019; Starr et al., 2012). In contrast, GWAS-derived PRSs are not theoretically derived, but include any SNPs associated with the outcome of interest, regardless of the function of that SNP. Given that PRSs from GWAS studies of depression may include variants that contribute to depression risk via indirect paths (e.g., variants that are associated with depressogenic environments via rGE), it is possible that depression PRSs may have stronger relations with factors that contribute to depression risk rather than depression itself. Supporting this proposition, the DEP-PRS in the current study explained 3.24% to 4.00% of the variance in stress exposure, but only 0.52% of variance in youth depression symptoms across the follow-ups. This proportion of variance explained for stress exposure is also greater than the amount of variance in depression risk accounted for by the same DEP-PRS in the original training samples (1.5% to 3.2%; Howard et al., 2019) or in a separate youth sample (0.37% to 2.21%; Kwong et al., 2021).

These results, therefore, bring up critical questions regarding the extent to which GWAS-derived DEP-PRSs only reflect risk specifically for depression, or also include genetic

variance related to stress exposure. Of note, other studies have also observed that GWAS-derived PRSs capture environmental contexts that are out of youth's control such as neighborhood socioeconomic status or parental education (e.g., Ensink et al., 2020; Krapohl et al., 2017). If these GWAS-derived PRSs do capture rGEs, it may be that the association between DEP-PRSs and prospective depression risk or other maladaptive outcomes could be due, at least in part, to increased stress exposure. This is consistent with suggestions that GWAS-derived PRSs may not simply capture genetic variance that has a direct effect on the outcome of interest, but may reflect environmentally-mediated pleiotropy (Avinun, 2020). Though replication is needed, the current findings may also have important implications for gene × environment interactions that are observed with GWAS-derived DEP-PRSs. At the very least, researchers examining PRS × environment models of depression risk should first test for rGE with the proposed environmental factors to determine whether the PRS and environmental influences are truly independent risk factors.

Linking the current results back to the larger literature on rGEs, we have equated genetic associations with independent events to passive rGE, in that these are events that are largely outside of the youth's control. We also equated genetic associations with dependent events to active or evocative rGE, as these events were caused, at least in part, by the actions of the youth. For example, if a youth possessed greater genetic liability for depression, youth's greater genetically-mediated depressive characteristics could directly contribute to a conflict with friends (i.e., dependent life event) due to the youth's irritability leading them to snap at a friend and instigate a fight (active rGE) or a friend getting frustrated due to the youth's pessimism (evocative rGE). In this light, however, we should note that the distinction between independent and dependent events may not be as rigid as is typically described. For example, dependent life events that involve an argument with a parent may also be caused, at least in part, by the parent's genetic traits, thereby reflecting passive rGE. Additionally, researchers have suggested that independent life events may still reflect stress generation processes (Harkness & Stewart, 2009). For example, some independent events ostensibly out of a person's control (e.g., having a friend attempt suicide) could reflect active rGEs due to self-selection into certain environments (e.g., selection of friend group). Therefore, although current results suggest the potential presence of multiple forms of rGEs, definitive conclusions cannot be drawn regarding the precise types of rGEs observed.

Although not the primary focus of the current study, findings regarding the impact of mothers' MDD history on youths' levels of dependent and independent stressful life events are consistent with previous research (Adrian & Hammen, 1993), including what has been observed at the baseline assessment with the current sample (Feurer et al., 2016). The current results also build upon these findings as the utilization of a GWAS-derived DEP-PRS allowed an examination of whether maternal MDD history was uniquely associated with offspring stress exposure while statistically controlling for the influence of currently known genetic correlates of depression risk. The current results indicate that the impact of maternal history of MDD on youth stress exposure is at least partially independent of these genetic influences. Although this may suggest non-genetic mechanisms of risk for heightened stress exposure, it is also possible that mothers' depression increases risk for youth stress exposure through other genetic variants that are not captured within the DEP-PRS or through epigenetic mechanisms. Future studies are needed to further disentangle potential genetic

and environmental mechanisms through which depression in mothers increases risk for offspring stress generation.

Finally, exploratory analyses indicated one instance in which youths' DEP-PRS and maternal history of MDD may interact to increase stress exposure. Specifically, offspring of mothers with a history of MDD who also possessed both a greater DEP-PRS exhibited the highest levels of self-generated dependent major life events. Therefore, whereas youth's DEP-PRS and maternal history of MDD were independently associated with the generation of dependent stress overall, the current findings suggest that the combined effect of both risk factors predicts the generation of dependent life events that are more severe and impactful. Although it is possible that the current study was underpowered to detect interactions between youth PRS and maternal MDD predicting overall dependent stress, it may be that this null finding was due to the inclusion of minor events in primary analyses. Specifically, when collapsing across major and minor events, it is indeterminable whether a greater stress score reflects exposure to a single, major stressor or the culmination of multiple, minor stressors. Therefore, if the combined effect of youth PRS and maternal MDD specifically contributes to the generation of more severe dependent stressors, this effect may have been obscured by analyses that did not differentiate minor and major stressors. Future studies with larger sample sizes are needed to confirm whether the combined effect of youth PRS and maternal MDD increases risk for the generation of dependent major life events, specifically. Importantly, as major life events confer greater risk for youth depression onset compared to minor life events (Vrshek-Schallhorn et al., 2015), if replicated in future studies, the current findings indicate that youth with both risk factors may be at particularly elevated risk for depression onset due to increased exposure to dependent major stressful life events.

