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# Does Prenatal Stress Amplify Effects of Postnatal Maternal Depressive and Anxiety Symptoms on Child Problem Behavior?

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Emerging evidence suggests that prenatal stress does not solely undermine child functioning but increases developmental plasticity to both negative and positive postnatal experiences. Here we test this proposition using the Norwegian Mother and Child Cohort study while implementing an extreme-group (i.e., high vs. low prenatal stress) design ($n$ = 27,889 children for internalizing and $n$ = 27,892 for externalizing problems). To measure prenatal stress, mothers reported on depressive and anxiety symptoms at gestational weeks 17 and 30 and of stressful life events at gestational week 30. We then evaluated whether, collectively, such prenatal stress amplified the effect of mothers' postnatal depressive and anxiety symptoms on children's internalizing and externalizing behavior problems at age 5 years. Results showed prenatal stress amplified effects of postnatal maternal depression/anxiety on child internalizing but not externalizing behavior, with some indication that this Prenatal-Stress-×-Postnatal-Maternal-Depression interaction proved more consistent with differential susceptibility than diathesis stress thinking: Children exposed to prenatal stress evinced greater internalizing problems if exposed to more postnatal maternal depressive/anxiety symptoms and, somewhat less strongly, displayed less internalizing problems if they experienced lower postnatal maternal depressive/anxiety symptoms. However, analyses using the whole sample instead of extreme groups yielded opposing results with children exposed to the least prenatal stress evincing greater sensitivity to postnatal maternal depressive/anxiety symptoms with regards to externalizing and internalizing behavior. Taken together, it appears that prenatal stress may have differing effects on plasticity depending on prenatal stress severity.

*Keywords:* prenatal stress, differential susceptibility, maternal depression, maternal anxiety, The Norwegian Mother and Child Cohort Study

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Extensive evidence indicates that prenatal stress is a risk factor for a variety of detrimental physical and mental health phenotypes (for review, see Van den Bergh et al., 2017). Although such human evidence suggests that prenatal stress disrupts "optimal" development, we entertain—and evaluate herein—an alternative possibility. Based on research on human infants showing (a) that prenatal stress is associated with heightened negative emotionality and physiological reactivity and (b) that these postnatal phenotypes are

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themselves associated with increased susceptibility to both positive and negative developmental experiences and environmental exposures postnatally, we test Pluess and Belsky's (2011) hypothesis that *prenatal stress programs postnatal plasticity*, making prenatally stressed infants disproportionately susceptible to effects of the postnatal rearing environment. Drawing on data from the large and nationally representative Norwegian Mother and Child Cohort study (MoBa) while implementing an extreme-group (i.e., high vs. low prenatal stress) design, we predicted that effects of postnatal adversity—operationalized as exposure to maternal depression and anxiety—would prove more pronounced for children exposed to greater prenatal stress (i.e., maternal depression/anxiety symptoms and stressful life events).

## Prenatal Stress and Behavioral–Physiological Dysregulation

Prenatal stress, measured in a variety of ways (e.g., maternal depression, anxiety, cortisol), predicts greater behavioral and physiological dysregulation in infancy and childhood (for reviews see Hartman & Belsky, 2018; Pluess & Belsky, 2011). Concerning behavioral dysregulation, prenatal stress is linked to increased displays of sadness, frustration, and fear, as well as a stable disposition of (negative) emotional reactivity (Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002; Van den Bergh, Mulder, Mennes, & Glover, 2005). Maternal psychological stress during pregnancy is associated with increased behavioral reactivity of 4-month-olds (Davis et al., 2004), irregular sleeping and eating patterns of 6-month-olds, and heightened inhibition and negative emotionality of 5-year-olds (Martin, Noyes, Wisenbaker, & Huttenen, 1999). Relatedly, elevated cortisol levels in pregnant women forecast greater infant negativity at 7 weeks (de Weerth, van Hees, & Buitelaar, 2003) and 2 months of age (Davis et al., 2007).

Concerning physiological functioning, prenatal stress is associated with dysregulation of the hypothalamic–pituitary–adrenal axis (HPA) in infants and children, as reflected in greater maternal depression in middle pregnancy predicting elevated basal cortisol concentrations in newborns (Field et al., 2004) and higher maternal cortisol in middle and late pregnancy predicting greater cortisol response to a heel-prick 24 hr after birth (Davis, Glynn, Waffarn, & Sandman, 2011). Such effects on children's cortisol levels as a function of expectant mothers' heightened pregnancy-specific fears and cortisol levels measured at multiple times throughout pregnancy extend to even the first day of school (Gutteling, de Weerth, & Buitelaar, 2005). Notably, a natural experiment revealed that pregnant mothers positioned near the NYC terrorist attacks on 9/11who subsequently developed posttraumatic stress disorder (PTSD) had infants with more dysregulated diurnal cortisol rhythms at one year of age than other infants (Yehuda et al., 2005). Such findings are consistent with rodent experiments indicating that prenatal stress promotes higher baseline and reactive corticosterone levels in offspring (Maccari, Krugers, Morley-Fletcher, Szyf, & Brunton, 2014).

