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RESEARCH ARTICLE

Maternal prenatal depression is associated with dysregulation over the first five years of life moderated by child polygenic risk for comorbid psychiatric problems

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Abstract

Dysregulation is a combination of emotion, behavior, and attention problems associated with lifelong psychiatric comorbidity. There is evidence for the stability of dysregulation from childhood to adulthood, which would be more fully characterized by determining the likely stability from infancy to childhood. Early origins of dysregulation can further be validated and contextualized in association with environmental and biological factors, such as prenatal stress and polygenic risk scores (PRS) for overlapping child psychiatric problems. We aimed to determine trajectories of dysregulation from 3 months to 5 years ($N = 582$) in association with maternal prenatal depression moderated by multiple child PRS ($N = 232$ pairs with available PRS data) in a prenatal cohort. Mothers reported depression symptoms at 24–26 weeks' gestation and child dysregulation at 3, 6, 18, 36, 48, and 60 months. The PRS were for major depressive disorder, attention deficit hyperactivity disorder, cross disorder, and childhood psychiatric problems. Covariates were biological sex, maternal education, and postnatal depression. Analyses included latent classes and regression. Two dysregulation trajectories emerged: persistently *low dysregulation* (94%), and increasingly *high dysregulation* (6%). Stable dysregulation emerged at 18 months. High dysregulation was associated with maternal prenatal depression, moderated by PRS for child comorbid psychiatric problems. Males were at greater risk of high dysregulation.

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KEYWORDS
child dysregulation, child psychiatric comorbidity, infant dysregulation, maternal prenatal depression, maternal prenatal stress, polygenic risk scores

1 | INTRODUCTION

Childhood dysregulation has been defined as a combination of emotion, behavior, and attention problems associated with lifelong psychiatric comorbidity (Holtmann et al., 2011; Meyer et al., 2009). In infancy, dysregulation pertains to reactive forms of behavior, whereas in early childhood it encompasses more advanced cognitive–behavioral functions (Montroy et al., 2016). Early indicators of dysregulation in infancy include persistent crying, sleeping and feeding problems, and being difficult to soothe, which are a cluster of symptoms sometimes referred to as a difficult temperament (Briggs-Gowan & Carter, 2007; Samdan et al., 2020). Indicators of dysregulation in childhood include difficulties regulating thoughts, emotions, and behaviors, which manifest as comorbid depression, anxiety, and aggressive or impulsive behavior problems (Althoff et al., 2010; Degangi et al., 2000; Kim et al., 2012). There is evidence for a stable, more severe form of dysregulation from childhood to early adulthood that has been associated with comorbid problems throughout the life span such as mood and personality disorders, substance abuse, and suicidal ideation (Althoff et al., 2010; Holtmann et al., 2011). Evidence for trajectories from infancy to early childhood would fill a gap in knowledge regarding the early origins, onset, and stability of dysregulation in early childhood; inform strategies for early identification and intervention; and help mitigate risk for the development of childhood psychiatric comorbidity.

Regulatory problems in infancy typically include abnormal patterns of crying, sleeping, and feeding at 6 months to 2.5 years of age, while dysregulation from 4 to 9.5 years of age includes symptoms of behavioral and emotional difficulties that can be measured using the Strengths and Difficulties Questionnaires (SDQ) (Muris et al., 2003). A developmental trajectory of dysregulation can be ascertained as early as age 3 years (Montroy et al., 2016), while its stability has been established as of age 4 years (Winsper & Wolke, 2014). Montroy et al. (2016) identified three groups of children aged 3–7 years, ranging from *early developers* (i.e., early to develop regulation skills, and the least dysregulated) to *later developers* (i.e., later to develop regulation skills, and the most dysregulated). In this group, the biologically female children and children whose mothers had higher education backgrounds were the least dysregulated (i.e., developed the best regulation skills). Winsper and Wolke (2014) identified four dysregulation groups from age 4 to 9.5 years, ranging from *low* to *very high* dysregulation, with trajectories that were strongly associated with regulatory problems first observed in infancy. In the current study, we aimed to provide evidence for the developmental origins and trajectory of dysregulation beginning in infancy and extending over the first 5 years of life.

