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Research paper

Transcriptional evidence of HPA axis dysregulation in adolescent females: Unique contributions of chronic early-life stressor exposure and maternal depression history

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ABSTRACT

Background: Depression risk increases dramatically for adolescent females following the pubertal transition. Although chronic early-life stressor exposure and a maternal history of depression are established risk factors for depression onset in this population, we know little about the biological mechanisms underlying these associations.

Method: To investigate, we examined how chronic early-life stressor exposure and maternal depression history were associated with stress-related gene expression patterns, using a high-risk family design in 48 psychiatrically healthy adolescent females, 20 of whom had a mother with a lifetime history of depression. Lifetime chronic stressor exposure was assessed using the STRAIN and gene expression patterns were estimated using transcriptional profiling of whole blood.

Results: Consistent with hypotheses, we found that adolescent females with greater chronic stressor exposure had higher *NR3C1* expression levels compared to those with less chronic stressor exposure. Additionally, youth with a depressed mother had lower levels of *FKBP5* expression compared to those without a depressed mother. Levels of *FKBP5* expression, in turn, interacted with chronic stressor exposure to predict *NR3C1* expression. Specifically, for those with low chronic stressor exposure, levels of *FKBP5* and *NR3C1* expression were strongly interrelated, whereas for those with high chronic stressor exposure, *NR3C1* expression was high regardless of levels of *FKBP5* expression.

Limitations: This study was correlational, the sample size was limited, and additional research is needed to elucidate the underlying mechanisms and predict who subsequently develops depression.

Conclusions: Notwithstanding these limitations, these data indicate that having low *FKBP5* expression, alongside high *NR3C1* expression, may be a potential *preclinical marker* of depression risk in adolescent females that warrants additional investigation.

1. Introduction

Rates of adolescent depression and suicidality are on the rise, with adolescent females bearing a larger portion of this mental health burden than adolescent males. Indeed, 57 % of female teenagers reported feeling sad or hopeless in 2021, twice the rate reported by their male peers (CDC, 2023). Furthermore, one in three female teenagers considered attempting suicide in 2021, which represents a 60 % increase from 2011 (CDC, 2023). Although many treatment options for depression are available, including cognitive behavior therapy and psychopharmacological medication (Beirão et al., 2020; Girardi et al., 2009; Oud et al., 2019), an ounce of prevention is worth a pound of cure. Assessing risk factors for depression in adolescent females allows for the identification of preclinical depression risk, which can in turn be used to allocate early intervention efforts toward those at the highest risk of developing depression.

One key risk factor that increases the risk of developing depression is life stressor exposure (Burani et al., 2023; Slavich and Irwin, 2014; Slavich and Sacher, 2019). Although biological sex does not influence the likelihood of encountering major life stressors, females are more likely than males to experience the specific interpersonal stressors that most strongly predict the onset of a major depressive episode (Slavich

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and Sacher, 2019). Other risk factors for depression, such as experiencing chronic early adversity (Furman et al., 2019; Hodes and Epperson, 2019) and having a depressed mother (Murphy et al., 2023), are also relatively stronger predictors of future depression for female vs. male adolescents. Although genetic and epigenetic mechanisms partly link mothers' and daughters' depression risk (Bowers and Yehuda, 2020), shared exposure to stressors (i.e., daughters experiencing their mothers' stressors or mothers and daughters engendering stressors in their lives) significantly increases daughters' depression risk as well (Hammen, 2018; Murphy et al., 2023).

Past research suggests that one way in which early-life stressor exposure influences depression risk is by dysregulating hypothalamic-pituitary-adrenal (HPA) axis functioning (Slavich and Irwin, 2014; Slavich and Sacher, 2019), which can promote inflammatory activity and, in turn, depression (Slavich et al., in press). Presently, however, we lack diagnostic biomarkers of HPA axis dysregulation that could serve as an early or preclinical marker of depression risk. Blood and salivary measures of cortisol can be used to detect severe HPA axis dysfunction, and elevated morning and nighttime cortisol levels are predictive of later depression in adolescents; however, the complex dynamics of the HPA axis, especially throughout this developmental period, preclude the ability to use these markers in isolation as biomarkers of preclinical depression risk in adolescents (Zajkowska et al., 2022). Although we know that early adversity and maternal depression are strong risk factors for depression, and that altered HPA axis functioning is implicated, the upstream biological mechanisms through which these risk factors translate into depression remain unclear.

