Title

HPA-axis multilocus genetic profile score moderates the association between maternal prenatal perceived stress and offspring depression in early adulthood

Journal

Development and Psychopathology, 33(1)

ISSN

0954-5794

Authors

McKenna, Brooke G
Hammen, Constance
Brennan, Patricia A

Publication Date

2021-02-01

DOI

10.1017/s0954579419001639

Peer reviewed

Development and Psychopathology (2020), 1–13
doi:10.1017/S0954579419001639

CAMBRIDGE UNIVERSITY PRESS

Regular Article

HPA-axis multilocus genetic profile score moderates the association between maternal prenatal perceived stress and offspring depression in early adulthood

Brooke G. McKenna[1], Constance Hammen[2] and Patricia A. Brennan[1]

[1]Department of Psychology, Emory University, Atlanta, GA, USA and [2]Department of Psychology, University of California, Los Angeles, Los Angeles, CA, USA

Abstract

Maternal stress during pregnancy can cause alterations to the fetal hypothalamus–pituitary–adrenal (HPA) axis, a phenomenon known as *fetal programming* that may have lasting effects on offspring outcomes, including depression. Evidence suggests that these effects may vary with respect to the offspring's genetic risk. Nonetheless, few studies have examined these effects into adulthood, when risk for depression onset is highest. The present study builds upon the extant literature by examining the interaction of maternal prenatal perceived stress (MPPS) and offspring HPA-axis polygenic risk to predict offspring depression in early adulthood. A total of 381 mother–child dyads participated in a prospective, longitudinal study that spanned from pregnancy until offspring were 20 years of age. Polygenic risk was defined by a multilocus genetic profile score (MGPS) that reflected the additive risk of three HPA-axis candidate genes. The results indicated that the interaction of MPPS and HPA-axis MGPS confers risk for offspring depression at age 20, in line with the *differential susceptibility* model. This interaction may be specific to prenatal stress, as maternal stress during early childhood did not interact with genetic risk to predict depression. These findings provide the first evidence that genetic variants that are associated with the HPA axis may act in a polygenic, additive fashion to moderate the association between fetal programming and adult depression.

Keywords: depression, fetal programming, HPA Axis, polygenic risk

(Received 19 May 2019; accepted 31 October 2019)

Major depressive disorder (MDD) is a debilitating condition that is experienced by 9 to 12% of men and 20 to 25% of women across the lifespan (Kessler, Chiu, Demler, & Walters, 2005). Decades of studies have indicated that environmental stress plays an indisputable role in the pathogenesis of MDD (Hammen, 2005). The majority of these studies focus on the influence of early life stress (for a review, see Heim & Binder, 2012) or stressful life events throughout adolescence and adulthood (e.g., Kessler, 1997). However, accruing evidence indicates that stress exposure in utero may also play an important role in the risk for MDD (Goodman & Gotlib, 1999). Recent animal studies have identified significant associations between maternal stress during pregnancy (i.e., maternal prenatal stress) and early childhood outcomes including altered immune function, anxious behaviors, reduced attention, and altered cardiovascular response to stress (Igosheva, Taylor, Poston, & Glover, 2007). These relationships are purported to be the result of *fetal programming*, in which prenatal exposures initiate an "adaptive" response in the fetus that carries forth to postnatal development, influencing both biology and behavior (Amiel-Tison et al., 2004; Barker, 2007; Gluckman et al., 2009; Gluckman & Hanson, 2005). In the case of maternal prenatal stress, the fetus may be programmed to anticipate a stressful postnatal environment through altered sensitivity to environmental stressors (Glover, O'Connor, & O'Donnell, 2010). Although this sensitivity may be adaptive in a threatening postnatal environment, it may be maladaptive in a nonthreatening environment, thus conferring risk for psychopathology, including depression.

To investigate the mechanisms that underlie fetal programming theory, researchers have sought to identify pathways by which maternal stress may affect fetal development. A key system that has been identified is the hypothalamic–pituitary–adrenal (HPA) axis (Glover, O'Connor, & O'Donnell, 2010). The HPA axis involves a complex interaction of molecular signaling that ultimately produces the glucocorticoid cortisol, a hormone that is broadly responsible for regulating the body's response to stress (Davis et al., 2007). Due to its role in the stress response, examining alterations in the HPA axis has become a primary focus of psychopathology research, particularly for major depression (Pariante & Lightman, 2008). This research has not only focused on individuals' own risk for depression but also how alterations in a mother's HPA axis may influence her offspring's risk. Evidence from rodent studies suggests that during pregnancy roughly 10–20% of the cortisol that is produced by a mother's stress response may pass through the placenta into the blood of her fetus (Gitau, Cameron, Fisk, & Glover, 1998). Once cortisol crosses the fetal blood-brain barrier, it can then program the development of

Author for Correspondence: Brooke McKenna, Department of Psychology, Emory University, 36 Eagle Row, Atlanta, GA 30322; E-mail: bgmcken@emory.edu.

Cite this article: McKenna BG, Hammen C, Brennan PA (2020). HPA-axis multilocus genetic profile score moderates the association between maternal prenatal perceived stress and offspring depression in early adulthood. *Development and Psychopathology* 1–13. https://doi.org/10.1017/S0954579419001639

fetal neural systems (Davis et al., 2007), including networks that are involved in fear regulation, behavioral inhibition, and the stress response (Dickerson, Lally, Gunnel, Birkle, & Salm, 2005). Although these causal mechanisms have not been studied in humans thoroughly, elevated maternal cortisol levels during pregnancy have been associated with infant negative emotional reactivity, dysregulated temperament, and an increased fear response to novel stimuli (Davis et al., 2007; de Weerth, van Hees, & Buitelaar, 2003; Lundy et al., 1990). These infant outcomes are particularly salient because they predict maladaptive responses (e.g., heightened responsivity to stress, known as *stress reactivity*) in children and adolescents (Belsky, Hsieh, & Crnic, 1998; Carson & Bittner, 1994), which in turn confer risk for depression and other psychopathology in later life (Starr, Hammen, Conway, Raposa, & Brennan, 2014).

Despite these associations, a dearth of studies has directly examined the association between maternal prenatal stress and offspring depressive outcomes into early adulthood. Given that current data show that rates of depression are increasing steadily—with the peak age of MDD onset being between 15 and 20 years old for both high- and low-risk populations (Weissman et al., 2016)—it is important to assess the role of prenatal exposures during this period of high developmental risk for depression. The present study focuses on offspring depressive outcomes at age 20 in order to take this risk period into consideration. Similarly, a paucity of studies has examined the association between maternal prenatal stress and offspring stress reactivity into early adulthood. Given the posited influence of maternal prenatal stress on an offspring's stress response system (i.e., the HPA axis) and the previously identified association between maternal prenatal stress and offspring stress reactivity in childhood, it is important to assess whether those effects may endure into early adulthood. Therefore, the present study also examines offspring stress reactivity outcomes at age 20.

Moderating Factors

A review of animal studies that was conducted by Glover, O'Connor, and O'Donnell (2010) indicates that maternal stress during pregnancy does affect the function of the fetal HPA axis, but the consequences vary with respect to the fetus's genetics. Specifically, researchers found that distinct genetic strains of mice were differentially affected by maternal prenatal stress (Weinstock, 2008). The specific genes that contribute to this effect have not been investigated in animals or humans, but evidence from human studies that have investigated the effects of *post*natal stress on mood- and stress-related disorders identifies a number of HPA-axis-related genes that may play a moderating role. One such gene is the corticotrophin receptor 1 (*CRHR1*) gene, which codes for the corticotrophin-releasing hormone receptor and functions as a key regulator of the HPA axis (Feurer et al., 2017). Candidate gene studies have shown that variation in the *CRHR1* genotype is associated with cortisol reactivity to laboratory stress tasks in both adults and children (Mahon, Zandi, Potash, Nestadt, & Wand, 2013; Sheikh, Kryski, Smith, Hayden, & Singh, 2013). Polymorphisms in the *CRHR1* gene have also been shown to interact with child abuse (Bradley et al., 2008; Heim & Binder, 2012; Polanczyk et al., 2009) and with physical neglect (Grabe et al., 2010) to predict adult depressive symptoms. Other candidate gene studies have suggested that three single nucleotide polymorphisms (SNPs) in *CRHR1* (rs7209436, rs110402, and rs242924) form a protective TAT haplotype, such that individuals who experience child maltreatment are less likely to develop adult depression if they possess the protective haplotype (Heim et al., 2009; Tyrka et al., 2009). Single SNPs within the TAT haplotype have been shown to independently moderate the relationship between child abuse and adult depression as well (Heim et al., 2009).

Another gene that plays a primary role in HPA-axis activity is the glucocorticoid receptor-regulating co-chaperone *FK506* binding protein 5 (*FKBP5*) gene, which serves a regulatory role in the glucocorticoid, oxytocinergic, serotonergic, and dopaminergic systems (Bet et al., 2009; Conway, Hammen, Brennan, Lind, & Najman, 2010; Luijk et al., 2010; Roy, Gorodetsky, Yuan, Goldman, & Enoch, 2010; Thompson, Parker, Hallmayer, Waugh, & Gotlib, 2010; Zimmerman et al., 2011). Polymorphisms of *FKBP5* have been associated with increased cortisol reactivity in laboratory stress tasks (Ising et al., 2008, Luikjk et al., 2010; Zannas & Binder, 2014), and variation in the *FKBP5* genotype has been shown to moderate the effects of negative life events on adult depression (Appel et al., 2011; Comasco et al., 2015; Lahti et al., 2016; Zimmerman et al., 2011). Multiple candidate gene studies have found that a specific SNP within *FKBP5*, rs9296158, interacts with child abuse to predict adult posttraumatic stress disorder symptoms (Binder et al., 2008). This SNP has also been shown to moderate the effects of adverse life events on adult depression (Zimmerman et al., 2011) such that individuals with two minor alleles (AA) exhibit higher rates of depression after adverse events than those with heterozygous (AG) or homozygous major allele (GG) individuals.