## Postnatal Developmental Plasticity

The research just summarized becomes especially intriguing when juxtaposed to independent work showing that highly negatively emotional and physiologically reactive children display enhanced developmental plasticity—in a manner reflecting differential susceptibility models of Person-×-Environment interaction (Belsky & Pluess, 2009). Specifically, evidence suggests highly reactive and negatively emotional children are not only more adversely affected than others by negative environmental exposures (e.g., harsh parenting), but also benefit more from supportive contextual conditions (e.g., sensitive-responsive parenting), which is consistent with the "for-better-and-for-worse" proposition central to differential-susceptibility theorizing (Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2007; Belsky & Pluess, 2009, 2013). In fact, Slagt and associates (Slagt, Dubas, Deković, & van Aken, 2016) recent meta-analysis found that negative emotionality in infancy moderates effects of various environmental factors on a range of child-adjustment outcomes (e.g., social competence, cognitive development) in just such a "for-better-and-for-worse," differential-susceptiblity-related manner (Belsky et al., 2007). In other words, infants characterized as having high negative emotionality displayed the most problem behavior (e.g., psychopathology) when exposed to adverse environments but the least problem behavior or the most competent functioning when raised in supportive circumstances.

Furthermore, children with heightened physiological reactivity are more susceptible to environmental influences, again in a manner consistent with differential susceptibility (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011). For example, heightened physiological reactivity moderates the effects of marital conflict on externalizing problems (Obradović, Bush, & Boyce, 2011) and family adversity on school achievement (Obradović, Bush, Stamperdahl, Adler, & Boyce, 2010) in a "for-better-and-for-worse" manner. Additionally, evaluations of experimental interventions (e.g., van den Berg & Bus, 2014) show that negatively emotional or physiologically reactive children benefit more and sometimes were the only ones who benefitted from such efforts than other children. In summary, more physiologically/behaviorally reactive children prove both most vulnerable to the negative effects of contextual adversity and most likely to benefit from environmental support.

## Prenatal Programming of Postnatal Plasticity

Consideration of research indicating (a) that prenatal stress is associated with elevated behavioral and physiological dysregulation and (b) that such phenotypic functioning is associated with heightened susceptibility to positive and negative environmental influences led Pluess and Belsky (2011) to hypothesize that *prenatal stress fosters, promotes, or "programs" postnatal developmental plasticity*. If true, this hypothesis could account for many of the adverse, later developing phenotypes associated with prenatal stress exposure. Perhaps the reason that prenatal stress is so often associated with problematic functioning in childhood and adolescence is because the very forces that engendered stress in pregnancy (e.g., poverty, marital conflict) continue postnatally for many whose prenatal experience fostered heightened developmental plasticity. Thus, when these children are subsequently exposed, postnatally, to conditions of adversity that persist beyond pregnancy, they prove especially responsive to them. Conversely, the hypothesis may also explain why beneficial prenatal stress effects

have been observed in well-resourced samples (e.g., DiPietro, Novak, Costigan, Atella, & Reusing, 2006).

This prenatal-programming-of-postnatal-plasticity hypothesis is in contrast with the traditional diathesis-stress way of thinking about development and pathology (Zuckerman, 1999). According to the latter perspective, prenatal stress would amplify vulnerability to postnatal adversity. Thus, a child exposed to prenatal stress would display problematic or poor functioning under conditions of contextual risk (e.g., poverty, maternal depression), but afford no benefit under enriched or even benign conditions.

## Current Study

Here we evaluate this prenatal-programming-of-postnatal-plasticity hypothesis by taking advantage of a large Norwegian cohort study, which assessed children's exposure to prenatal stress in the form of maternal depression and anxiety symptoms and stressful life events. Indeed, we do so by implementing an extreme-group design, contrasting mothers with the highest 10% composite prenatal stress scores (indicating scoring in the clinical range) against mothers scoring zero on such a measure, predicting that prenatal-stress exposure will amplify effects of postnatal maternal depression and anxiety on children's problem behavior. We chose this quasi-experimental approach in hopes of sharpening the contrast at hand.

Consistent with differential-susceptibility theorizing (Belsky & Pluess, 2009, 2013), we expect that prenatally stressed children will develop the most and least behavior problems of all children, depending on whether exposed, respectively, to high or low levels of maternal depression and anxiety postnatally. In order to contrast this prediction with that derived from diathesis-stress thinking (Zuckerman, 1999)—which stipulates that some individuals are only more susceptible to adversity—we employ the Widaman method, which statistically compares models based on contrasting a priori predictions (Belsky & Widaman, 2018; Widaman et al., 2012). We focus on behavior problems because prior evidence links prenatal maternal anxiety and/or depression with increased child internalizing (e.g., Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; O'Connor, Heron, & Glover, 2002) and externalizing behavior (e.g., Luoma et al., 2001; Van den Bergh & Marcoen, 2004), including in the Norwegian study on which this report is based (Gjerde et al., 2017).