Fortunately, cortisol is just one molecule operating in a complex biological system that can be explored to understand stress-related processes. In the present study, we focused specifically on two components of the HPA axis—namely, expression of FK506 binding protein 51 (*FKBP5*) and the glucocorticoid receptor (nuclear receptor subfamily 3 group C member 1; *NR3C1*). Both *FKBP5* and *NR3C1* mRNA encode key proteins that regulate the HPA axis-mediated stress response. *FKBP5* encodes FKBP51, a chaperone protein that regulates one's glucocorticoid receptor sensitivity and stress-reactivity. FKBP51 levels increase following mineralocorticoid and glucocorticoid receptor activation, functionally decreasing glucocorticoid receptor responses and sensitivity, and are typically positively correlated with cortisol levels (Matosin et al., 2018; Zannas et al., 2016; Yurtsever et al., 2019). In contrast, *NR3C1* encodes the glucocorticoid receptor. Both the levels and sensitivity of the glucocorticoid receptor determine how cortisol released by the body impacts stress-related outcomes. In the present study, therefore, we investigated differences in stress-related gene expression patterns using a high-risk family design that sampled female adolescents at high vs. low risk for depression, but who have never had any Axis I affective disorder, including depression. More specifically, we compared HPA axis-related gene expression patterns between female adolescents with or without depressed mothers, examining the pathways through which mothers' depression status and daughters' chronic early-life stressor exposure were associated with HPA axis-related gene expression.

1.1. Stress-related gene expression and depression

Both *FKBP5* and *NR3C1* have been explored in the context of depression. For example, past research has found that possessing key genotypes (e.g., the single nucleotide polymorphism [SNP] rs1360780) and alleles typically associated with elevated *FKBP5* expression (e.g., the "risky allele" T) increases an individual's risk of developing depression as well as posttraumatic stress disorder (PTSD) in response to childhood trauma, in addition to other health problems commonly associated with decreased glucocorticoid sensitivity and increased cortisol levels (for a review, see Wang et al., 2018). Other studies, however, have found reduced expression of *FKBP5*—and *NR3C1*—mRNA in peripheral blood mononuclear cells (PBMCs) of adults with major depressive disorder (MDD) compared to healthy controls, alongside of hypermethylation in promoter regions of these genes (Roy et al., 2017). Likewise, many studies have reported associations between *NR3C1* and depression (Park et al., 2019). Generally, past studies have focused on adults with depression, and associations between stress-related gene expression and depression in adolescents has been insufficiently characterized.

1.1.1. Early-life stress

An extensive body of research has documented the impact of early-life stress on *NR3C1* methylation and, in turn, stress reactivity and depression risk. In some studies, early-life stressor exposure has been found to predict *NR3C1* methylation, decreased *NR3C1* expression, glucocorticoid insensitivity, and blunted cortisol reactivity to acute stress (Holmes et al., 2019; Watkeys et al., 2018). Other researchers have found that bullying and social stressors are associated with *NR3C1* hypermethylation and, in turn, internalizing symptoms, in adolescents (Efstathopoulos et al., 2018). Additionally, evidence suggests that a blunted stress response, which often co-occurs with increased *NR3C1* expression, confers increased risk for depression. Specifically, depressed individuals, as compared to controls, appear to show reduced cortisol reactivity to stress (Cunningham et al., 2021; Morris et al., 2014). Further, when compared to those with lower depression severity, those with greater depression severity show blunted cortisol reactivity to stress (Harkness et al., 2011).

Although relatively under studied, there is also evidence that the interaction between *FKBP5* and *NR3C1* expression has implications for the functioning of an individual's stress response system and stress-related outcomes such as depression and PTSD. For example, Mehta et al. (2011) found an interaction between risk allele A carriers of rs929615 and glucocorticoid sensitivity in predicting PTSD in a sample of traumatized individuals. Further, Lukic et al. (2015) found that depressed patients had significantly more glucocorticoid receptors in cytoplasm compared to control participants and this was associated with higher FKBP5 levels. Similarly, individuals who carried the *FKBP5* risk allele showed glucocorticoid resistance in response to a stressor, suggesting a dysregulated HPA axis-meditated stress response system (Menke et al., 2013).

Although the effects of early-life stress on individual components of the HPA axis are mixed, early adversity does reliably predict dysregulation within the HPA axis and, in turn, increased risk for developing psychiatric disorders. As described above, expression of *FKBP5* and *NR3C1* are associated with depression risk; however, past research has found that chronic early-life stress impacts each of these factors. Therefore, it is critical to consider how early-life stress may impact the associations between stress-related gene expression and depression. For example, in their meta-analysis, Wang et al. (2018) reported substantial evidence that *FKBP5* and early-life stress interact to influence risk of developing stress-related disorders, including MDD. However, most extant research investigating associations between risk factors for depression and stress-related gene expression has been conducted in adults and, consequently, very little is known about these dynamics in adolescence. More specifically, despite adolescent females having twice the risk of developing depression compared to adolescent males, few studies have examined transcriptional risk factors for depression in adolescent females.