Finally, the nuclear receptor subfamily 3 group C memory 1 (*NR3C1*) gene has been implicated in life stress and depression. A glucocorticoid receptor, *NR3C1* plays a vital role in stress regulation by modulating gene transcription that is related to the HPA axis (DeRijk, Schaaf, & de Kloet, 2002). Genetic variation in *NR3C1* has been shown to predict baseline salivary cortisol levels (Palma-Gudiel, Córdova-Palomera, Leza, & Fañanás, 2015), and disruption in this gene can cause glucocorticoid resistance, a disorder that leads to increased plasma concentration and high urinary free cortisol (Gene, 2018). The SNP, rs6198, has specifically been tied to this disease (Kumsta et al., 2008), and allelic variation at this locus has been shown to decrease glucocorticoid receptor sensitivity (van Rossum et al., 2004). Candidate gene studies demonstrate that this SNP is also associated with MDD and depressive symptoms within bipolar disorder (Szczepankiewicz, Leszczyńska-Rodziewicz, Pawlak, & Rajewska, 2011) such that individuals with at least one copy of the minor allele (CC or CT) are at higher risk than individuals with two copies of the major allele (TT) are. Epigenetic studies suggest that *NR3C1* is implicated in the intergenerational transmission of depression as well. Oberlander et al. (2008) examined differential methylation at a prime cytosine-guanine dinucleotide (CpG) region of the *NR3C1* gene and determined that infants who were exposed to maternal prenatal depression in the third trimester exhibited increased methylation of *NR3C1* compared with infants of nondepressed mothers. This increased methylation was, in turn, associated with increased salivary cortisol reactivity in the infants.

Multilocus Genetic Profile Scores

Recent research has shown that the additive effects of multiple genes within a biological pathway contribute significantly more to an interaction than any single gene does (e.g., Nikolova, Ferrell, Manuck, & Hariri, 2011; Vrshek-Schallhorn et al., 2015). As such, researchers have begun to use a new measure of

polygenic risk, known as a multilocus genetic profile score (MGPS), to examine the interaction of genetics and environmental stress (G × E). Unlike a polygenic risk score (PGR), which employs an exploratory approach to identifying risk genes, MGPSs approach polygenic risk in a biologically informed manner such that a score reflects the unweighted summed effect of previously identified risk SNPs (Nikolova, Ferrell, Manuck, & Hariri, 2011). The score can then be used to examine the additive influence of those polymorphisms on outcomes of interest. For example, a recent study used an HPA-axis MGPS that consisted of polymorphisms in *FKBP5*, *NR3C2*, and the *CRHR1* TAT haplotype to identify a moderating effect of HPA-axis genes on the association between interpersonal stress and depressive symptoms in early childhood (Feurer et al., 2017). Others used an MGPS that consisted of stress-response-related genes to determine whether that score moderated the effects of life stress on amygdala volume and function (di Iorio et al., 2017; Pagliaccio et al., 2015), which in turn has been associated with MDD in adulthood (Beesdo et al., 2009; Hastings et al., 2004).

Several studies have found that the cumulative effect of allelic variation within an MGPS exhibits greater predictive power than any single SNP within the score does. One study examined five polymorphisms in dopaminergic genes and found that while none of the individual SNPs predicted reward-related brain activity (which is often disrupted in the context of depression), the MGPS did (Nikolova, Ferrell, Manuck, & Hariri, 2011). Another investigated the interaction of a serotonergic MGPS with interpersonal stress to predict depressive symptoms and found similar results—the MGPS exhibited greater predictive utility than did any single SNP considered alone (Vrshek-Schallhorn et al., 2015). These results again highlight the potential advantage of applying a polygenic approach to the study of G × E interactions.

Differential Susceptibility versus Diathesis-Stress

Researchers have acknowledged the joint and interactive role of genetics and stress exposures for decades. Until recently, the primary theory driving this literature had been the *diathesis–stress model*, which views genetic predisposition as a risk factor that can compound the risk that is associated with environmental stress. A variety of studies have supported this model, with evidence indicating that those at high genetic "risk" demonstrate poorer outcomes in the presence of stress than those at low genetic risk do (Heim & Nemeroff, 1999; Monroe & Simmons, 1991). However, more recent studies have begun to suggest that the previous conceptualization of genetic "risk" may actually reflect genetic "susceptibility" such that those with certain genetic profiles are more susceptible to negative influences (e.g., environmental stress) but are also more susceptible to positive influences, such as clinical interventions (e.g., Bakermans-Kranenburg & van IJzendoorn, 2015). In other words, those who are at high genetic risk are more susceptible to environmental influences broadly, which can serve to be detrimental or beneficial. This theory, referred to as the *differential susceptibility model* (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011), has demonstrated greater empirical support than its predecessor has, based on a meta-analysis (see Leighton, Botto, Silva, Jiménez, & Luyten, 2017), and it has been supported by numerous studies of maternal prenatal stress (for a review, see Abbott, Gumusoglu, Bittle, Beversdorf, & Stevens, 2018). The present study seeks to further inform these theories by examining the relationship between genetics and depressive outcomes at both high and low levels of prenatal stress exposure.

The Present Study

Despite the evidence that (a) prenatal stress can influence the HPA axis, (b) alterations in the HPA axis have been closely tied to stress reactivity and depression, and (c) genes that are related to the HPA axis have been shown to moderate environmental risk for these outcomes, few studies have examined how HPA-axis genes may interact with fetal programming to predict stress reactivity and depressive outcomes in offspring. Moreover, no studies to our knowledge have examined these associations in adult offspring. The present study seeks to fill these gaps by using offspring genetic data on three loci of interest: *CRHR1* (rs242924), *FKBP5* (rs9296158), and *NR3C1* (rs6198). We hypothesized that an offspring's genetic risk—as defined by an HPA-axis MGPS—would moderate the effect of maternal prenatal perceived stress on early adult outcomes. Specifically, increases in HPA-axis MGPS would be associated with stronger associations between maternal prenatal perceived stress and offspring stress reactivity as well as between maternal prenatal perceived stress and offspring depression. Further, given the theory that HPA-axis programming is specific to the prenatal period, we hypothesized that these effects would be present for prenatal stress but not for stress later in development.

Method

Participants

The participants consisted of women and their young adult offspring, drawn from a sample of 815 mother–child dyads that were enrolled in the Mater-University of Queensland Study of Pregnancy (MUSP; Keeping et al., 1989). The original MUSP cohort included over 7,000 women and offspring who were studied longitudinally to investigate the effects of pregnancy conditions on children's physical, cognitive, and psychological development. The subsample of 815 dyads was enriched for mothers with depressive symptomatology, based on self-reported depressive symptoms on the Delusions-Symptoms-State Inventory (Bedford & Foulds, 1978). Full details of the subsample selection can be found in Hammen and Brennan (2001). Of the 815 mother–child dyads that were recruited for the study, 705 were followed longitudinally until their offspring were age 20. Between age 22 and 25, these 705 offspring were recontacted and asked to participate in DNA sample collection. A total of 512 individuals consented, and 416 of them were genotyped for the three loci of interest. From the original subsample of 815, there were no differences between those who did and did not participate in the genotyping, with the exception that the genotyped participants were more likely to be female. In the present study, the genotyped offspring and their mothers were included if data were available on either offspring stress reactivity or offspring depression at age 20. These inclusion criteria resulted in a sample of 399 offspring (156 males, 243 females) with stress reactivity data, 383 offspring (149 males, 234 females) with depressive symptom data, and 416 offspring (165 males, 251 females) with dichotomous depressive disorder data. In order to maximize the use of the available data, missing data were multiply imputed by using the multivariate imputation by chained equations (MICE) package in R (Buuren & Groothuis-Oudshoorn, 2010).

Measures

Maternal Perceived Stress

Previous studies of fetal programming have varied in the use of objective (e.g., King, Dancause, Turcotte-Tremblay, Veru, & Laplante, 2012) versus subjective (e.g., Leung et al., 2010) measures of maternal stress. Although offspring outcomes have been associated with both objective stress exposure and subjective stress response, it is of note that results vary between these two factors and they should not be conflated (Harkness and Monroe, 2016). In the present study, we specifically focused on the role of subjective (i.e., perceived) maternal stress on the development of an offspring's HPA axis by using the Reeder Stress Inventory (RSI; Reeder, Schrama, & Dirken, 1973). The RSI is a four-item measure of self-perceived daily strain that probes individuals' physiological and psychological reactions to personal situations such as daily hassles, major events, and coping resources. During pregnancy and at offspring-age 5 years, the mothers indicated the extent to which four statements applied to them on a 4-point Likert-type scale: 1 = "*In general, I am usually tense or nervous*"; 2 = "*There is a great amount of nervous strain connected with my daily activities*"; 3 = "*At the end of the day I am completely exhausted mentally and physically*"; and 4 = "*My daily activities are extremely trying and stressful.*" The measure demonstrated high internal consistency, with a Cronbach alpha of 0.804 for the pregnancy measure and 0.836 for the 5-year measure. The RSI also showed adequate construct validity, given its correlation with maternal self-report measures of depressive ($r = .502$) and anxiety symptoms ($r = .542$) in pregnancy, in line with previous studies (e.g., Hewitt, Flett, & Mosher, 1992; Schechter et al., 2017).