## Method

### Sample

The present study is a subproject of the Norwegian Mother and Child Cohort study (MoBa), conducted by the Norwegian Institute of Public Health (NIPH). MoBa is a prospective, ongoing, pregnancy cohort study (for details, see Magnus et al., 2006, 2016). Participants were recruited from 1999 to 2009 at a routine ultrasound examination offered to all pregnant women in Norway at 17–18 weeks' gestation. The total sample now includes >114,500 children; 41% of eligible women participated. For the current report, we use information obtained at 17 (Q1) and 30 weeks gestation (Q3), 1.5 (Q5), 3 (Q6) and 5 years (Q-5year) postpartum on mothers and at 5 years (Q-5year) on their children. The total number of participants at the selected time points Q1–Q5 was, respectively, 103,837 (participation rate = 90.5%), 95,821 (83.5%), 76,417 (66.6%), 58,841 (51.3%), and 41,608 (36.3%). The analytic sample comprising our extreme-group research design (i.e., high vs. low prenatal stress) included 48,497 children. Criteria for inclusion in our extreme-case design are delineated below.

We used Version 9 of the quality-assured MoBa data files, which was released in 2015. Written informed consent was obtained from all participants upon recruitment. The MoBa study has been granted a license from the Norwegian Data Inspectorate; the present study was approved by the Regional Committee for Medical Research Ethics.

### Measures

Table 1 presents descriptive statistics and Table 2 presents bivariate relations for all variables.

**Prenatal stress.** A composite index of prenatal stress was created based on maternal reports of depressive and anxiety symptoms and stressful life events during pregnancy. Specifically, we relied on 3 and 4 depressive-symptoms items and 2 and 4 anxiety-symptoms items responded to at, respectively, week 17 and week 30 of pregnancy, and a 9-item stressful-life-events' rating scale administered at 30 weeks. Maternal depressive and anxiety symptoms were measured with short forms of the 90-item Symptom Checklist (SCL-90; Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974). These were the 5-item SCL-5 (available at Q1) and the longer, overlapping 8-item SCL-8 (available at all consecutive time points), which are both derived from the short form SCL-25, intended to measure symptoms of anxiety and depression (Hesbacher, Rickels, Morris, Newman, & Rosenfeld, 1980). The SCL-5 and SCL-8 have been validated and thoroughly described elsewhere (Tambs & Moum, 1993; Tambs & Røysamb, 2014). Items measuring depressive (e.g., "Worrying too much about things", "Feeling blue") and anxiety (e.g., "Feeling fearful", "Nervousness or shakiness inside") symptoms were rated on a 4-point scale (1 = *not at all bothered*; 4 = *quite a bit bothered*). Internal consistency was good for the combined depression and anxiety items (week 17: $\alpha = .80$; week 30: $\alpha = .83$).

We created separate average depression and anxiety (dep/anx) scores for gestation week 17 and 30 for all cases with a minimum of four responses. We further classified the participants into two groups: those who endorsed no dep/anx symptoms and those who endorsed the highest 10% number of symptoms. The 10% cutoff corresponds closely to what have been found to be useful cutoffs for identifying clinical cases (Sandanger et al., 1999; Strand, Dalgard, Tambs, & Rognerud, 2003). Because of this dichotomization, 39,304 cases (39% of the total sample) were excluded from the measure at gestation week 17, and 50,785 cases (53.5%) from the measure at gestation week 30.

With regard to each of nine stressful life events experienced over the past 12 months (e.g., financial problems; divorced, separated or ended a relationship; seriously ill or injured), mothers indicated whether they had been exposed and rated how painful or difficult the experience was from 1 (*not too bad*) to 3 (*very painful/difficult*). For each respondent who had answered a minimum of two items, a mean subjective-life-stress score was created and then divided into two groups: those who had not experienced stressful life events, and the 10% most extreme responding. Those

Table 1
*Descriptive Statistics*

| Variable | Low prenatal stress | High prenatal stress | Analytic sample |
|---|---|---|---|
| | Demographics | | |
| Child sex (*N*, %) | | | |
| Boys | 18,831 (51) | 5,957 (51) | 24,788 (51) |
| Girls | 18,010 (49) | 5,636 (49) | 23,646 (49) |
| Parental education (*N*, %) | | | |
| 9 years secondary school | 461 (1) | 446 (4) | 907 (2) |
| 1–2 years high school | 1,155 (3) | 764 (7) | 1919 (4) |
| Vocational high school | 3,872 (11) | 1,666 (15) | 5,538 (12) |
| 3 years high school | 4,440 (13) | 1,932 (18) | 6,372 (14) |
| Bachelor's degree | 15,883 (45) | 3,832 (35) | 19,715 (43) |
| Master's degree or higher | 9,326 (27) | 2,193 (20) | 11,519 (25) |
| Parity (*N*, %) | | | |
| 0 | 17,069 (46) | 5,703 (49) | 22,772 (47) |
| 1 | 13,003 (35) | 3,773 (33) | 16,776 (35) |
| 2 | 5,404 (15) | 1,627 (14) | 7,031 (15) |
| 3 | 1,050 (3) | 366 (3) | 1,416 (3) |
| 4 | 315 (1) | 124 (1) | 439 (1) |
| Maternal age at birth | | | |
| Mean | 30.5 | 29.6 | 30.32 |
| *SD* | 4.29 | 4.93 | 4.47 |
| Marital status (*N*, %) | | | |
| Married | 18,774 (51) | 4,917 (43) | 23,691 (49) |
| Divorced | 40 (0) | 68 (1) | 108 (0) |
| Cohabitant | 17,189 (47) | 5,761 (50) | 22,950 (48) |
| Widow | 4 (0) | 1 (0) | 5 (0) |
| Single | 343 (1) | 492 (4) | 835 (2) |
| Other | 243 (1) | 214 (2) | 457 (1) |
| Income (*N*, %) | | | |
| No income | 585 (2) | 372 (3) | 957 (2) |
| <150 000 NOK | 4,230 (12) | 2,375 (21) | 6,605 (14) |
| 150 000–199 000 NOK | 3,447 (10) | 1,420 (13) | 4,867 (10) |
| 200 000–299 000 NOK | 12,458 (35) | 3,595 (32) | 16,053 (34) |
| 300 000–399 000 NOK | 10,061 (28) | 2,342 (21) | 12,403 (26) |
| 400 000–499 000 NOK | 2,956 (8) | 669 (6) | 3,625 (8) |
| >500 000 NOK | 1,926 (5) | 368 (3) | 2,294 (5) |
| | Predictor | | |
| Postnatal dep/anx | | | |
| Mean | .11 | .57 | .22 |
| *SD* | .30 | .48 | .40 |
| | Outcomes | | |
| Child internalizing symptoms | | | |
| Mean | 48.3 | 53.1 | 49.39 |
| *SD* | 8.75 | 12.1 | 9.81 |
| Child externalizing symptoms | | | |
| Mean | 48.5 | 52.4 | 49.36 |
| *SD* | 9.28 | 11.3 | 9.9 |