1.2. The present study

To address these issues, we investigated potential transcriptional mechanisms and early indices of depression risk in adolescent females at high vs. low risk for developing depression. To elucidate pathways linking early-life chronic stressor exposure to dysregulated HPA axis-mediated stress responses and adult depression risk, we investigated stress-related gene expression patterns in adolescents, in order to identify potential mechanisms through which early-life risk factors for depression may impact adult depression risk. Although protein levels are

commonly studied, gene expression can provide unique insights into the function of molecular regulatory systems given that gene expression patterns drive protein production and are strongly related to social and environmental influences (Cole et al., 2012; Slavich and Cole, 2013; Slavich et al., 2023). This makes gene expression especially relevant when investigating early, preclinical markers of depression risk in adolescents, as changes in gene expression patterns are expected to precede changes in protein levels. Moreover, in contrast with measuring protein levels, which result from highly complex transcriptional signaling dynamics, focusing on specific transcriptional signals provides a more straightforward window into the regulatory logic underlying protein levels and, in turn, depression risk.

To investigate associations between chronic stressor exposure occurring prior to adulthood, maternal depression, and HPA axis-related gene expression, we took advantage of a high-risk family design that sampled female adolescents at high vs. low risk for depression, but who have not developed depression. In doing so, we aimed to provide promising targets for future research into preclinical markers of depression risk in adolescent females. Based on the extant research summarized above, we hypothesized that (*H1*) female adolescents with high levels of chronic stressor exposure would exhibit dysregulation between their *FKBP5* and *NR3C1* expression compared to those who experienced low levels of chronic stressor exposure, and that (*H2*) female adolescents at high risk for depression, based on having a depressed mother, would exhibit more dysregulation between their *FKBP5* and *NR3C1* expression compared to those at low risk for developing depression. Finally, we conducted an exploratory analysis to test the hypothesis that (*H3*) having both a high risk for depression and elevated chronic stressor exposure, together, would be associated with the greatest dysregulation of the HPA axis, as indexed by desynchronized associations between *FKBP5* expression and *NR3C1* expression.

2. Method

2.1. Participants

Data were drawn from the Psychobiology of Stress and Adolescent Depression (PSY SAD) Study, which recruited fifty-two females between the ages of 12–18 years old ($M = 14.90$, $SD = 1.35$) from the Los Angeles area using fliers, announcements in local schools, and word of mouth. All participants had no current or past lifetime history of any Diagnostic and Statistical Manual-IV (DSM-IV) Axis I affective or substance use disorder. Moreover, they lived with their biological mothers, had a body mass index ≤ 30, spoke English, and were free of factors known to influence inflammation, including: inflammatory disorders, major sleep disturbance, prescription drug use, and excessive caffeine use (O'Connor et al., 2009). Participants self-identified as White (32.7 %; $n = 17$), Hispanic (28.8 %; $n = 15$), multi-racial (23.1 %; $n = 12$), Black (7.7 %; $n = 4$), Asian (3.8 %; $n = 2$), and other race/ethnicity (3.8 %; $n = 2$). Complete characteristics of the study sample and protocol were described by Sichko et al. (2021). For the present analyses, a *post-hoc* power calculation revealed adequate power to detect large effects (i.e., $d > 0.82$) at $\alpha = 0.05$.

2.2. Procedure

All procedures were pre-approved by the Institutional Review Board at UCLA. In brief, participants and their biological mothers were first screened over the phone for inclusion and exclusion criteria. Participants likely to meet all inclusion criteria were then invited to attend an in-person intake session to confirm their eligibility. After obtaining informed consent, trained diagnostic interviewers—directly supervised by senior author, G.M.S.—evaluated the mothers and daughters for the presence of psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997) for daughter, and the Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 1995) for mothers. If daughters were determined to meet the criteria for an Axis I disorder, they were excluded from participation. Next, daughters were classified as being either at high-risk or low-risk for depression based on their mother's lifetime history of MDD. Daughters in the high-risk group had mothers who had experienced at least one major depressive episode ($n = 22$), whereas those in the low-risk group had mothers who had never experienced an Axis I disorder ($n = 30$). Again, none of the daughters had ever experienced an Axis I affective disorder, regardless of risk group.

Next, participants attended a three-hour experimental study session. During this session, the participants first had an intravenous catheter inserted into their arm to allow for multiple blood draws throughout the course of the study visit. Then, participants completed the Stress and Adversity Inventory for Adolescents (Adolescent STRAIN; Slavich et al., 2019) to assess their exposure to both acute and chronic stressors over the life course (see below). Following this assessment, participants had their baseline blood samples drawn before completing a social evaluative stress task while in an MRI scanner as a part of a larger study. Immediately after being removed from the MRI scanner, about 90 min later, participants had their second blood sample taken. Thirty minutes later, a final blood sample was obtained.