The present study had several strengths including the use of a previously validated GWAS-derived DEP-PRS, repeated interviewer-based assessments of life stress, and a relatively large at-risk sample of youth. However, there were also some limitations that warrant attention. First, the analyses only included youth of European ancestry to match the original training sample for the GWAS-derived DEP-PRS, thereby limiting the extent to which current findings can be generalized to youth of other racial identities. As the vast majority of GWAS are limited to European samples (Duncan et al., 2019b), it is of vital importance that future GWAS include samples of increased racial diversity to allow for generalization of results to marginalized racial and ethnic populations (Clyde, 2019). Second, the current sample size is not large by the standards of genetic studies and may have been underpowered to detect smaller main or interaction effects. Consequentially, replication in larger samples is necessary to confirm current findings. Third, the current study did not collect information regarding paternal psychopathology, thereby precluding the examination of whether the PRS results would also be maintained after taking paternal depression into account.

In summary, the current findings contribute to the literature on rGEs by highlighting the association between a GWAS-derived DEP-PRS and increased levels of both dependent and independent stress exposure in youth. The current findings also raise important questions regarding whether GWAS-derived PRSs capture genetic propensity towards stress exposure in addition to genetic variance specific to depression risk. Future studies are needed to replicate and extended current findings to both understand what, precisely, these GWAS-

derived PRSs are capturing and to test increased stress exposure as a mechanism through which genetic variance contributes to depression risk in youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Descriptive Statistics (Means and Standard Deviations) for Main Study Variables

	Mothers with MDD (*n* = 81)	Never-Depressed Mothers (*n* = 99)	$r_{effect\ size}$
Youth Age	11.62 (2.00)	11.23 (1.81)	.10
Youth Sex (% Female)	46.9%	56.6%	−.10
Family Income (median)	$40,001–$45,000	$60,001–$65,000	−.25***
Youth DEP-PRS	−0.085 (0.087)	−0.091 (0.078)	.04
T1 Dependent Stress	1.19 (1.45)	0.57 (0.76)	.23**
T2 Dependent Stress	0.87 (1.36)	0.38 (0.57)	.22**
T3 Dependent Stress	1.03 (1.39)	0.71 (2.01)	.17*
T4 Dependent Stress	0.66 (0.86)	0.43 (0.82)	.18*
T5 Dependent Stress	1.04 (1.85)	0.46 (0.68)	.28***
T1 Independent Stress	1.38 (1.38)	1.20 (1.32)	.07
T2 Independent Stress	1.78 (2.12)	0.98 (1.13)	.19**
T3 Independent Stress	2.02 (1.85)	1.15 (1.59)	.27***
T4 Independent Stress	1.56 (1.62)	1.11 (1.13)	.12
T5 Independent Stress	1.42 (1.84)	1.17 (1.39)	.03

Note. DEP-PRS = Depression polygenic risk score. T = Time. Youth DEP-PRS was multiplied by a constant of 1000 to allow for successful model convergence in analyses and is presented with this transformation applied here.

* $p < .05$

** $p < .01$

*** $p < .001$.

Table 2

Summary of Primary Analyses

	Dependent Stress					Independent Stress				
	B	***SE***	***t***	$r_{effect\ size}$	***p***	***B***	***SE***	***t***	$r_{effect\ size}$	***p***
Step 1:										
Youth DEP-PRS	0.46	0.17	2.77	.20	**.006**	0.96	0.38	2.50	.18	**.013**
Step 2:										
Youth DEP-PRS	0.43	0.16	2.75	.20	**.007**	0.92	0.38	2.45	.18	**.015**
Mother MDD	0.12	0.03	4.53	.32	**<.001**	0.19	0.06	3.08	.23	**.002**

Note. DEP-PRS = Depression polygenic risk score. Mother MDD = Mother history of major depressive disorder (yes = 1, no = 0).

Table 3

Summary of Analyses Examining Minor and Major Episodic Stress

	Minor Life Events									
	Dependent Stress					**Independent Stress**				
	B	*SE*	*t*	$r_{effect\ size}$	*p*	*B*	*SE*	*t*	$r_{effect\ size}$	*p*
Step 1:										
Youth DEP-PRS	0.29	0.14	2.12	.16	**.036**	0.63	0.29	2.17	.16	**.031**
Step 2:										
Youth DEP-PRS	0.27	0.13	2.07	.16	**.040**	0.62	0.29	2.13	.16	**.035**
Mother MDD	0.09	0.02	4.21	.30	**<.001**	0.06	0.05	1.27	.10	.207
	Major Life Events									
	Dependent Stress					**Independent Stress**				
	B	*SE*	*t*	$r_{effect\ size}$	*p*	*B*	*SE*	*t*	$r_{effect\ size}$	*p*
Step 1:										
Youth DEP-PRS	0.25	0.10	2.51	.18	**.013**	0.21	0.13	1.56	.12	.122
Step 2:										
Youth DEP-PRS	0.24	0.10	2.46	.18	**.015**	0.19	0.13	1.48	.11	.141
Mother MDD	0.06	0.02	3.77	.27	**<.001**	0.09	0.02	4.45	.32	**<.001**

Note. DEP-PRS = Depression polygenic risk score. Mother MDD = Mother history of major depressive disorder (yes = 1, no = 0).