*Note*. Dep/anx = symptoms of depression and anxiety; *M* = mean; *SD* = standard deviation; *N* (%) = number of individuals and percentage; NOK = Norwegian Krone.

who scored in between (41,436 individuals, 43% of the total sample) did not receive a score on subjective life stress.

Prenatal stress was then defined by two groups: absence of dep/anx symptoms at gestation weeks 17 and 30 and subjective life stress (scored as 0), or a high score on at least one of these (scored as 1). Of the mothers that had children with data on the internalizing outcome, 21,592 (77% of the analytic sample) received a score of 0, and 6,297 (23%) a score of 1. For the externalizing outcome, the numbers were 21,595 (77%) and 6,297 (23%), respectively.

**Postnatal depression and anxiety.** The same items tapping depressive and anxiety symptoms at gestation week 30 were readministered postnatally when children were 1.5, 3 and 5 years of age (alpha's = 0.85, 0.87, 0.86, respectively). We followed the same procedure as for the prenatal depression and anxiety variables outlined above, with cut-offs at 1.75, 1.75, and 1.63, respectively. The final postnatal depression/anxiety variable was an average of the extreme scores of depressive and anxiety symptoms at 1.5, 3, and 5 years after birth for which there was at least one score. This variable was quantitative, and had the following pos-

Table 2
*Bivariate Relations Among Variables*

| Variable | Prenatal stress | Postnatal anxiety and depression | Internalizing symptoms | Externalizing symptoms |
|---|---|---|---|---|
| Prenatal stress | 1 | | | |
| Postnatal anxiety and depression | .55 | 1 | | |
| Internalizing symptoms | .20 | .27 | 1 | |
| Externalizing symptoms | .17 | .24 | .39 | 1 |

*Note*. All correlations are significant with $ps < .001$.

sible scores: 0 (78% of the analytic sample), 0.33 (0.5%), 0.5 (4%), 0.67 (0.5%) and 1 (17%). "0" represents no endorsed symptoms, and "1" represent the most depressive and anxiety symptoms.

**Developmental outcomes.** Child internalizing and externalizing symptoms at age 5 years were reported by mothers using 11 items taken from the Child Behavior Checklist preschool version (CBCL; Achenbach, 1992); each was rated using a three-point Likert Scale (*not true/somewhat-or-sometimes true/very-or-often true*). The items were selected by a team of psychologists based on clinical expertise, theory, and factor loadings on internalizing and externalizing behavior. Mean scores on all the children with data were created for internalizing symptoms ($\alpha = .67$) and externalizing symptoms ($\alpha = .77$), respectively. Responses on a minimum of five items on each scale were required. Finally, the mean scores were converted to *T* scores (based on the whole MoBa sample to make the *T* scores as representative as possible), using the formula $10z + 50$.

## Sample Attrition

There is a considerable amount of attrition in the MoBa study. This opens up the possibility that high scores on exposures is associated with nonresponse, which can bias the generalizability of findings. We found that increasing one unit on prenatal stress increased the risk for nonresponse when the children were 5 years old with 36% ($\exp(\beta) = 1.359$, 95% CI [1.306, 1.415], $p < .000$). The attrition in MoBa and longitudinal studies in general has been studied previously, and it has been concluded that although prevalence estimates become biased even at low attrition rates, estimates of association are much more robust (Gustavson, von Soest, Karevold, & Røysamb, 2012; Nilsen et al., 2009). Furthermore, a simulation study has shown that if some responders with high scores are included, estimates of association may be relatively unbiased, even in situations with very low response rate (Gustavson, Røysamb, & Borren, 2019).