2.3. Measures

2.3.1. Lifetime stressor exposure

The Adolescent STRAIN is a NIMH/RDoC-recommended instrument for assessing cumulative lifetime stressor exposure across a variety of life domains (i.e., housing, education, financial) and social-psychological characteristics (e.g., interpersonal loss, physical danger, role change/disruption) (for more information, see https://www.strainsetup.com). Participants were asked to indicate whether they had experienced each of 75 different acute life events and chronic difficulties, and for each stressor they endorsed, follow-up questions ascertained the stressor's severity, frequency, exposure timing, and duration. Because all participants were under 18 years old at assessment, all stressors were considered early-life stressors. Based on prior research showing that chronic early-life stressors have a large and lasting impact on girls' HPA axis functioning (Goodwill et al., 2019; Marin et al., 2007; Miller and Chen, 2007, 2010; Miller et al., 2009), we computed the total lifetime count of chronic stressors (i.e., those that persisted for at least four weeks) that each participant experienced across all life domains and social-psychological characteristics to create an index of chronic early-life stressor exposure. The STRAIN has very good concurrent, discriminant, and test-retest validity, and has been shown to predict a wide variety of psychological, biological, and clinical outcomes, including HPA axis functioning and depression (Cazassa et al., 2020; Lam et al., 2019; Slavich and Shields, 2018; Slavich et al., 2019; Sturmbauer et al., 2019).

2.3.2. Gene expression

At each blood draw timepoint, multiple tubes were collected. For the present analysis, 2.5 mL of blood was drawn into a PAXgene Blood RNA tube, which was immediately put on ice and, at the end of the study session, transferred to a −80 °C freezer at the UCLA Center for Pathology Research Services. Next, samples were transferred to the UCLA Social Genomics Core Laboratory for RNA extraction (RNeasy; Qiagen, Valencia, CA), tested for suitable mass (Nanodrop ND1000) and integrity (Agilent Bioanalyzer), converted to barcoded cDNA (Lexogen QuantSeq 3′ FWD), and sequenced on an Illumina HiSeq4000 system (Illumina, San Diego, CA) in the UCLA Neuroscience Genomics Core Laboratory, per manufacturer recommendations. Sequencing assays targeted >10 million 65-nt single-stranded sequence reads for each sample, each of which was mapped to the reference human transcriptome using the STAR aligner and quantified as gene transcripts per million mapped reads.

2.4. Data analytic plan

To prepare data for analysis, we first summed the total lifetime count of chronic stressors reported in the STRAIN for each participant. Gene expression data were unavailable for four participants, resulting in a data analytic sample of 48 participants. Although whole genome data were available, based on our specific *a priori* hypotheses, only expression of *FKBP5* and *NR3C1* were analyzed. Mean composites of each *FKBP5* and *NR3C1* expression were computed by averaging each adolescent's expression across the three blood collection time points. To investigate the associations between depression risk group and stress-related gene expression, we classified participants as either being at a high-risk for depression (if her mother had a depression diagnosis; $n = 20$) or at a low-risk for depression (if her mother did not have a depression diagnosis; $n = 28$).

To assess the impact of chronic stressor exposure on stress-related gene expression, we first assessed correlations between chronic stressor exposure and *FKBP5* and *NR3C1* expression. Next, we used a moderated regression analysis to assess the interaction between chronic stressor exposure and *FKBP5* expression on *NR3C1* expression (*H1*). To assess the impact of depression risk on stress-related gene expression, we used standard *t*-tests to compare *FKBP5* and *NR3C1* expression between high-risk and low-risk participants, and a moderated regression analysis to assess the interaction between depression risk and *FKBP5* expression on *NR3C1* expression (*H2*). Finally, we used a cross-sectional meditation analysis to determine if *FKBP5* expression mediated the association between depression risk and *NR3C1* expression. Based on prior research showing that *FKBP5* interacts with early-life stressor exposure to predict risk of developing stress-related disorders (Appel et al., 2011; Roy et al., 2010; Zimmermann et al., 2011), we assessed the extent to which chronic early-life stressor exposure interacted with *FKBP5* expression to predict *NR3C1* expression (*H3*).

3. Results

3.1. Chronic stressor exposure

Chronic stressor exposure was positively associated with levels of *NR3C1* expression and was unrelated to *FKBP5* expression. Further, *FKBP5* expression was negatively correlated with *NR3C1* expression. See Table 1 for a summary of the corresponding statistics.

Next, we investigated if chronic stressor exposure impacted the association between *FKBP5* and *NR3C1* expression using a moderated regression analysis. As depicted in Fig. 1, results revealed a significant two-way interaction between chronic stressor exposure and *FKBP5* expression on *NR3C1* expression, $b = 0.02$, $SE = 0.01$, $t = 2.57$, $p = .014$, 95 % CI [0.01, 0.04]. Simple slope analyses revealed a negative association between *FKBP5* expression and *NR3C1* expression for adolescent females with low levels ($-1SD$) of chronic stressor exposure ($p \leq .001$), and no association between *FKBP5* expression and *NR3C1* expression for those with high levels ($+1SD$) of chronic stressor exposure ($p = .529$).