Offspring Stress Reactivity

Stress reactivity was established in 20-year-old offspring by calculating appraisal bias scores from the University of California, Los Angeles Life Stress Interview (LSI; Hammen and Brennan, 2001). The participants were asked to rate the stress severity of each stressful event that they reported on a 5-point scale. *Appraisal bias scores* were calculated by regressing mean subjective severity rating scores on mean objective severity rating scores (i.e., those that were determined by a trained team of raters who were blind to the participants' subjective responses). These scores have been established as a reliable measure of stress reactivity in numerous studies that have used the LSI (e.g., Cole, Martin, Peake, Seroczynski, & Hoffman 1998; Conway et al., 2012; De Los Reyes & Prinstein, 2004; Krackow & Rudolph, 2008), and they have been shown to predict levels of depression and anxiety in response to stressor occurrence (Espejo, Hammen, & Brennan, 2012).

Offspring Depression

Offspring depression at age 20 was measured by using the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995) and the Beck Depression Inventory-II (BDI; Beck, Steer, & Brown, 1997). A dichotomous diagnosis of depression was established by using the SCID, which was administered by trained Master's-level clinical research staff at the age-20 visit. A depressive disorder was coded as being present if the offspring met the criteria for depression and/or dysthymia. In addition, the BDI was used to measure continuous symptom data (rather than a dichotomous diagnosis of depression), thus providing greater statistical power for detecting interaction effects. The BDI is widely used to measure depressive symptoms in both clinical and community samples. In the present study, the BDI demonstrated high internal consistency with a Cronbach alpha of 0.92.

Maternal Lifetime Depressive Disorder

A dichotomous diagnosis of lifetime maternal depression/dysthymia was established by using the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon & Williams, 1995). The interview was administered by trained Master's-level clinical research staff at the age-20 visit. A depressive disorder was coded as present if mothers reached criteria for depression and/or dysthymia at any point during her life. Given that the sample was enriched for mothers with depressive symptoms early in the offspring's life, maternal depressive disorder at offspring-age 20 was included as a covariate when examining offspring depressive symptoms and stress reactivity at age 20.

Genotyping

Between ages 22 and 25 (with a mean of 23.32 years), the participants were mailed blood collection kits and had blood samples drawn at local health facilities. The samples were delivered to the Genetic Epidemiological Laboratory of the Queensland Institute of Medical Research, and aliquots were later shipped to the Social Genomics Core of the USC/UCLA Biodemography Center. Genotyping of the three polymorphisms was conducted by using a commercial TaqMan Genotyping Assay (Applied Biosystems, Foster City, CA), performed on an iCycler real-time polymerase chain reaction instrument (BioRad, Hercules, CA). Test-retest reliability analyses based on duplicated samples yielded a total genotyping error rate of < 1%. There were no differences between participants whose samples were successfully genotyped versus those who were not genotyped. Preliminary analyses of the three loci of interest and offspring ethnicity revealed statistically significant differences in the distribution of one of the three alleles in White versus other ethnic groups (*CRHR1*, $\chi^2 = 24.2$, $p < .001$). Further, bivariate correlations indicated that the HPA-axis MGPS was significantly associated with offspring ethnicity ($r = -.148$, $p = .002$). Therefore, all of the reported analyses were restricted to the White offspring in the sample ($N = 381$). Within this White-only sample, all of the SNPs remained consistent with Hardy–Weinberg equilibrium (*p*s > .05; *CRHR1*: $\chi^2 = 1.42$; *FKBP5*: $\chi^2 = 1.42$; *NR3C1*: $\chi^2 = 0.37$).

Multilocus Genetic Profile Score

Each polymorphism was coded such that increasing values corresponded to increasing risk according to the literature. To model an unweighted additive effect, the polymorphisms were coded as 0, 1, or 2 such that individuals that were homozygous for a protective allele received a 0 and individuals that were homozygous for a risk allele received a 2 (see Table 1). We then summed all three polymorphism scores to calculate each participant's total risk score, the HPA-axis MGPS.

Results

Descriptive Statistics and Main Effects

Table 2 displays the descriptive statistics for the study variables for the present sample. Table 3 lists the bivariate correlations for the study variables. The bivariate correlations indicated that both maternal prenatal perceived stress and maternal perceived stress

Table 1. Allele classifications for offspring's HPA-axis multilocus genetic profile score (MGPS)

Locus of Interest		Polymorphism Score		
Gene	Polymorphism	0	1	2
CRHR1	rs242924	TT	GT	GG
		(*n* = 129)	(*n* = 176)	(*n* = 76)
FKBP5	rs9296158	GG	AG	AA
		(*n* = 188)	(*n* = 157)	(*n* = 36)
NR3C1	rs6198	TT	CT	CC
		(*n* = 276)	(*n* = 94)	(*n* = 11)

Table 2. Descriptive statistics

Predictors	M (*SD*)
Offspring HPA-Axis MGPS	2.12 (1.2)
Maternal Prenatal Stress	9.45 (3.6)
Maternal Postnatal Stress at age 5	12.38 (4.2)
Outcomes	
Offspring Stress Reactivity at age 20[a]	−0.03 (0.93)
Offspring Depressive Symptoms at age 20	7.61 (8.6)
Offspring Depressive Disorder at age 20	11.80%
Demographic Characteristics	
Sex	
Male	38.90%
Female	61.10%
Maternal Lifetime Depressive Disorder at age 20	54.10%
Ethnicity[b]	
White	91.40%
Asian	5.00%
Maori/Islander	1.80%
Australian Aborigine	1.80%

Note: [a]Stress reactivity scores were the residuals of objective team stress regressed on subjective participant stress. The residuals ranged from 2.28 (positive appraisals, or low stress reactivity) to -2.46 (negative appraisals, or high stress reactivity).
[b]Only White individuals were included in the primary analyses. Other than Ethnicity, the descriptive statistics provided above refer to the White-only sample.

at offspring-age 5 were significantly associated with age-20 depressive symptoms, but they were not associated with age-20 depressive disorder or age-20 stress reactivity. HPA-axis MGPS was not significantly associated with any of the age-20 outcomes.

Regarding covariates, age-20 depressive symptoms and age-20 stress reactivity both showed a significant bivariate correlation with offspring sex, while age-20 depressive disorder did not. Maternal depressive disorder at offspring-age 20 was significantly associated with age-20 depressive symptoms and age-20 depressive disorder, but it was not correlated with age-20 stress reactivity. Therefore, all of the subsequent analyses included the relevant covariates to each outcome of interest. Regression analyses were conducted by using the 'robust' Package in R (Wang et al., 2017).

After entering the covariates in the first step (i.e., sex and maternal depressive disorder), maternal prenatal perceived stress and HPA-axis MGPS were entered simultaneously into a robust regression to predict age-20 stress reactivity. Both predictors' association with age-20 stress reactivity remained nonsignificant (see Table 4).

Next, after entering the covariates in the first step (sex and maternal depressive disorder), maternal prenatal perceived stress and HPA-axis MGPS were entered simultaneously into a regression to predict age-20 depressive symptoms. The results indicated that maternal prenatal perceived stress was no longer significantly associated with depressive symptoms at age 20, $\Delta R^2 = .007$, $t = 1.54$, $p = .13$, and HPA-axis MGPS remained nonsignificant, $\Delta R^2 = .007$, $t = -0.21$, $p = .83$).

Finally, after entering the covariate in the first step, (i.e., maternal depressive disorder), maternal prenatal perceived stress and HPA-axis MGPS were entered simultaneously into a logistic regression to predict age-20 depressive disorder. Both predictors' association with age-20 depressive disorder remained nonsignificant, $t = 0.95$, $p = .34$; $t = -0.41$, $p = .68$, respectively.

Although the main effects for maternal prenatal perceived stress and MGPS were found to be nonsignificant for all of the depressive outcomes, interactions between the two predictors were investigated to test a model of differential susceptibility. Given that crossover interactions, consistent with this model, may conceal or (in effect) "cancel out" a main effect, it was relevant to investigate G × E interactions for each outcome of interest.

Interaction of Maternal Prenatal Perceived Stress and MGPS in Predicting Age-20 Stress Reactivity

Given the potential effects of G × E interactions, we examined whether genetic susceptibility (HPA-axis MGPS) was associated with susceptibility to maternal prenatal perceived stress, using age-20 stress reactivity as the outcome. Both predictor variables were mean-centered. We entered covariates in the first step (i.e., sex), the main effects for maternal prenatal perceived stress and MGPS in the second step, and their interaction in the third step. The interaction term was nonsignificant (see Table 4).

Interaction of Maternal Prenatal Perceived Stress and MGPS in Predicting Age-20 Depressive Symptoms

We next examined whether genetic susceptibility (i.e., HPA-axis MGPS) was associated with susceptibility to maternal prenatal perceived stress, using age-20 depressive symptoms as the outcome. We entered the covariates in the first step, the (i.e., sex, maternal depressive disorder), main effects for maternal prenatal perceived stress and MGPS in the second step, and their interaction in the third step. The interaction term was significant (see Table 4). To corroborate these results without an available replication sample, we conducted the same analyses in random split halves of the existing sample. The effect sizes remained comparable, although statistical significance was no longer met in one of the halves, likely due to reduced statistical power (see Table 4).