## Statistical Analyses

To evaluate which of four possible Person-×-Environment models—strong and weak differential susceptibility and diathesis stress—best fit our data, we first conducted traditional and exploratory regression analyses followed by the competitive-confirmatory, model-fitting approach. Notably, strong and weak models of both differential susceptibility and diathesis stress can be distinguished and evaluated using the Widaman et al. (2012) method. In the case of strong models, some individuals (i.e., least susceptible) are totally unaffected by the contextual conditions under investigation (i.e., zero-order association between environmental predictor and developmental outcome), whereas in the case of weak models, the effect of the environmental predictor is greater for some than others, but all are affected. Analyses were conducted in RStudio Version 0.99.903 (RStudio Team, 2015).

To determine whether it is appropriate to proceed with confirmatory analyses, main effects of prenatal stress and postnatal stress—and their interaction—are evaluated. Only if the F ratio of the interaction term in this exploratory regression analysis exceeds 1.0 does one proceed to the second stage (Belsky & Widaman, 2018). In the second, model-fitting stage, the crossover point of the interaction becomes critical for evaluating the best-fitting model (Widaman et al., 2012). Evidence of differential susceptibility emerges when that point is near the midpoint of the (postnatal stress) predictor, whereas evidence of diathesis stress emerges when it is near the low point of the predictor.

To further compare weak and strong differential-susceptibility and diathesis-stress models, four different specifications of the models are implemented and compared using the F comparison tests, Akaike Information Criterion (AIC; Akaike, 1987), the Bayesian Information Criterion (Schwartz, 1978), and variance explained using the R-squared statistic ($R^2$).

# Results

Because first-stage, exploratory regression analysis indicated that we could proceed to the competitive-confirmatory model-fitting second stage only in the case of internalizing problems (see F ratio of Model 2 in Table 3), further statistical reporting in this subsection is restricted to this outcome. Confirmatory model testing indicated that a weak-differential-susceptibility model fit the data best. Inspection of Table 3 reveals that this model (3b) explained the most variance compared to the other three models (i.e., 3a, 3c, 3d; see Table 3). However, the crossover point ($c = -1.21$, $SE = 0.36$) was low, falling outside the range of measured maternal postnatal depression and anxiety (i.e., 0 to 1; higher scores indicate greater depressive/anxious symptoms), a result more consistent with a diathesis-stress interaction (see Figure 1). Despite this, indices of model fit (i.e., AIC and BIC) were the lowest for the weak-differential-susceptibility model, thus indicating better model fit compared to all other models.

## Sensitivity Analyses

To clarify the findings of the main analyses and determine whether the results just summarized could be artifacts of the extreme-group design, we repeated, at the urging of reviewers, all analyses using continuous variables. Hence, in these sensitivity analyses, all data for all individuals were analyzed, not just for

Table 3
*Results of Model Fitting for Internalizing Problems*

| | Standard parameterization | | | Re-parameterized regression equation | | | |
|---|---|---|---|---|---|---|---|
| | Main effects | + Interaction | | Differential susceptibility | | Diathesis stress | |
| Parameter | Model 1 | Model 2 | Parameter | Strong: Model 3a | Weak: Model 3b | Strong: Model 3c | Weak: Model 3d |
| B0 | 47.73 (.07) | 47.80 (.07) | B0 | 48.31 (.06) | 41.61 (2.03) | 48.46 (.06) | 48.03 (.06) |
| B1 | 5.81 (.17) | 5.13 (.22) | B1 | .00 (−) | 5.13 (.22) | .00 (−) | 4.88 (.22) |
| B2 | 2.30 (.15) | 1.80 (.19) | C | −.19 (.03) | −1.21 (.36) | 1 | 1 |
| B3 | — | 1.49 (.33) | B3 | 6.62 (.25) | 1.49 (.33) | 7.81 (.18) | 3.38 (.27) |
| $R^2$ | .081 | .082 | $R^2$ | .06 | .082 | .06 | .079 |
| *F* | 1236.1 | 831.2 | *F* | 968.6 | 831.2 | 1887.9 | 1197.57 |
| *df* | 2, 27,886 | 3, 27,885 | *df* | 2, 27,886 | 3, 27,885 | 1, 27,887 | 2, 27,886 |
| *p* | <.0001 | <.0001 | *p* | <.0001 | <.0001 | <.0001 | <.0001 |
| *F* vs 1 | — | 19.8551 | *F* vs 3a | — | 520.34 | 46.34 | — |
| *df* | — | 1, 27,885 | *df* | — | 1, 27,885 | 1, 27,886 | — |
| *p* | — | <.0001 | *p* | — | <.0001 | <.0001 | — |
| | | | *F* vs 3b | 520.34 | — | 283.77 | 90.8 |
| | | | *df* | 1, 27,885 | — | 2, 27,885 | 1, 27,885 |
| | | | *p* | <.0001 | — | <.0001 | <.0001 |
| AIC | 204142.9 | 204125.1 | AIC | 204638.7 | 204125.1 | 204683.0 | 204213.8 |
| BIC | 204175.9 | 204166.3 | BIC | 204671.6 | 204166.3 | 204707.7 | 204246.7 |

*Note*. B0 = intercept; B1 = postnatal depression and anxiety; B2 = prenatal stress; B3 = product of B1 and B2 for standard parameterization models. Values indicate parameter estimates, with standard errors in parentheses. *F* vs 1 stands for an *F* test of the difference in $R^2$ for Model 2 versus Model 1. *F* vs 3a and *F* vs 3b stand for *F* test of the difference in $R^2$ for a given model versus Model 3a and Model 3b, respectively. AIC = Akaike information criterion; BIC = Bayesian information criterion. When numbers are reported without standard errors (−), this indicates that the parameters were fixed at the reported value (e.g. at 0 for B1 in Model 3a).

those exposed to the most and least prenatal stress. Continuous versions of prenatal stress (and postnatal dep/anx) symptoms were constructed using mean scores (see Table S1 in the online supplemental materials for descriptives).