3.2. Depression risk group

With respect to depression risk group, we found that adolescent females at high risk for depression had significantly lower expression of *FKBP5* compared to those at a low risk for depression ($p = .005$). Further, adolescent females at a high risk for depression had marginally higher levels of *NR3C1* expression compared to those at low risk for depression, although this difference was not significant ($p = .098$). See Table 2 for the corresponding descriptive and inferential statistics.

Next, we investigated if depression risk impacted the association between *FKBP5* and *NR3C1* expression using a moderated regression analysis. Results revealed that although *FKBP5* expression was negatively associated with *NR3C1* expression, $b = -0.14$, $SE = 0.06$, $t = 2.42$, $p = .020$, 95 % CI [−0.26, −0.02], depression risk did not interact with *FKBP5* expression to predict *NR3C1* expression, $b = 0.12$, $SE = 0.12$, $t = 1.00$, $p = .321$, 95 % CI [−0.13, 0.37].

Table 1
Correlations between chronic stressor exposure, FKBP5 expression, and NR3C1 expression.

	FKBP5	*NR3C1*
Chronic early-life stressor exposure	$r = -0.081$	$r = 0.305$*
FKBP5		$r = -0.448$*

Note. $n = 48$; * $p \leq .05$.

3.3. Exploratory path model

Building upon the results from models assessing associations between chronic stressor exposure and depression risk on stress-related gene expression, we estimated an exploratory moderated mediation model using SPSS PROCESS macro, Model 14. In this model, we assessed the mediating role of *FKBP5* expression in the association between depression risk and *NR3C1* expression, along with the moderating role of chronic stressor exposure on the association between *FKBP5* expression and *NR3C1* expression. Results revealed that being at high risk of depression was related to low levels of *FKBP5* (*a* path). *FKBP5* levels, in turn, interacted with chronic stressor exposure to predict *NR3C1* levels (*b* paths). Specifically, adolescent females with high levels of chronic stressor exposure had high levels of *NR3C1* expression that did not depend upon their levels of *FKBP5* expression; in contrast, adolescent females with low levels of chronic stressor exposure had high levels of *NR3C1* expression only if their *FKBP5* expression levels were low. See Fig. 2 for all for the corresponding model and inferential statistics.

4. Discussion

To investigate novel, preclinical markers of depression risk in adolescent females, we examined how two key risk factors for depression were associated with stress-related gene expression patterns in adolescent females. We hypothesized that each of these risk factors—namely, chronic early-life stressor exposure (*H1*) and maternal depression (*H2*)—would predict dysregulation between *FKBP5* and *NR3C1* expression, and that these patterns of dysregulation would be strongest for adolescent females who possessed both risk factors (*H3*). We found at least partial support for each of our hypotheses, with results indicating that both risk factors for depression were associated with stress-related gene expression through distinct mechanistic pathways.

More specifically, we first found that low levels of chronic early-life stressor exposure were associated with low levels of *NR3C1*, which were negatively associated with *FKBP5* levels, demonstrating a well-regulated pattern of stress-related gene expression in adolescent females without substantial chronic stressor exposure. On the other hand, high levels of chronic early-life stressor exposure were associated with high levels of *NR3C1* expression, which were unrelated to levels of *FKBP5* expression, suggesting possible dysregulation of the HPA axis. These results are consistent with the hypothesis that exposure to chronic early-life stressors predicts dysregulation between *FKBP5* and *NR3C1* expression, and with past research showing that such early-life stressors can dysregulate the HPA axis and HPA axis-mediated stress response (Alexander et al., 2018; Carpenter et al., 2010; Juruena et al., 2021; Miller and Chen, 2010; Miller et al., 2009; Young et al., 2021).

Next, we investigated how elevated risk for developing depression, conferred through a positive maternal lifetime history of the disorder, impacted associations between *FKBP5* and *NR3C1* expression in these youth. Although we found that adolescent females with depressed mothers had lower levels of *FKBP5* expression compared to those without depressed mothers, levels of *FKBP5* expression did not interact with maternal depression to influence levels of *NR3C1* expression. As such, we only found partial support for our second hypothesis.