Behavioral and physiological dysregulation in infancy and childhood has been associated with maternal prenatal stress, as measured in a variety of ways (e.g., maternal anxiety and depression symptoms, cortisol) (Hartman & Belsky, 2021). Prenatal stress is theorized to influence child neurodevelopment through prenatal programing, where environmental and biological factors interact to shape fetal development and offspring susceptibility to disease (Monk et al., 2019; Szekely et al., 2020) through changes in fetal–placental biology and gene expression (Monk et al., 2016; Moog et al., 2017; Van den Bergh et al., 2020). The most common forms of prenatal stress are symptoms of depression and anxiety (Monk et al., 2019)—although highly comorbid (Barker et al., 2011), each has been separately associated with a wide range of childhood outcomes (Kochanska et al., 2011, 2009; Sandman et al., 2011). During pregnancy, 8%–12% of women meet criteria for major depression (Melville et al., 2010), and 30% report subclinical depressive symptoms (Bowen & Muhajarine, 2006; Records & Rice, 2007), making depression the most frequent prenatal complication (Committee on Obstetric Practice, 2018).

The unique influence of maternal prenatal depression on child outcomes is difficult to disentangle from that of the postnatal environment including maternal postnatal depression. However, based on sophisticated statistical modeling and analyses, prenatal depression has been prospectively associated with child outcomes after controlling for postnatal depression (Barker et al., 2011; Lahti et al., 2017). In one example, Pearson et al. (2013) found that the association between maternal postnatal depression and child depression was moderated by lower maternal education level, whereas the association between maternal prenatal depression and child depression was not, and remained significant regardless of the presence or absence of maternal postnatal depression.

Genetic risk is one possible biological factor that can moderate the influence of prenatal stress on offspring development (Abbott et al., 2018). Genome-wide genotyping of common single-nucleotide polymorphisms (SNPs) has made it possible to quantify the polygenic risk of human complex traits, including common and comorbid psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Fullerton & Nurnberger, 2019). Although individual SNPs typically only have a small effect and limited predictive power, a considerable amount of heritability can be explained by aggregating the effect of individual SNPs across the genome, thereby providing an estimate of genetic liability to a given trait (Choi et al., 2020). These aggregate polygenic risk scores (PRS) are calculated by computing the sum of risk alleles an individual has weighted by the risk allele effect size estimated previously by a separate genome-wide association study (GWAS) of the trait in question. For example, Jermy et al. (2022) estimated individuals' genetic liability for major depressive disorder (MDD) by computing their PRS for MDD using previously published GWAS summary statistics for this disorder (Wray et al., 2018) to derive the list of associated risk alleles and their corresponding effect sizes. They summed the

individual risk alleles multiplied by their effect size in each individual. Depending on the researchers' preference regarding the strength of the effect of disease-associated alleles, PRS can be computed at multiple *p*-value thresholds. In sum, PRS capture aggregate effects of common genetic variants that individually contribute modest effects and together form scores associated with specific psychiatric disorders, enabling researchers to identify genetic susceptibility or risk for given traits and disorders and to make comparisons across individuals based on these factors (Chen et al., 2018).

With genetic correlations among most psychiatric disorders averaging .41 (Anttila et al., 2018), PRS for specific disorders are also likely to predict other psychiatric symptoms and disorders. Although PRS capture main effects of common DNA variants on a given trait, interactions between PRS and environmental stressors have also been found (Ursini et al., 2018). For example, the probability of schizophrenia from the schizophrenia PRS is more than five times greater when associated with complications during pregnancy (Ursini et al., 2018). PRS have been generated for distinct disorders such as MDD (i.e., MDD PRS) (Howard et al., 2019) and attention deficit hyperactivity disorder (ADHD) (i.e., ADHD PRS) (Demontis et al., 2019). Other PRS that are likely to be associated with child dysregulation are those that predict multiple or comorbid disorders, for example, the Cross Disorder PRS from the Psychiatric Genomics Consortium (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) that captures overlapping genetic risk for five major psychiatric disorders (i.e., autism spectrum disorder, ADHD, schizophrenia, bipolar disorder, and MDD). Additionally, the Total Problems PRS from the EArly Genetics and Lifecourse Epidemiology (EAGLE) Consortium (Neumann, 2019; Neumann et al., 2022) captures overlapping genetic risk for childhood psychiatric problems (i.e., symptoms of ADHD, anxiety, depression, and insomnia). Despite their clear pertinence, PRS have yet to be associated with measures of infant or child dysregulation.

In the present study, we aimed to determine (1) trajectories of dysregulation from 3 months to 5 years of age and (2) associations between maternal prenatal depression symptoms and our trajectories of dysregulation, moderated by child PRS (i.e., MDD, ADHD, Cross Disorder, and Total Problems PRS). Our hypothesis was that greater maternal prenatal depression symptoms would be associated with a trajectory of higher levels of dysregulation from 3 months to 5 years, moderated by higher child PRS.