Sensitivity analyses were conducted in the same manner as the main analyses. For both internalizing and externalizing symptoms, exploratory regression results indicated that we could proceed to the competitive-confirmatory model fitting (see F ratios in Table S2 and Table S3). Once again, the best-fitting model was that of weak differential susceptibility—for both outcomes. Importantly, the crossover points for both internalizing (c = 2.33, *SE* = 0.10) and externalizing problems (c = 1.91, *SE* = 0.06) fell within the range of potential postnatal depression and anxiety mean scores. In contrast to the extreme-group analyses (where those exposed to "normal" prenatal stress were dropped), the interaction between prenatal stress and postnatal depression and anxiety had a negative value (internalizing: B3 = −4.20, *SE* = 0.41; externalizing: B3 = −5.55, *SE* = 0.41). This indicated that children exposed to the least prenatal stress proved more reactive to maternal postnatal depression and anxiety symptoms, which is the opposite of what emerged in the extreme-group analyses. The finding that children exposed to the least prenatal stress had both the fewest and most problems, depending on the level of maternal postnatal depression and anxiety, emerged for both the internalizing and the externalizing outcome (see Figures S1 and S2).

## Post Hoc Analyses

These contrasting findings of the main and sensitivity analyses raised the possibility that the moderating effect of prenatal stress on the effects of postnatal stress on children's problems might reflect different processes, depending on whether prenatal stress was "normal" or "extreme." That is, the moderating effect of being in the top 10% of prenatal stress (i.e., "severe") might be different from being in the bottom 90% (i.e., "normal"). To test this post hoc hypothesis, we reran separate analyses with (1) a normal-prenatal-stress sample (i.e., pregnant women who scored in the bottom 90% of prenatal stress) and (2) a severe-prenatal-stress sample (i.e., pregnant women who scored in the top 10% of prenatal stress).

Results indicated that for the normal-prenatal-stress sample, the F-ratio exceeded the criterion of 1.0 for both outcomes (see Tables S4 and S5) and that the best-fitting model for both outcomes was weak differential susceptibility (see Tables S4 and S5). For the internalizing outcome, the crossover point was 7.66 (*SE* = 4.16), once again falling outside of the data range (Figure S3), with the same being true for the externalizing outcome (c = 5.82, *SE* = 2.63; Table S5, Figure S4). Although children exposed to the highest levels of maternal prenatal stress, then, developed the most internalizing and externalizing problems, it was those exposed to the lowest levels of prenatal stress who proved most reactive to their mothers' postnatal symptoms of depression and anxiety (Figures S4 and S5). Recall that this was the opposite of what emerged in the main analyses.

When we turned to the severe-prenatal-stress group, results proved different. While the F-ratio for proceeding with competitive-confirmatory model fitting exceeded the 1.0 threshold for both outcomes once again (see Tables S6 and S7), the best-fitting model now proved to be the strong diathesis stress one (Model 3c, Tables S6 and S7). Inspection of Figures S6 and S7 indicates that children exposed to the very highest levels of maternal prenatal stress develop the most problems when exposed to high levels of maternal postnatal depressive and anxiety symptoms, but not the fewest when exposed to low levels of maternal