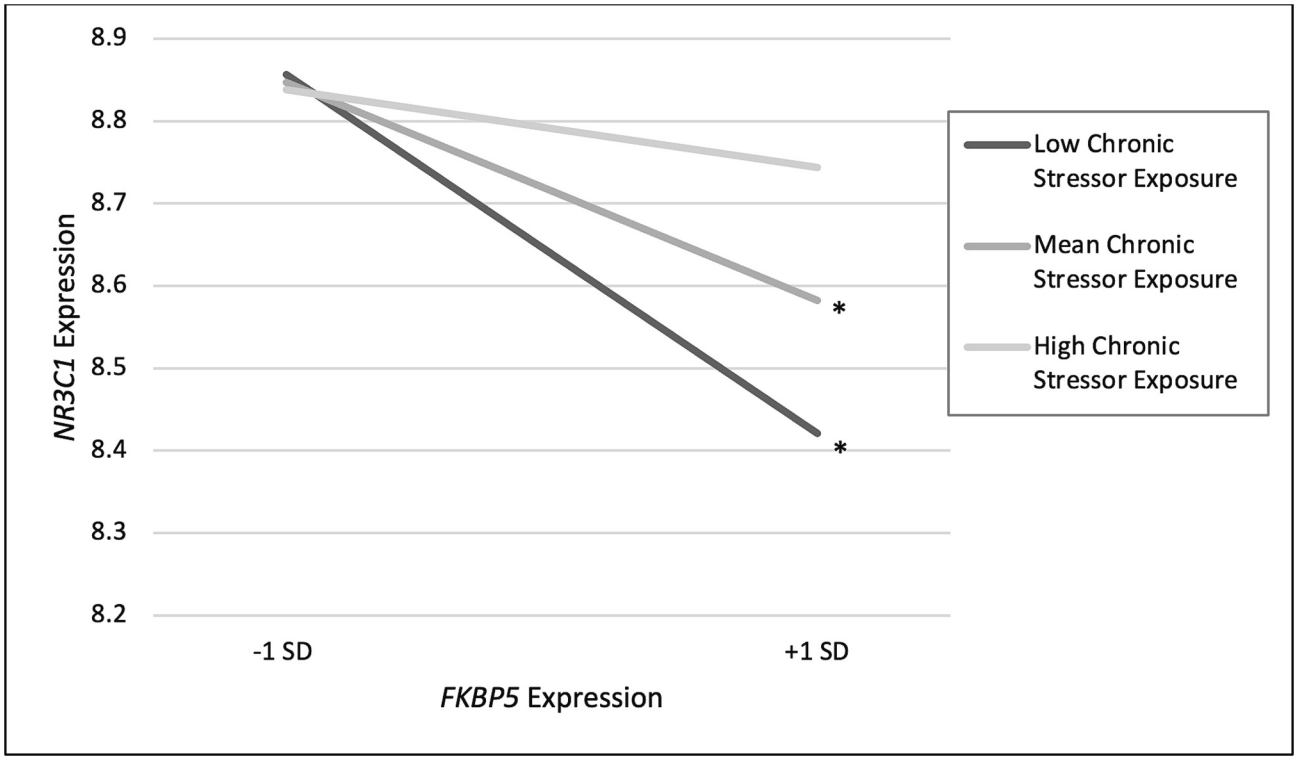

Fig. 1. Chronic stressor exposure interacts with levels of *FKBP5* expression to predict *NR3C1* expression in whole blood. In those with low levels of chronic stress exposure, there is a significant negative association between *FKBP5* expression and *NR3C1* expression, which is absent in those with high levels of chronic stress exposure. Note. * = $p \leq .05$; *SD* = standard deviation.

Table 2
Stress-related gene expression by depression risk group.

Outcome	High-risk adolescent females ($n = 20$) *M* (*SD*)	Low-risk adolescent females ($n = 28$) *M* (*SD*)	*T* (*df*)	*p*-Value
FKBP5 Expression	3.62 (0.63)	4.25 (0.79)	2.92 (46)	0.005
NR3C1 Expression	8.78 (0.29)	8.62 (0.32)	1.69 (46)	0.098

Building upon these results, we then explored how chronic stressor exposure and depression risk, together, influenced associations between *FKBP5* and *NR3C1* expression. We found that adolescent females at high risk for depression had lower levels of *FKBP5* expression compared to those at low risk for depression. Levels of *FKBP5* expression, in turn, interacted with chronic early-life stressor exposure to predict *NR3C1* expression. Specifically, adolescent females with low levels of *FKBP5* expression exhibited elevated levels of *NR3C1* expression that did not vary based on their chronic stressor exposure. This combination of low expression of *FKBP5* coupled with high expression of *NR3C1* suggests a dysregulated stress response system that may not be able to effectively react to, and recover from, stressors (Zannas et al., 2016). The fact that these results do not vary based on chronic early-life stressor exposure suggests that having a mother with depression can confer risk for a dysregulated HPA axis-mediated stress response system regardless of chronic stressor exposure, through associations with low levels of *FKBP5* expression. However, these results mirror the patterns observed in those with high levels of chronic early-life stressor exposure, for whom levels of *FKBP5* expression were unrelated to levels of *NR3C1* expression. This latter pathway suggests that chronic early-life stressors may confer risk for a dysregulated HPA axis-mediated stress response system by promoting high levels of *NR3C1* expression. Together, these results indicate that although both chronic early-life stressor exposure and maternal depression influence the association between *FKBP5* and *NRC31* expression levels, that these risk factors influence stress-related gene expression through distinct mechanistic pathways.