To probe the interaction further, we estimated the *regions of significance* (Roisman et al., 2012) for the crossover interaction by using the PROCESS macro for SPSS (Version 3.3; Hayes, 2017). The results indicated that individuals with greater genetic susceptibility reported significantly higher depressive symptoms in the context of greater maternal prenatal perceived stress (at scores > 13.96, *p*s < .05) and significantly fewer depressive symptoms in the context of lower maternal prenatal perceived stress (at

Table 3. Bivariate correlations between the major study variables

	Offspring HPA-Axis MGPS	Maternal Prenatal Perceived Stress	Maternal Perceived Stress at age 5	Offspring Stress Reactivity at age 20	Offspring Depressive Symptoms at age 20	Offspring Depressive Disorder at age 20
Maternal Prenatal Perceived Stress	0.026					
Maternal Perceived Stress at age 5	−0.005	***0.406***				
Offspring Stress Reactivity at age 20	0.052	0.039	0.030			
Offspring Depressive Symptoms at age 20	0.025	***0.114***	***0.183***	***0.204***		
Offspring Depressive Disorder at age 20	−0.004	0.075	0.068	***0.131***	***0.499***	
Offspring Sex[a]	−0.025	−0.003	−0.045	***0.144***	***0.119***	0.079
Maternal Lifetime Depressive Disorder at Offspring age 20	***0.134***	***0.213***	***0.284***	0.056	***0.150***	***0.125***

Note: [a]Sex was coded as 1 (male) or 2 (female); Bold/italics indicate significance at the .05 level.

scores < 5.35, *p*s < .05). Figure 1a illustrates this interaction. Given that BDI scores are typically categorized as 0–9 for minimal depression, 10–18 for mild/moderate depression, 19–29 for moderate/severe depression, and 30–63 for severe depression (Beck, Steer, & Garbin, 1988), these results suggest that the interaction of maternal prenatal perceived stress and genetic susceptibility is associated with clinically significant differences between offspring with minimal versus mild/moderate levels of depression.

Interaction of Maternal Prenatal Perceived Stress and MGPS in Predicting Age-20 Depressive Disorder

We then examined whether genetic susceptibility (i.e., HPA-axis MGPS) was associated with susceptibility to maternal prenatal perceived stress, using age-20 depressive disorder as the outcome. Both predictor variables were mean-centered. Using logistic regression, we entered covariates in the first step (i.e., maternal depressive disorder), main effects for maternal prenatal perceived stress and MGPS in the second step, and their interaction in the third step. The interaction term was significant (see Table 4). In probing the interaction further, the results indicated that individuals with greater genetic susceptibility were more likely to meet the criteria for a depressive disorder in the context of greater maternal prenatal perceived stress (at scores > 14.76, *p*s < .05) and were less likely to meet the criteria in the context of lower maternal prenatal perceived stress (at scores < 7.70, *p*s < .05) compared with individuals with lower genetic susceptibility. Figure 1b illustrates this interaction.

Sensitivity Analyses

In order to differentiate genetic susceptibility to prenatal stress (i.e., fetal programming) from susceptibility to postnatal life stress, we next examined whether higher HPA-axis MGPS increased susceptibility to maternal perceived stress at age 5, first using age-20 depressive symptoms as the outcome. Both predictor variables were mean-centered. We entered the covariates in the first step, main effects for age-5 maternal perceived stress and MGPS in the second step, and their interaction in the third step. The interaction term was not significant (see Table 5), indicating that MGPS does not moderate the influence of maternal perceived stress during childhood on early adult depressive symptoms. In other words, the moderating effect of MGPS may be specific to prenatal stress. In repeating these analyses using age-20 depressive disorder as the outcome, the results were similar (see Table 5).

To assess the contribution of each SNP to the interaction between MGPS and maternal prenatal perceived stress, we first conducted nine G × E tests by using the individual SNPs from the MGPS (three tests for age-20 stress reactivity, three tests for age-20 depressive symptoms, and three tests for age-20 depressive disorder). The results indicated that no single SNP significantly interacted with maternal prenatal perceived stress to predict age-20 stress reactivity, depressive symptoms, or depressive disorder (see Table 5). Next, nine additional G × E tests were conducted with 2-SNP MGPS variables that were created by removing each SNP, one at a time, from the original 3-SNP MGPS. The G × E interactions remained nonsignificant for all three tests for predicting age-20 stress reactivity, and the G × E interactions remained significant for all three tests for predicting age-20 depressive symptoms. The G × E interactions remained significant for one of the three tests for predicting age-20 depressive disorder, with scores that were missing *CRHR1* or *FKBP5* becoming nonsignificant (see Table 5).

Discussion

The present study demonstrated that an HPA-axis multilocus genetic profile score (MGPS) significantly interacts with maternal prenatal perceived stress to predict offspring depression in early adulthood. We showed that the accumulation of genetic risk, quantified through the MGPS, interacted with maternal prenatal perceived stress more robustly than did any single polymorphism that was included in the profile score. These findings provide preliminary evidence that suggests that particular genetic variants that are associated with the HPA axis may act in a polygenic,

Table 4. Multiple regression results for Maternal Prenatal Perceived Stress × HPA-axis MGPS analyses

Model	Variable	ΔR^2	*t*	*p* value
1. Stress Reactivity	Block 1 (Covariates)			
	Offspring Sex	***.028***	***3.33***	***.002***
	Maternal Depressive Disorder	.028	1.13	.26
	Block 2 (Main Effects)			
	Maternal Prenatal Stress	.002	.209	.83
	Offspring HPA-Axis MGPS	.005	1.08	.28
	Block 3			
	Prenatal Stress × MGPS	<.001	.106	.91
2. Depressive Symptoms	Block 1 (Covariates)			
	Offspring Sex	***.016***	***2.20***	***.03***
	Maternal Depressive Disorder	***.016***	***2.19***	***.03***
	Block 2 (Main Effects)			
	Maternal Prenatal Stress	.011	1.95	.052
	Offspring HPA-Axis MGPS	.011	.603	.55
	Block 3			
	Prenatal Stress × MGPS	***.02***[a]	***2.99***	***.003***
Model	Variable		*B*	*p* value
3. Depressive Disorder[b]	Block 1 (Covariates)			
	Maternal Depressive Disorder		***−.83***	***.02***
	Block 2 (Main Effects)			
	Maternal Prenatal Stress		.042	.34
	Offspring HPA-Axis MGPS		−.06	.68
	Block 3			
	Prenatal Stress × MGPS		***.085***	***.023***

Note: Bold/italics indicate significance at the .05 level. [a]Similar effect sizes were demonstrated in the random split-halves analysis of these variables (ΔR^2 = .015, p = .077; ΔR^2 = .040, p = .011); [b]Logistic regression was used for the dichotomous Depressive Disorder variable, rather than multiple regression.

additive fashion to interact with maternal prenatal perceived stress to predict depression. Further, we demonstrated that this interaction may be specific to maternal stress that occurs during pregnancy, as maternal perceived stress during early childhood does not exhibit the same interactive effects. These findings are consistent with the fetal programming hypothesis, which purports that stress exposure during pregnancy can reprogram the HPA axis and have long-term effects on offspring outcomes. To our knowledge, this is the first study demonstrating that the duration of programming effects on offspring depression extends into early adulthood while also corroborating findings from animal studies that have identified a moderating role of genetic risk on these programming effects (Weinstock, 2008).

Before providing an interpretation of our results, it is important to first address the size of the effects that were identified in the present study. Post hoc power analyses indicated that we were well powered to detect small effects ($1 - \beta = 0.75$), which are typical and expected in studies of G × E interactions. Indeed, the effects that we identified were small in magnitude, despite their statistical significance. This can be partially explained by the wide variety of factors that contribute to depressive symptomatology, as will be outlined below. However, there are also genetic factors that may explain these small effects. Although the size of our MGPS was consistent with that of other MGPSs (e.g., Nikolova, Ferrell, Manuck, & Hariri, 2011; Vrshek-Schallhorn et al., 2015), the number of SNPs that contribute to depression undoubtedly exceeds the three SNPs we included. Findings from genome-wide association studies (GWAS) of depression (e.g., Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium) suggest that the confluence of hundreds, or even thousands, of common genetic variants likely confers risk for depression. As such, risk SNPs that are isolated by candidate gene studies—including those involved in this study—have not been identified with large-scale GWAS approaches due to the marginal effects of individual SNPs (Ripke et al., 2013). Our findings align with the results of these GWAS studies as well as with the candidate-gene studies that have failed to identify significant main effects for the individual SNPs (i.e., *CRHR1*, rs242924; *FKBP5*, rs9296158; and *NR3C1*, rs6198) on depression (Heim & Binder, 2012). However, multilocus genetic profile scores provide a unique opportunity to examine polygenic risk in a biologically informed manner (i.e., with a focus on a specific physiological system that underlies depression, the HPA axis), which is not possible by using a GWAS approach. Previous G × E studies have used polygenic risk scores (which use GWAS data but are not biologically informed), and they