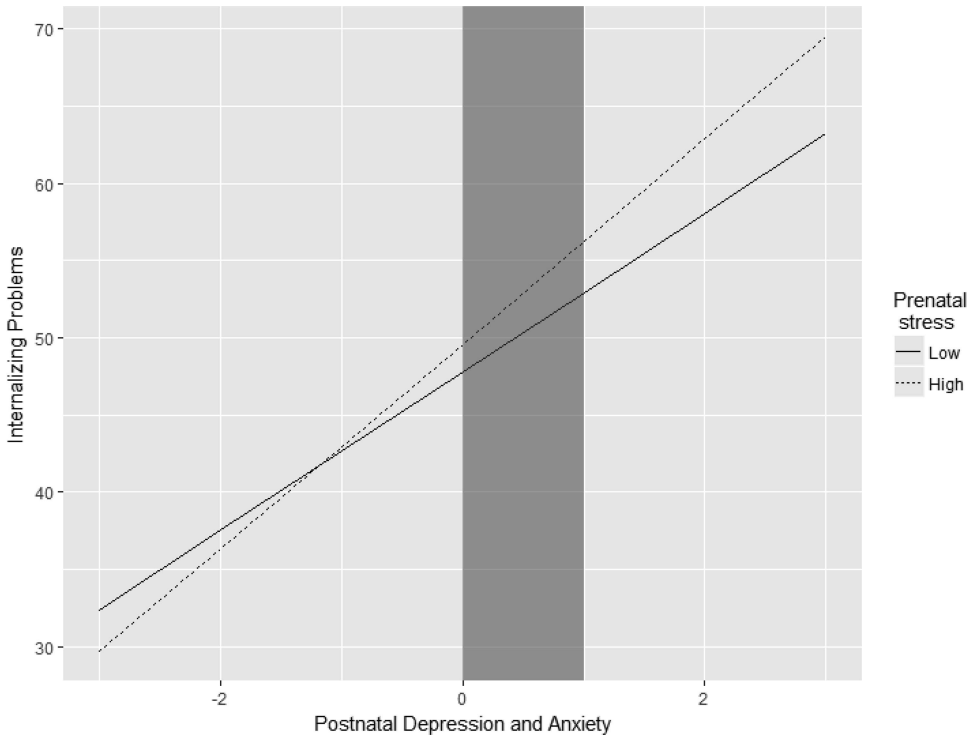


*Figure 1.* Predicted child internalizing problems as a function of maternal postnatal depression and anxiety score for children that were exposed to low versus high levels of maternal prenatal stress. Shaded area indexes data range.



postnatal depressive and anxiety symptoms, as would be the case had a differential-susceptibility model proved best fitting.

## Discussion

Based on Pluess and Belsky's (2011) hypothesis that prenatal stress programs postnatal developmental plasticity, we examined the interaction of prenatal stress and postnatal maternal depression/anxiety in predicting child problem behavior using a confirmatory-model-testing approach (Belsky & Widaman, 2018; Widaman et al., 2012) in the context of an extreme-group research design (i.e., very high vs. very low prenatal stress). Prenatal stress, reflecting both depressive/anxiety symptoms and stressful life events, and postnatal maternal depression and anxiety did interact to predict internalizing, but not externalizing problems. Consistent with expectations, exposure to high levels of prenatal stress amplified effects of maternal postnatal depression and anxiety in a manner reflective of (weak) differential susceptibility. Specifically, while exposure to more and less postnatal maternal depressive and anxiety symptoms predicted, respectively, more and fewer internalizing problems, this association proved stronger for children who experienced high rather than low levels of prenatal stress. Had children not exposed to prenatal stress proven completely unaffected by postnatal maternal depression and anxiety, that would have provided support for the strong differential susceptibility model.

Although we originally set out to examine our hypotheses using a quasi-experimental design involving extreme groups, we followed up these analyses, at the urging of reviewers, with a sensitivity analysis using the whole sample, thereby treating prenatal stress as a continuous rather than categorical, very-high/very-low variable. While results once again indicated that the weak-differential-susceptibility model fit the data best, this time it was the least prenatally stressed children who emerged as most susceptible to postnatal maternal depression and anxiety effects in their externalizing and internalizing behavior. This finding, that children who received the least prenatal stress were the most affected by postnatal maternal depressive/anxiety symptoms, was opposite of the results from the main analyses.

Reflection on these contrasting findings emerging from alternative research designs—extreme groups versus all cases—raised the possibility that prenatal stress may affect developmental plasticity differently, depending on the severity of prenatal stress. This led to our post hoc analyses examining the moderating effect of prenatal stress on effects of postnatal stress (a) for those exposed to "normal" prenatal stress (i.e., 0–90th percentile of prenatal stress) and (b) for those exposed to "severe" prenatal stress group (i.e., top 10% of prenatal stress). Results proved consistent with the supposition that the moderating effect of prenatal stress varied depending on its severity. Recall that among those exposed to "normal" prenatal stress, results were in line, perhaps not surprisingly, with those of the sensitivity analyses that included all cases: Children who experienced the least prenatal stress proved most sensitive to postnatal maternal depressive/anxiety symptoms, and in a differential-susceptibility-like manner. In contrast, in the case

of children exposed to "severe" prenatal stress, those exposed to the most prenatal stress displayed the most externalizing and internalizing problems when exposed to greater postnatal maternal depressive/anxiety symptoms but were no different from less-prenatally-stressed children (within the severely stressed group) when postnatal maternal depressive/anxiety symptoms were low. In other words, these latter results were consistent with diathesis-stress thinking.

As it turns out, such contrasting—and unanticipated—results regarding the moderating effect of prenatal stress on postnatal developmental plasticity have emerged in other work, at least with rodents. For example, in rats, mild prenatal stress compared to extreme prenatal stress yielded opposite effects on offspring brain weight, locomotive behavior, and global methylation patterns in the brain (Mychasiuk, Ilnytskyy, Kovalchuk, Kolb, & Gibb, 2011). Consider next work chronicling opposing effects of different types of prenatal stress that vary in their intensity (e.g., water immersion, footshock, sleep deprivation), on adult sexual behavior (Velazquez-Moctezuma, Dominguez Salazar, & Cruz Rueda, 1993). Perhaps relatedly, research on human and nonhuman primates documents opposing effects, dependent on stress severity, of early postnatal stress on development (e.g., Lyons, Parker, & Schatzberg, 2010).