Some researchers have hypothesized that having a depressed mother confers increased depression risk for the child through adverse experiences, such as poor maternal care or mother-infant bonding (Slomian et al., 2019), or through shared environmental stress (Murphy et al., 2023). However, given that having a depressed mother predicts low *FKBP5* expression, and that low *FKBP5* expression is associated with high *NR3C1* expression regardless of chronic early-life stressor exposure, having a mother with depression may confer risk for dysregulated HPA axis-mediated stress reactivity and, therefore, mood disorders, *regardless of early-life adversity*, which is critical for early detection of depression risk and determinations of who is likely to benefit from primary intervention efforts.

Given known associations between HPA axis dysregulation and depression in adults (e.g., Ceruso et al., 2020), the dysregulated patterns of HPA axis-related gene expression observed here should be investigated as potential antecedents of depression. Given that none of the participants in this sample had ever experienced a major depressive episode, our results suggest that this combination of low *FKBP5* expression with high *NR3C1* expression could be a *preclinical marker* of depression risk in adolescent females. However, longitudinal studies that follow youth forward in time, and that assess subsequent psychiatric diagnoses, are needed to confirm this possibility.

4.1. Strengths, limitations, and future directions

The present research has several strengths. First, the use of a high-risk family design enabled us to elucidate potential preclinical markers of depression risk that cannot be confounded with having the disorder (e.g., a symptom or co-contaminant of the disorder), which is rarely

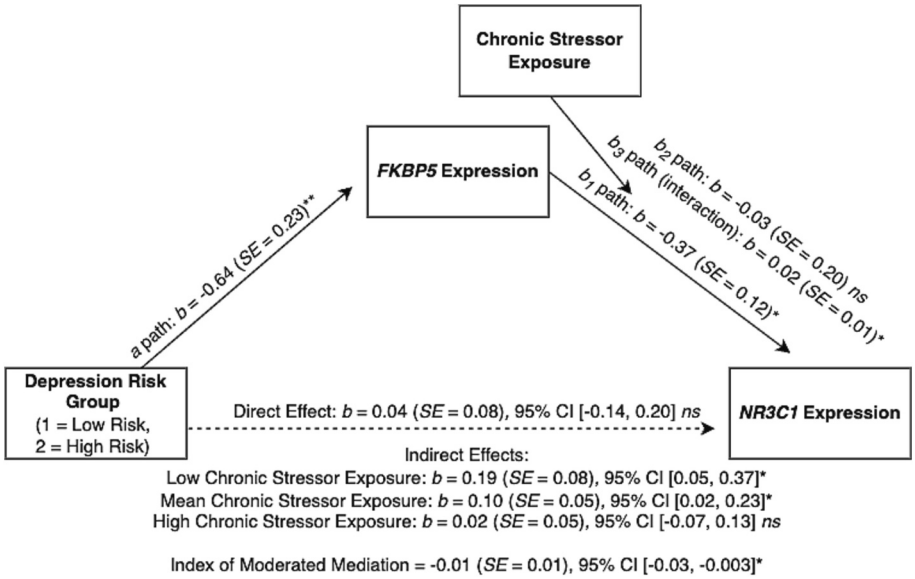

Fig. 2. Being at a high risk for depression predicts lower *FKBP5* expression, which, in turn, interacts with chronic stressor exposure to predict *NR3C1* expression. Specifically, adolescent females with high chronic stressor exposure had high levels of *NR3C1* expression that did not depend upon their levels of *FKBP5* expression; in contrast, adolescent females with low chronic stressor exposure had high levels of *NR3C1* expression only if their *FKBP5* expression levels were low. Note. *SE* = standard error; * = $p \leq .05$; *ns* = non-significant ($p > .05$).

done but absolutely critical for investigating mechanisms underlying the pathogenesis of mental and physical health problems. Likewise, by studying HPA axis-related gene expression in this high-risk, but psychiatrically healthy, sample, we were able to characterize the dynamics of a developing system that has not yet reached clinical levels of dysregulation, providing insight into the developmental trajectory of HPA axis-related dysregulation before it is fully realized. Third, we used a well-validated system for assessing lifetime stressor exposure that is not sensitive to social desirability or negative mood effects (Slavich and Shields, 2018). Finally, we focused on functional genomics, as opposed to protein levels, which provides more straightforward insight into the mechanistic pathways linking chronic early-life stressor exposure and maternal depression with depression risk.