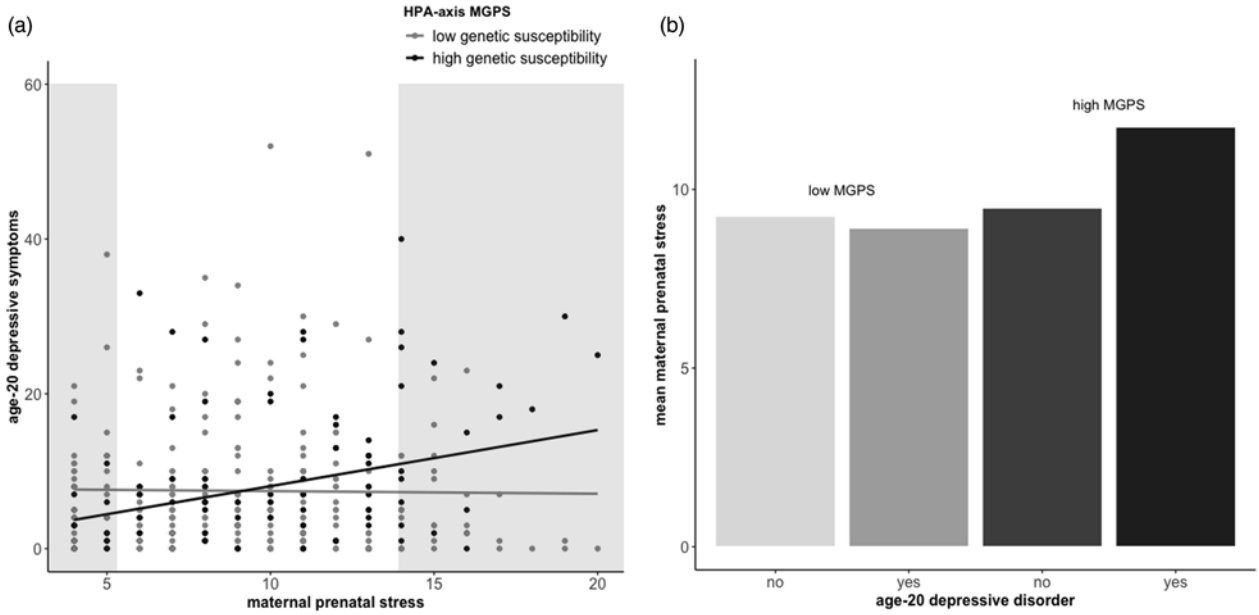

Figure 1. Crossover interaction of HPA axis MGPS and maternal prenatal perceived stress to predict offspring (a) depressive symptoms and (b) depressive disorder at age 20. Gray regions in (a) indicate the regions of significance (i.e., levels of maternal prenatal perceived stress at which offspring at high genetic susceptibility significantly differ in severity of depression from offspring at low genetic susceptibility). MGPS was dichotomized (i.e., median-split) for the purposes of visualization only; regions of significance were identified using the continuous MGPS variable.

repeatedly find that polygenic risk scores explain no more than 1% to 2% of the variance in depressive outcomes (Demirkan et al., 2011; Ripke et al., 2013), and a recent meta-analysis indicated that the G × E effects are similarly marginal (Peyrot et al., 2018). In the present study, we targeted a specific mechanism of interest and were able explain a similar proportion of the variance by using only three SNPs. Although each SNP has a marginal effect on depressive outcomes and even the additive burden of these SNPs remains marginal in isolation, the collective influence of these three HPA-axis-related SNPs emerges in the presence of environmental risk (i.e., maternal prenatal stress) that is known to act on the HPA axis. The findings from the present study illustrate the importance of using a biologically informed multilocus approach to studying physiological systems that are affected by environmental factors. While acknowledging the small effect of this genetic burden, our findings have a number of important implications for research in depression.

Depressive disorders have been associated with a variety of factors including genetic predisposition (Silberg, Maes, & Eaves, 2010), prenatal exposures (Graignic-Philippe, Dayan, Chokron, Jacquet, & Tordjman, 2014), and postnatal environment (e.g., parenting, stressors; Hammen, Brennan, & Le Brocque, 2011). Although these factors have been individually studied for decades and the interaction of genetic risk and *post*natal environment has been widely researched (Nugent, Tyrka, Carpenter, & Price, 2011), there is a dearth of studies that explore the interaction of genetic risk with *pre*natal exposures in humans. In this study, we examined this interaction in order to interrogate a potential mechanism by which maternal prenatal perceived stress might confer risk for offspring stress reactivity and depression (both as a dichotomous diagnosis and a continuum of symptoms). Given the role of each considered gene (i.e., *CRHR1*, *NR3C1*, and *FKBP5*) in the development and functioning of the HPA axis, the body's primary stress response system (Glover, O'Connor, & O'Donnell, 2010), it was hypothesized that variants within these genes would have a particularly strong influence on offspring outcomes when compounded with prenatal stress.

Our results indicated that this was true for offspring depression but not for stress reactivity. Given that previous studies that have identified an association between maternal prenatal stress and offspring stress reactivity (Davis, Glynn, Waffarn, & Sandman, 2011; Gutteling, deWeerth, & Buitelaar, 2005; O'Connor, Bergman, Sarkar, & Glover, 2013) have not followed offspring past childhood, it is possible that the effects of fetal stress exposure on stress reactivity do not persist over the long term. However, it is also of note that our measure of stress reactivity differed from many of those that are reported in the literature, as we did not have a measure of cortisol reactivity in the present sample. Considering that previous studies have identified discrepancies between cognitive appraisals of stress and physiological measures of stress reactivity (Voegtline et al., 2013), future studies may choose to use cortisol reactivity or another physiological measure of stress reactivity to further investigate these prenatal programming G × E effects in young adulthood. Similarly, our focus on maternal *perceived* stress, as opposed to an objective measure of stress exposure, may explain our findings that maternal prenatal perceived stress predicted offspring depression but not offspring stress reactivity. Previous studies have suggested that self-reports of stress may be influenced by personality (e.g., neuroticism) and/or psychopathology (e.g., anxiety or depression), which themselves confer risk for offspring depression (Halligan et al., 2007). Although we accounted for the influence of maternal psychopathology by including maternal lifetime depressive disorder at age-20 as a covariate, it may be useful for future studies to parse maternal neuroticism and other related traits from reports of perceived stress.

With regard to offspring depressive outcomes, our analyses not only supported the hypothesis that genetic risk would confer greater risk for depression when compounded with stress but also indicated that a high HPA-axis MGPS was *beneficial* in the

Table 5. Multiple regression interaction (Block 3) results for the sensitivity analyses

Model	ΔR^2	*t*	*p* value
1. Stress Reactivity			
Maternal Stress at age 5 × MGPS	.005	−1.47	.14
Maternal Prenatal Stress × *CRHR1* [rs242924]	6.50E-05	−0.22	.83
Maternal Prenatal Stress × *NR3C1* [rs6198]	4.50E-05	0.09	.93
Maternal Prenatal Stress × *FKBP5* [rs9296158]	.002	0.86	.39
Maternal Prenatal Stress × MGPS [w/o *CRHR1*]	.002	0.78	.44
Maternal Prenatal Stress × MGPS [w/o *NR3C1*]	.002	0.68	.5
Maternal Prenatal Stress × MGPS [w/o *FKBP5*]	−5.30E-05	−0.16	.87
2. Depressive Symptoms			
Maternal Stress at age 5 × MGPS	.006	1.44	.15
Maternal Prenatal Stress × *CRHR1* [rs242924]	.005	1.38	.17
Maternal Prenatal Stress × *NR3C1* [rs6198]	.006	1.48	.14
Maternal Prenatal Stress × *FKBP5* [rs9296158]	.008	1.74	.08
Maternal Prenatal Stress × MGPS [w/o *CRHR1*]	***.012***	***2.19***	***.03***
Maternal Prenatal Stress × MGPS [w/o *NR3C1*]	***.012***	***2.2***	***.03***
Maternal Prenatal Stress × MGPS [w/o *FKBP5*]	***.011***	***2***	***.05***
3. Depressive Disorder[a]			
Maternal Stress at age 5 × MGPS		0.03	.97
Maternal Prenatal Stress × *CRHR1* [rs242924]		1.51	.14
Maternal Prenatal Stress × *NR3C1* [rs6198]		1.18	.24
Maternal Prenatal Stress × *FKBP5* [rs9296158]		1.36	.17
Maternal Prenatal Stress × MGPS [w/o *CRHR1*]		1.7	.09
Maternal Prenatal Stress × MGPS [w/o *NR3C1*]		***1.91***	***.05***
Maternal Prenatal Stress × MGPS [w/o *FKBP5*]		1.82	.07

Note: [a]Logistic regression was used for the dichotomous Depressive Disorder variable, so ΔR^2 was not obtained.

context of low maternal prenatal perceived stress. These findings align with the differential susceptibility model, which contends that individuals differ in their sensitivity to environmental exposures based on their biological predispositions (Ellis et al., 2011). In other words, individuals at high genetic risk are more susceptible to environmental influences, both positive and negative. This model differs from the traditional diathesis-stress model, which views genetic risk as being harmful in the presence of stress exposure but neutral in the absence of stress (Heim & Nemeroff, 1999). A recent meta-analysis (Leighton et al., 2017) comparing these two models indicated greater empirical support for differential susceptibility, and numerous studies of maternal prenatal stress have suggested the same (Abbott et al., 2018). The present study adds to the growing body of literature suggesting that individuals at high genetic risk for depression or other psychopathology may also be the most responsive to positive exposures, while those at low genetic risk show reduced variability in outcomes in the context of positive versus negative influences (see van IJzendoorn and Bakermans-Kranenburg, 2015).

Interestingly, our analyses revealed that the interaction of MGPS and stress exposure may be specific to stress that occurs prenatally, as the HPA-axis MGPS did not interact with maternal perceived stress at offspring-age five. These results align with the fetal programming hypothesis, which posits that programming of the HPA axis is altered in response to stress (i.e., cortisol) exposure during fetal development (Amiel-Tison et al., 2004; Barker, 2007; Gluckman et al., 2009; Gluckman & Hanson, 2005). Evidence indicates that the HPA axis is most vulnerable to environmental influences during pregnancy and the first year postpartum (Gunnar, Brodersen, Krueger, & Rigatuso, 1996; Lewis & Ramsay, 1995), suggesting that stress exposure after infancy would have less influence on long-term HPA-axis functioning. Although post hoc analyses did not identify a statistically significant difference between prenatal and age-5 G × E effects, our findings that maternal perceived stress at age 5 did confer risk for offspring depression at age 20 but did not interact with HPA-axis-related genes supports this theory. Therefore, the mechanism underlying the effects of early life stress on adult depression may differ from that of perinatal stress. Although previous studies have identified a significant influence of early postnatal stress on childhood cortisol reactivity (e.g., Gunnar et al., 2009), it is unclear whether these stressors have a lasting effect on the HPA axis into adulthood. Future research is needed to delineate the biological mechanisms that are affected by stress exposure at different periods of development.