How might we explain the differential moderating effects of prenatal stress on postnatal developmental plasticity that emerged in the current inquiry? One possibility involves physiological changes in the fetus and placenta when exposed to different levels of maternal cortisol. Specifically, the hypothalamic–pituitary–adrenal (HPA) axis is a well-studied mediator of the relationship between maternal stress and fetal development (Matthews, Owen, Banjanin, & Andrews, 2002). In particular, the placenta plays a crucial role in moderating fetal exposure to maternal cortisol by converting cortisol into inactive cortisone, thereby drastically reducing fetal exposure to maternal cortisol (see O'Donnell, O'Connor, & Glover, 2009, for review). However, even though the placenta and the fetus have developed mechanisms to protect the fetus from maternal cortisol, this mechanism can only compensate up to a certain threshold (White, Mune, & Agarwal, 1997). This observation raises the possibility the effects of prenatal stress on postnatal developmental plasticity may be dependent on whether certain physiological thresholds are crossed, thus stimulating alternative physiological cascades.

Furthermore, one might speculate that intense-chronic stress encountered by the pregnant mother may communicate notably different signals to the fetus about the nature of the potential postnatal milieu compared to more mild or intermittent stress. In fact, chronic high-intensity stress may send a strong signal that is reliably passed on to offspring compared to intermittent or acute stressors that might be less reliable indicators of environmental quality. Indeed, this higher level of prenatal stress may actually de-canalize development, a potentially costly strategy (D.W. Belsky, personal communication, January 26, 2018). The evolutionary logic underlying such a process might be that the very high levels of stress that we refer to as "severe" may convey to the developing organism that its otherwise canalized development is not likely to foster its survival and reproductive success; thus, it makes biological sense to deviate from its canalized path. This line of reasoning would seem consistent with our results indicating that it was only extreme levels of prenatal stress that were associated with increased susceptibility to postnatal experiences.

There should be little doubt that the preceding discussion of our results is speculative, due in large part to the unexpected nature of our findings. Clearly, there is a need for further work to evaluate whether our results are replicable. In highlighting this need, we should also call attention to the limits of our own efforts. One such limitation is that our postnatal measure, maternal depressive/anxiety symptoms, may not have accurately captured the more positive side of the postnatal environment. Reporting few or no symptoms of depression and anxiety postnatally only indicates the absence of such symptoms; it does not necessarily imply high levels of psychological health. Consider in this regard that the depression item addressing "feeling hopeless about the future" cannot capture feelings of optimism and that the one assessing "feeling blue" cannot index feelings of happiness and satisfaction.

Another factor to consider is that we relied in the current study on a more distal (i.e., maternal depression/anxiety) rather than more proximate (e.g., parenting quality) postnatal developmental exposure. While there is ample evidence that depression and anxiety affect parenting, the correspondence is small to moderate in size, as revealed in Lovejoy et al.'s (Lovejoy, Graczyk, O'Hare, & Neuman 2000) meta-analysis. Thus, having more mental health symptomology does not always translate into less supportive parenting. In other words, maternal depression and anxiety may serve as a proxy for a greater likelihood of experiencing harsh or disengaged parenting, but by no means provides a guarantee of it. Because the infant directly experiences parenting, whereas the same is not necessarily true of maternal psychological state, it seems possible that a more proximate rather than more distal environmental-exposure index could have yielded stronger results. Unfortunately, we were unable to address this possibility due to the absence of high-quality early parenting measurements in the MoBa.

An additional limitation that should be noted is that our predictor (i.e., postnatal maternal depression and anxiety symptoms) and moderator (i.e., prenatal stress) variables were significantly correlated in the present study. Although prenatal stress and postnatal maternal mental health have been shown to be linked in this study and others (e.g., Kingston, McDonald, Austin, & Tough, 2015), a significant association between a predictor and moderator is not statistically ideal for moderation analyses. Future work may address this issue by utilizing natural experiments such as exposure to natural disasters which may demonstrate less prenatal–postnatal linkage.

Lastly, it should be noted that the current research design is observational in nature and does not provide evidence that prenatal stress causes increased plasticity. One experiment, done in rodents, has documented such causal effects in that prairie voles randomly assigned to a prenatal stress condition were more sensitive to postnatal parenting quality in terms of their later stress reactivity than voles not prenatally stressed (Hartman, Freeman, Bales, & Belsky, 2018). However, this study is in need of replication and it is unclear whether such results translate to humans. Therefore, future studies should endeavor to illuminate whether prenatal stress causes increased plasticity, using experimental designs in both humans and animal models. Another important limitation that should be highlighted for the current investigation is that it cannot rule out the presence of gene-environment correlations. Thus,

more work is needed to determine what role genetics may play in these relations.

Whatever its real and acknowledged limits, the research reported herein suggests that prenatal stress may program increased developmental plasticity when such stress is truly extreme, as revealed in our main analyses and the post hoc ones. Thus, extremely high levels of prenatal stress may induce greater plasticity while moderate levels of prenatal stress may actually reduce plasticity, maintaining developmental canalization rather than reregulating it. If nothing else, these unexpected findings call attention to the need to distinguish very high from just high levels of prenatal stress, at least when seeking to illuminate its potential effects on postnatal developmental plasticity.

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