Despite these strengths, several limitations should also be noted. First, as the present study is correlational, directionality and causality cannot be assumed. Second, the exact mechanistic processes through which the risk factors for depression we explored (i.e., maternal depression and experiencing chronic early-life stressors) impact expression of stress-related genes (i.e., *FKBP5* and *NR3C1*), and in turn, depression risk, have yet to be determined. Third, the sample size was limited for a functional genomic analysis and was adequately powered only to detect large ($d > 0.82$) effects using a targeted analysis approach. Therefore, the results should be replicated before strong conclusions can be drawn.

Fourth, our results differed from some prior research insofar as we found that depression risk was associated with low levels of *FKBP5* expression in whole blood. Although some studies in adults have found that possessing SNPs that result in elevated *FKBP5* expression is associated with depression (Wang et al., 2018), the extant literature is inconsistent, with other studies reporting that depression is related to low *FKBP5* expression in PBMCs (Roy et al., 2017). It is important to differentiate between studies that focus on genotype × environment interactions and those that focus on gene expression × environment interactions. Indeed, past research linking *FKBP5* expression to depression risk is largely based upon one's genotype, which we did not explore in the present study, but should be included in future research. Although the patterns of *FKBP5* expression that we found for adolescent females at high risk for depression are unlikely to mirror what would be found in adults with clinical depression, it is important to note that this study examined *preclinical* markers of depression risk, as none of the participants in our study have ever had MDD or any other Axis I affective disorder for that matter. As such, these adolescent females should not be expected to exhibit the same patterns of gene expression as adults with clinical depression. Likewise, associations between risk factors and stress-related gene expression likely differ throughout development and before HPA axis dysregulation is fully realized and, as such, caution should be used when comparing results between studies of adolescents and adults. Additionally, differences in sample types, methodology, and assay procedures preclude comparisons of absolute levels of expression between studies. What we describe as high or low expression is sample-specific, and a lack of appropriate comparisons in past literature preclude definition of ideal/normal associations between these transcript levels.

Fifth, the structure of the associations we modeled between *FKBP5* and *NR3C1* expression implies that *FKBP5* influences *NR3C1* expression; however, it is important to keep in mind that bidirectional influences between *FKBP5* and *NR3C1* are constantly occurring. Indeed, it is likely that *FKBP51* operates as a part of an autoregulatory process in a negative feedback loop in which glucocorticoid receptors limit their own activity. It is difficult to identify clear patterns of dysregulation or optimal functioning within complex, dynamic, and self-modulating systems such as the HPA axis-mediated stress response system, particularly during developmental periods in which rapid change is expected to occur (i.e., adolescence).

Looking forward, because this was an initial investigation into potential preclinical biomarkers of depression risk in adolescent females, future clinical and experimental research is needed. Specifically, extensions of this research should include investigating different spicing isoforms of the *NR3C1* gene to confirm the biological significance of the present results, investigations of the utility of these markers of preclinical depression risk in other populations and developmental stages, and comparisons with protein levels and other potential biomarkers of depression risk (e.g., Fusar-Poli et al., 2021). More broadly, additional research with larger sample sizes and longitudinal follow-ups is needed to help characterize trajectories in depression over time and to move us further toward discovering the risk and protective factors that predict patterns of HPA axis dysregulation that influence subsequent risk for depression in adulthood.

5. Conclusion

In conclusion, with adolescent female depression and suicidality on the rise, discovering preclinical markers of depression risk is vital. The gravity of depression and suicidality, especially in adolescents, demands proactive—as opposed to reactionary—approaches. Characterizing markers of early risk for depression, as we have done here, will enable clinicians and policymakers to use secondary prevention strategies to reduce depression risk by targeting those most likely to develop MDD in the future.

To this end, we found that low levels of *FKBP5* expression, along with elevated levels of *NR3C1* expression, were associated with maternal depression and chronic stressor exposure, respectively, and that together, these risk factors predicted dysregulation in HPA axis-related gene expression in a high-risk sample of adolescent females who had not developed clinical depression. Future research should aim to replicate the present results and determine if the gene expression patterns we have observed in adolescent females at high risk for depression generalize to other populations (e.g., adolescent males, non-western populations) and developmental time periods (e.g., prepubertal, adulthood). Although these results are only one step toward fully characterizing the transcriptional mechanisms through which psychosocial and environmental risk factors predict depression risk in adolescent females, we believe they provide promising targets for future research and a novel way to examine HPA axis dynamics in depression research.

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CRediT authorship contribution statement

Summer Mengelkoch: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **Jenna C. Alley:** Writing – review & editing, Writing – original draft, Conceptualization. **Steven W. Cole:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **George M. Slavich:** Writing – review & editing, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest with respect to this work.

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Data availability

Data will be made available upon request.

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