Similarly, it remains unclear how different stress exposures may interact with one another to predict adult psychopathology. Preliminary studies have suggested that the effects of maternal prenatal stress may be moderated by later exposures to environmental stress, as posited by the *three-hit hypothesis*. This model theorizes that offspring risk for depression increases as prenatal stress, postnatal stress, and genetic risk are compounded, as demonstrated by Daskalakis, Bagot, Parker, Vinkers, and de Kloet (2013). Unfortunately, examining a three-way interaction of maternal prenatal stress, offspring postnatal stress, and HPA-axis MGPS was beyond the scope of this study due to the limited sample size. However, future studies with larger samples may use this life-span developmental approach to corroborate these findings and examine the accumulating effects of prenatal and postnatal stress exposure on individuals with a background of genetic risk.

A recent review of animal studies suggests that the effects of prenatal stress may also vary with respect to timing (Glover, O'Connor, & O'Donnell, 2010). Similar effects have been indicated in humans. For example, one study of 247 mother–infant pairs found that the gestational timing of stress exposure affected the outcomes of infant temperament and negative reactivity at 2 months of age such that only third-trimester stress had a significant influence (Davis et al., 2007). Some have proposed that these

timing effects may be due to critical periods of brain development during gestation, as different brain systems develop at different stages (Andersen et al., 2008; Rice & Barone, 2000). In other words, the effect of fetal exposures is contingent on the period of fetal brain development that coincides with the environmental stressor (Barker, 2002; Kajantie, 2006). We were not able to examine these timing effects in the present study, as there was little variability in the timing of the prenatal visit. Further, the majority of the prenatal visits occurred during the first trimester of pregnancy, so the identified relationship between maternal prenatal perceived stress and offspring depression may have shown an even stronger effect had we collected measures of prenatal stress during the second or third trimesters. Similarly, the association between maternal prenatal perceived stress and offspring stress reactivity may be specific to later gestational periods. Future studies may benefit from considering both gestational timing and genetic risk as moderators of the prenatal stress–offspring depression relationship.

Finally, previous studies have also identified potential sex differences in fetal susceptibility to prenatal exposures. A number of studies have determined that higher levels of maternal cortisol or self-reported stress during pregnancy influence cognitive, psychological, and physical development more strongly in male than in female offspring (Ellman et al., 2008; Sandman, Glynn, & Davis, 2013). Other studies have found that maternal prenatal stress is associated with cortisol reactivity in female offspring only (de Bruijn, van Bakel, Wijnen, Pop, & van Baar, 2009). Although the literature is mixed on how male and female offspring may differ in their susceptibility to prenatal exposures, it is apparent that sex may play an important moderating role in their influence on later offspring development. Again, our ability to investigate a three-way interaction of maternal prenatal stress, offspring sex, and HPA-axis MGPS was constrained by the limited sample size. However, future research may consider teasing apart differences in male and female responsivity to fetal exposures in order to further clarify the complex interplay of biological and environmental factors that contribute to developmental psychopathology.

Conclusion

This study expands on prior work that has identified an influence of prenatal stress on child and adolescent outcomes, providing evidence for the persistence of fetal programming effects into early adulthood. The results highlight the importance of reducing maternal stress during pregnancy, and they further suggest that providing clinical interventions during pregnancy may help prevent adult depressive outcomes in genetically high-risk offspring. Overall, this illustrates the utility of using an MGPS approach not only to clarify biological mechanisms of risk but also to identify mothers who may benefit most strongly from intervention practices.

Acknowledgments. The authors thank the MUSP, M900, and M20 Research Teams and the participating families. We also thank the principal investigators of the Mater-University Study of Pregnancy study, the Brisbane, Australia staff coordinators, and the Genetic Epidemiology Unit of the Queensland Institute for Medical Research. Finally, the authors acknowledge Shelby for her endless support throughout the production of this project.

Financial Support. This research was supported by NIMH R01MH052239 and by a seed grant from the UCLA Cousins Center for Psychoneuroimmunology.

References

Abbott, P. W., Gumusoglu, S. B., Bittle, J., Beversdorf, D. Q., & Stevens, H. E. (2018). Prenatal stress and genetic risk: How prenatal stress interacts with genetics to alter risk for psychiatric illness. *Psychoneuroendocrinology*, *90*, 9–21.

Amiel-Tison, C., Cabrol, D., Denver, R., Jarreau, P. H., Papiernik, E., & Piazza, P. V. (2004). Fetal adaptation to stress: Part I: Acceleration of fetal maturation and earlier birth triggered by placental insufficiency in humans. *Early Human Development*, *78*, 15–27.

Andersen, S. L., Tomada, A., Vincow, E. S., Valente, E., Polcari, A., & Teicher, M. H. (2008) Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *20*, 292–301.

Appel, K., Schwahn, C., Mahler, J., Schulz, A., Spitzer, C., Fenske, K., … Grabe, H. J. (2011). Moderation of adult depression by a polymorphism in the *FKBP5* gene and childhood physical abuse in the general population. *Neuropsychopharmacology*, *36*, 1982–1991.

Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2015). The hidden efficacy of interventions: Gene × environment experiments from a differential susceptibility perspective. *Annual Review of Psychology*, *66*, 381–409.

Barker, D. J. (2002). Fetal programming of coronary heart disease. *Trends in Endocrinology & Metabolism*, *13*, 364–368.

Barker, D. J. (2007). The origins of the developmental origins theory. *Journal of Internal Medicine*, *261*, 412–417.

Beck, A. T., Steer, R. A., & Brown, G. K. (1997). *Beck Depression Inventory: Second Edition*. San Antonio: The Psychological Corporation.

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, *8*, 77–100.

Bedford, A., & Foulds, G. *Delusions-Symptoms-States Inventory of Anxiety and Depression*. Windsor, England: NFER.

Beesdo, K., Lau, J. Y., Guyer, A. E., McClure-Tone, E. B., Monk, C. S., Nelson, E. E., … Ernst, M. (2009). Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. *Archives of General Psychiatry*, *66*, 275–285.

Belsky, J., Hsieh, K., & Crnic, K. (1998). Infant positive and negative emotionality: One dimension or two? In M. Hertzig & E. Farber (Eds.), *Annual progress in child psychiatry and child development* (pp. 29-44). Philadelphia, PA: Brunner/Mazel.

Bet, P. M., Penninx, B., Bochdanovits, Z., Uitterlinden, A. G., Beekman, A., van Schoor, N. M., … Hoogendijk, W. (2009). Glucocorticoid receptor gene polymorphisms and childhood adversity are associated with depression: New evidence for a gene–environment interaction. *Neuropsychiatric Genetics*, *150B*, 660–669.

Binder, E. B., Bradley, R. G., Liu, W., Epstein, M., Deveau, T., Mercer, K., … Nemeroff, C. B. (2008). Association of *FKBP5* polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *Journal of the American Medical Association*, *299*, 1291–1305.

Bradley, R. G., Binder, E. B., Epstein, M. P., Tang, Y., Nair, H. P., Liu, W., … Ressler, K. J. (2008). Influence of child abuse on adult depression: Moderation by the corticotropin-releasing hormone receptor gene. *Archives of General Psychiatry*, *65*, 190–200.

Buuren, S. V., & Groothuis-Oudshoorn, K. (2010). MICE: Multivariate imputation by chained equations in R. *Journal of Statistical Software*, *45*, 1–68.

Carson, D. K., & Bittner, M. T. (1994). Temperament and school-aged children's coping abilities and responses to stress. *The Journal of Genetic Psychology*, *155*, 289–302.

Cole, D. A., Martin, J. M., Peake, L. G., Seroczynski, A. D., & Hoffman, K. (1998). Are cognitive errors of underestimation predictive or reflective of depressive symptoms in children: A longitudinal study. *Journal of Abnormal Psychology*, *107*, 481–496.

Comasco, E., Gustafsson, P. A., Sydsjö, G., Agnafors, S., Aho, N., & Svedin, C. G. (2015). Psychiatric symptoms in adolescents: *FKBP5* genotype—early life adversity interaction effects. *European Child & Adolescent Psychiatry*, *24*, 1473–1483.

Conway, C. C., Hammen, C., Brennan, P. A., Lind, P. A., & Najman, J. M. (2010). Interaction of chronic stress with serotonin transporter and

catechol-O-methyltransferase polymorphisms in predicting youth depression. *Depression and Anxiety*, *27*, 737–745.

Conway, C. C., Hammen, C., Espejo, E. P., Wray, N. R., Najman, J. M., & Brennan, P. A. (2012). Appraisals of stressful life events as a genetically-linked mechanism in the stress–depression relationship. *Cognitive Therapy and Research*, *36*, 338–347.

Daskalakis, N. P., Bagot, R. C., Parker, K. J., Vinkers, C. H., & de Kloet, E. R. (2013). The three-hit concept of vulnerability and resilience: Toward understanding adaptation to early-life adversity outcome. *Psychoneuroendocrinology*, *38*, 1858–1873.

Davis, E. P., Glynn, L. M., Schetter, C. D., Hobel, C., Chicz-Demet, A., & Sandman, C. A. (2007). Prenatal exposure to maternal depression and cortisol influences infant temperament. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*, 737–746.

Davis, E. P., Glynn, L. M., Waffarn, F., & Sandman, C. A. (2011). Prenatal maternal stress programs infant stress regulation. *Journal of Child Psychology and Psychiatry*, *52*, 119–129.

de Bruijn, A. T., van Bakel, H. J., Wijnen, H., Pop, V. J., & van Baar, A. L. (2009) Prenatal maternal emotional complaints are associated with cortisol responses in toddler and preschool aged girls. *Developmental Psychobiology*, *51*, 553–563.

De Los Reyes, A., & Prinstein, M. J. (2004). Applying depression distortion hypotheses to the assessment of peer victimization in adolescents. *Journal of Clinical Child and Adolescent Psychology*, *33*, 325–335.

Demirkan, A., Penninx, B. W., Hek, K., Wray, N. R., Amin, N., Aulchenko, Y. S., … Hottenga, J. J. (2011). Genetic risk profiles for depression and anxiety in adult and elderly cohorts. *Molecular Psychiatry*, *16*, 773–783.

DeRijk, R. H., Schaaf, M., & de Kloet, E. R. (2002) Glucocorticoid receptor variants: Clinical implications. *The Journal of Steroid Biochemistry and Molecular Biology*, *81*, 103–122.

de Weerth, C., van Hees, Y., & Buitelaar, J. K. (2003). Prenatal maternal cortisol levels and infant behavior during the first 5 months. *Early Human Development*, *74*, 139–151.

Dickerson, P. A., Lally, B. E., Gunnel, E., Birkle, D. L., & Salm, A. K. (2005). Early emergence of increased fearful behavior in prenatally stressed rats. *Physiology & Behavior*, *86*, 586–593.

di Iorio, C. R., Carey, C. E., Michalski, L. J., Corral-Frias, N. S., Conley, E. D., Hariri, A. R., & Bogdan, R. (2017). Hypothalamic–pituitary–adrenal axis genetic variation and early stress moderates amygdala function. *Psychoneuroendocrinology*, *80*, 170–178.

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary–neurodevelopmental theory. *Development and Psychopathology*, *23*, 7–28.

Ellman, L. M., Schetter, C. D., Hobel, C. J., Chicz-DeMet, A., Glynn, L. M., & Sandman, C. A. (2008). Timing of fetal exposure to stress hormones: Effects on newborn physical and neuromuscular maturation. *Developmental Psychobiology*, *50*, 232–241.

Espejo, E. P., Hammen, C., & Brennan, P. A. (2012). Elevated appraisals of the negative impact of naturally occurring life events: A risk factor for depressive and anxiety disorders. *Journal of Abnormal Child Psychology*, *40*, 303–315.

Feurer, C., McGeary, J. E., Knopik, V. S., Brick, L. A., Palmer, R. H., & Gibb, B. E. (2017). HPA axis multilocus genetic profile score moderates the impact of interpersonal stress on prospective increases in depressive symptoms for offspring of depressed mothers. *Journal of Abnormal Psychology*, *126*, 1017–1028.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1995). *Structured Clinical Interview for DSM-IV Axis I Disorders*. Washington, D.C.: American Psychiatric Press.

Gene [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004–[cited 2018-03-16]. Available from: https://www.ncbi.nlm.nih.gov/gene/

Gitau, R., Cameron, A., Fisk, N., & Glover, V. (1998). Fetal exposure to maternal cortisol. *Developmental Psychobiology*, *50*, 232–251.

Glover, V., O'Connor, T. G., & O'Donnell, K. (2010). Prenatal stress and the programming of the HPA axis. *Neuroscience and Biobehavioral Reviews*, *35*, 17–22.

Gluckman, P., & Hanson, M. (2005). *The fetal matrix: Evolution, development, and disease*. Cambridge, UK: Cambridge University Press.

Gluckman, P. D., Hanson, M. A., Bateson, P., Beedle, A. S., Law, C. M., Bhutta, Z. A., … West-Eberhard, M. J. (2009). Towards a new developmental synthesis: Adaptive developmental plasticity and human disease. *Lancet*, *373*, 1654–1657.

Goodman, S. H., & Gotlib, I. H. (1999). Risk for psychopathology in the children of depressed mothers: A developmental model for understanding mechanisms of transmission. *Psychological Review*, *106*, 458–490.

Grabe, H. J., Schwahn, C., Appel, K., Mahler, J., Schulz, A., Spitzer, C., … John, U. (2010). Childhood maltreatment, the corticotropin-releasing hormone receptor gene and adult depression in the general population. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *153*, 1483–1493.

Graignic-Philippe, R., Dayan, J., Chokron, S., Jacquet, A. Y., & Tordjman, S. (2014). Effects of prenatal stress on fetal and child development: A critical literature review. *Neuroscience & Biobehavioral Reviews*, *43*, 137–162.

Gunnar, M. R., Brodersen, L., Krueger, K., & Rigatuso, J. (1996). Dampening of adrenocortical responses during infancy: Normative changes and individual differences. *Child Development*, *67*, 877–889.

Gunnar, M. R., Frenn, K., Wewerka, S. S., & Van Ryzin, M. J. (2009). Moderate versus severe early life stress: Associations with stress reactivity and regulation in 10–12-year-old children. *Psychoneuroendocrinology*, *34*, 62–75.

Gutteling, B. M., de Weerth, C., & Buitelaar, J. K. (2005). Prenatal stress and children's cortisol reaction to the first day of school. *Psychoneuroendocrinology*, *30*, 541–549.

Halligan, S. L., Murray, L., Martins, C., & Cooper, P. J. (2007). Maternal depression and psychiatric outcomes in adolescent offspring: A 13-year longitudinal study. *Journal of Affective Disorders*, *97*, 145–154.

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, *1*, 293–319.

Hammen, C., & Brennan, P. (2001). Depressed adolescents of depressed and nondepressed mothers: Tests of an interpersonal impairment hypothesis. *Journal of Consulting and Clinical Psychology*, *69*, 284–294.

Hammen, C., Brennan, P. A., & Le Brocque, R. (2011). Youth depression and early childrearing: Stress generation and intergenerational transmission of depression. *Journal of Consulting and Clinical Psychology*, *79*, 353–363.

Harkness, K. L., & Monroe, S. M. (2016). The assessment and measurement of adult life stress: Basic premises, operational principles, and design requirements. *Journal of Abnormal Psychology*, *125*, 727–745.

Hastings, R. S., Parsey, R. V., Oquendo, M. A., Arango, V., & Mann, J. J. (2004). Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology*, *29*, 952–959.

Hayes, A. F. (2017). *Introduction to mediation, moderation, and conditional process analysis second edition: A regression-based approach*. New York: Guilford Press.

Heim, C., & Binder, E. B. (2012). Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. *Experimental Neurology*, *233*, 102–111.

Heim, C., Bradley, B., Mletzko, T., Deveau, T. C., Musselmann, D. L., Nemeroff, C. B., … Binder, E. B. (2009). Effect of childhood trauma on adult depression and neuroendocrine function: Sex-specific moderation by CRH receptor 1 gene. *Frontiers in Behavioral Neuroscience*, *3*, Article 41.

Heim, C., & Nemeroff, C. B. (1999). The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biological Psychiatry*, *46*, 1509–1522.

Hewitt, P. L., Flett, G. L., & Mosher, S. W. (1992). The Perceived Stress Scale: Factor structure and relation to depression symptoms in a psychiatric sample. *Journal of Psychopathology and Behavioral Assessment*, *14*, 247–257.

Igosheva, N., Taylor, P. D., Poston, L., & Glover, V. (2007). Prenatal stress in the rat results in increased blood pressure responsiveness to stress and enhanced arterial reactivity to neuropeptide Y in adulthood. *Journal of Physiology*, *582*, 665–674.

Ising, M., Depping, A. M., Siebertz, A., Lucae, S., Unschuld, P. G., Kloiber, S., … Holsboer, F. (2008). Polymorphisms in the *FKBP*5 gene region modulate recovery from psychosocial stress in healthy controls. *The European Journal of Neuroscience*, *28*, 389–398.

Kajantie, E. (2006). Fetal origins of stress-related adult disease. *Annals of the New York Academy of Sciences*, *1083*, 11Y27.

Keeping, J. D., Najman, J. M., Morrison, J., Western, J. S., Andersen, M. J., & Williams, G. M. (1989). A prospective longitudinal study of social, psychological, and obstetrical factors in pregnancy: Response rates and demographic characteristics of the 8,556 respondents. *British Journal of Obstetrics and Gynecology*, *96*, 289–297.

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology*, *48*, 191–214.

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*, 617–627.

King, S., Dancause, K., Turcotte-Tremblay, A. M., Veru, F., & Laplante, D. P. (2012). Using natural disasters to study the effects of prenatal maternal stress on child health and development. *Birth Defects Research Part C: Embryo Today: Reviews*, *96*, 273–288.

Krackow, E., & Rudolph, K. D. (2008). Life stress and the accuracy of cognitive appraisals in depressed youth. *Journal of Clinical Child & Adolescent Psychology*, *37*, 376–385.

Kumsta, R., Moser, D., Streit, F., Koper, J. W., Meyer, J., & Wüst, S. (2008). Characterization of a glucocorticoid receptor gene (GR, *NR3C1*) promoter polymorphism reveals functionality and extends a haplotype with putative clinical relevance. *American Journal of Medical Genetics*, *150B*, 476–482.

Lahti, J., Ala-Mikkula, H., Kajantie, E., Haljas, K., Eriksson, J. G., & Räikkönen, K. (2016). Associations between self-reported and objectively recorded early life stress, *FKBP5* polymorphisms, and depressive symptoms in midlife. *Biological Psychiatry*, *80*, 869–877.

Leighton, C., Botto, A., Silva, J. R.; Jiménez, J. P., & Luyten, P. (2017). Vulnerability or sensitivity to the environment? Methodological issues trends, and recommendations in gene–environment interactions research in human behavior. *Frontiers in Psychiatry*, *8*, Article 106.

Leung, E., Tasker, S. L., Atkinson, L., Vaillancourt, T., Schulkin, J., & Schmidt, L. A. (2010). Perceived maternal stress during pregnancy and its relation to infant stress reactivity at 2 days and 10 months of postnatal life. *Clinical Pediatrics*, *49*, 158–165.

Lewis, M., & Ramsay, D. S. (1995). Developmental change in infants' responses to stress. *Child Development*, *66*, 657–670.

Luijk, M. P. C. M., Velders, F. P., Tharner, A., van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., Jaddoe, V. W. V., … Tiemeier, H. (2010). *FKBP5* and resistant attachment predict cortisol reactivity in infants: Gene–environment interaction. *Psychoneuroendocrinology*, *35*, 1454–1461.

Lundy, B. L., Jones, N. A., Field, T., Nearing, G., Davalos, M., Pietro, P. A., … Kuhn, C. (1990). Prenatal depression effects on neonates. *Infant Behavior and Development*, *22*, 119–129.

Mahon, P. B., Zandi, P. P., Potash, J. B., Nestadt, G., & Wand, G. S. (2013). Genetic association of *FKBP5* and *CRHR1* with cortisol response to acute psychosocial stress in healthy adults. *Psychpharmacology* (*Berl*), *227*, 231–241.

Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin*, *110*, 406–425.

Nikolova, Y. S., Ferrell, R. E., Manuck, S. B., & Hariri, A. R. (2011). Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. *Neuropsychopharmacology*, *36*, 1940–1947.

Nugent, N. R., Tyrka, A. R., Carpenter, L. L., & Price, L. H. (2011). Gene–environment interactions: Early life stress and risk for depressive and anxiety disorders. *Psychopharmacology*, *214*, 175–196.

Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., & Devlin, A. M. (2008) Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (*NR3C1*) and infant cortisol stress response. *Epigenetics*, *3*, 97–106.

O'Connor, T. G., Bergman, K., Sarkar, P., & Glover, V. (2013). Prenatal cortisol exposure predicts infant cortisol response to acute stress. *Developmental Psychobiology*, *55*, 145–155.

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., … Barch, D. M. (2015). Amygdala functional connectivity, HPA axis genetic variation, and life stress in children and relations to anxiety and emotion regulation. *Journal of Abnormal Psychology*, *124*, 817–833.

Palma-Gudiel, H., Córdova-Palomera, A., Leza, J-C., & Fañanás, L. (2015). Glucocorticoid receptor gene (*NR3C1*) methylation processes as mediators of early adversity in stress-related disorders causality: A critical review. *Neuroscience & Behavioral Reviews*, *55*, 520–535.

Pariante, C. M., and Lightman, S. L. (2008). The HPA axis in major depression: Classical theories and new developments. *Trends in Neurosciences*, *31*, 464–468.

Peyrot, W. J., Van der Auwera, S., Milaneschi, Y., Dolan, C. V., Madden, P. A., Sullivan, P. F., … Mullins, N. (2018). Does childhood trauma moderate polygenic risk for depression? A meta-analysis of 5,765 subjects from the psychiatric genomics consortium. *Biological Psychiatry*, *84*, 138–147.

Polanczyk, G., Caspi, A., Williams, B., Price, T. S., Danese, A., Sugden, K., … Moffitt, T. E. (2009). Protective effect of *CRHR1* gene variants on the development of adult depression following childhood maltreatment: Replication and extension. *Archives of General Psychiatry*, *66*, 978–985.

Reeder, L. G., Schrama, P. G. M., & Dirken, J. M. (1973). Stress and cardiovascular health: an international cooperative study—I. *Social Science & Medicine (1967)*, *7*, 573–584.

Rice, D., & Barone Jr., S. (2000) Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. *Environmental Health Perspectives*, *108*, 511–33.

Ripke, S., Wray, N. R., Lewis, C. M., Hamilton, S. P., Weissman, M. M., Breen, G., … Heath, A. C. (2013). A mega-analysis of genome-wide association studies for major depressive disorder. *Molecular psychiatry*, *18*, 497–511.

Roisman, G. I., Newman, D. A., Fraley, R. C., Haltigan, J. D., Groh, A. M., & Haydon, K. C. (2012). Distinguishing differential susceptibility from diathesis–stress: Recommendations for evaluating interaction effects. *Development and Psychopathology*, *24*, 389–409.

Roy, A., Gorodetsky, E., Yuan, Q., Goldman, D., Enoch., M-A. (2010). Interaction of *FKBP5*, a stress-related gene, with childhood trauma increases risk for attempting suicide. *Neuropsychopharmacology*, *35*, 1674–1683.

Sandman, C. A., Glynn, L. M., & Davis, E. P. (2013). Is there a viability-vulnerability tradeoff? Sex differences in fetal programming. *Journal of Psychosomatic Research*, *75*, 327–335.

Schechter, J. C., Brennan, P. A., Smith, A. K., Stowe, Z. N., Newport, D. J., & Johnson, K. C. (2017). Maternal prenatal psychological distress and preschool cognitive functioning: The protective role of positive parental engagement. *Journal of Abnormal Child Psychology*, *45*, 249–60.

Sheikh, H. I., Kryski, K. R., Smith, H. J., Hayden, E. P., & Singh, S. M. (2013). Corticotropin-releasing hormone system polymorphisms are associated with children's cortisol reactivity. *Neuroscience*, *229*, 1–11.

Silberg, J. L., Maes, H., & Eaves, L. J. (2010). Genetic and environmental influences on the transmission of parental depression to children's depression and conduct disturbance: An extended children of twins study. *Journal of Child Psychology and Psychiatry*, *51*, 734–744.

Starr, L. R., Hammen, C., Conway, C. C., Raposa, E., & Brennan, P. A. (2014). Sensitizing effect of early adversity on depressive reactions to later proximal stress: Moderation by 5-*HTTLPR* and *CRHR1* in a 20-year longitudinal study. *Developmental Psychopathology*, *26*, 1241–1254.

Szczepankiewicz, A., Leszczyńska-Rodziewicz, J., Pawlak, J., & Rajewska, A. (2011). Glucocorticoid receptor polymorphism is associated with major depression and predominance of depression in the course of bipolar disorder. *Journal of Affective Disorders*, *134*, 138–144.

Thompson, R. J., Parker, K. J., Hallmayer, J. F., Waugh, C. E., & Gotlib, I. H. (2010). Oxytocin receptor gene polymorphism (rs2254298) interacts with familial risk for psychopathology to predict symptoms of depression and anxiety in adolescent girls. *Psychoneuroendocrinology*, *36*, 144–147.

Tyrka, A. R., Price, L. H., Gelernter, J., Schepker, C., Anderson, G. M., & Carpenter, L. L. (2009). Interaction of childhood maltreatment with the corticotropin-releasing hormone receptor gene: Effects on hypothalamic–pituitary–adrenal axis reactivity. *Biological Psychiatry*, *66*, 681–685.

van IJzendoorn, M. H., & Bakermans-Kranenburg, M. J. (2015). Genetic differential susceptibility on trial: Meta-analytic support from randomized controlled experiments. *Development and Psychopathology*, *27*, 151–162.

van Rossum, E. F., Roks, P. H., de Jong, F. H., Brinkman, A., Pols, H., Koper, J. & Lamberts, S. (2004). Characterization of a promoter polymorphism in the

glucocorticoid receptor gene and its relationship to three other polymorphisms. *Clinical Endocrinololgy* (*Oxford*), *61*, 573–581.

Voegtline, K. M., Costigan, K. A., Kivlighan, K. T., Laudenslager, M. L., Henderson, J. L., & DiPietro, J. A. (2013). Concurrent levels of maternal salivary cortisol are unrelated to self-reported psychological measures in low- risk pregnant women. *Archives of Women's Mental Health*, *16*, 101–108.

Vrshek-Schallhorn, S., Stroud, C. B., Mineka, S., Zinbarg, R. E., Adam, E. K., Redei, E. E., … Craske, M. G. (2015). Additive genetic risk from five serotonin system polymorphisms interacts with interpersonal stress to predict depression. *Journal of Abnormal Psychology*, *124*, 776–790.

Wang, J., Zamar, R., Marazzi, A., Yohai, V., Salibian-Barrera, M., Maronna, R., … Konis, K. (2017) robust. R package version 0.4-18.1. Vienna, Austria: R Core Team.

Weinstock, M. (2008). The long-term behavioural consequences of prenatal stress. *Neuroscience & Biobehavioral Reviews*, *32*, 1073–1086.

Weissman, M. M., Wickramaratne, P., Gameroff, M. J., Warner, V., Pilowsky, D., Kohad, R. G., … Talati, A. (2016). Offspring of depressed parents: 30 years later. *American Journal of Psychiatry*, *173*, 1024–1032.

Zannas, A. S., & Binder, E. B. (2014). Gene-environment interactions at the *FKBP*5 locus: Sensitive periods, mechanisms and pleiotropism. *Genes Brain & Behavior*, *13*, 25–37.

Zimmerman, P., Brückl, T., Nocon, A., Pfiser, H., Binder, E. B., Manfred, U., … Ising, M. (2011). Interaction of *FKBP*5 gene variants and adverse life events in predicting depression onset: Results from a 10-year prospective community study. *American Journal of Psychiatry*, *168*, 1107–1116.