2 | METHOD

2.1 | Participants

The participants were mother–child dyads from the Maternal Adversity, Vulnerability, and Neurodevelopment (MAVAN) project, a Canadian community-based birth cohort based in Montreal, Quebec, and Hamilton, Ontario (see Babineau et al., 2015; O'Donnell et al., 2014). Eligibility criteria were maternal age ≥18 years at delivery and singleton gestation (≥37 weeks). The present study included 582 mother–child pairs for whom at least one measure of child dysregulation was available from 3 to 60 months of age, in order to determine trajectories of dysregulation. The analyses of PRS included 232 pairs with available child PRS data. By 60 months of age, missing data was attributed to 133 dropouts (i.e., 77% retention rate), 40 cases of incomplete prenatal data, 67 cases of missing maternal postnatal depression symptom data, one case removed due to participant reliability issues, and 109 cases with missing PRS data. Missing PRS data was in part due to unsuccessful genotyping, and insufficient funding for obtaining complete genetic information from all of the participants. When comparing the participants who left the study to those who remained, the mothers did not differ on measures of age at delivery, pre- or postnatal depression symptoms, or education, and children did not differ on measures of dysregulation ($p > .05$). Further, when comparing the participants in the final analysis with PRS ($N = 232$), they did not differ from the participants in the original sample ($N = 582$) on demographic variables or dysregulation scores ($p < .05$) (see Supplemental Table S1).

2.2 | Measures

2.2.1 | Prenatal depression symptoms

The Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) is a 20-item self-report measure of depressive symptomatology validated for pregnancy (Sandman et al., 2011), and was completed at 24–26 weeks' gestation. Scores were centered. The CES-D was used as a continuous measure of maternal prenatal depression symptoms.

2.2.2 | Child PRS

Genome-wide genotyping, imputation strategies, and quality control procedures for the MAVAN were as previously described (Chen et al., 2018; Silveira et al., 2017). DNA was extracted from buccal epithelial cells and analyzed using the PsychChip and PsychArray (Illumina) genotyping platforms. Only SNPs shared across the two platforms were retained for further analysis. In line with best practices, QC steps included sample call rate (retained <95%), minor allele frequency (retained ≥1%), deviations from Hardy–Weinberg equilibrium (retained if $p < 10^{-13}$), samples' heterozygosity rate, biological sex estimate, and cryptic relatedness (identity-by-descent) between samples. Data were imputed to the HRC 1.1 reference panel using the Sanger Imputation Service (McCarthy & Haplotyde Reference Consortium, 2016). SNPs with a minor allele frequency below 1% or imputation quality metric (R^2) below .80 were excluded (for more detailed method descriptions, please see Garg et al., 2018; O'Donnell et al., 2014).

As previously described, PRS are calculated by computing the sum of risk alleles in a given individual, weighted by the risk allele effect size estimated from the GWAS for the specific disorder(s) of interest. The strength of the effect of disease-associated alleles can be computed at different *p*-value thresholds; we chose .0001, .001, .01, .05, .1, .2, .3, .4, and .5 (Neumann, 2019; Neumann et al., 2022). Our first three PRS were computed using the genome-wide mega-analysis results from the Psychiatric Genomics Consortium, specifically for

MDD (Ripke et al., 2013), ADHD (Demontis et al., 2019), and Cross Disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). The MDD PRS included genetic variants based on 246,363 adults diagnosed with MDD as compared to 561,190 comparison participants (Howard et al., 2019). The ADHD PRS included genetic variants based on 20,183 children and adults diagnosed with ADHD and 35,191 comparison participants (Demontis et al., 2019). The Cross Disorder PRS included genetic variants for five major psychiatric disorders (i.e., autism spectrum disorder, ADHD, schizophrenia, bipolar disorder, MDD) in 33,332 adult cases as compared to 27,888 comparison participants (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Our fourth and final PRS was computed from the EAGLE Consortium for Total Problems (Neumann, 2019; Neumann et al., 2022). The Total Problems PRS included genetic variants associated with ratings of ADHD, anxiety, depression, and insomnia from 29,446 children ages 5–16 years (Neumann, 2019; Neumann et al., 2022).

2.2.3 | Dysregulation

Infant dysregulation at 3 and 6 months

The Infant Behavior Questionnaire-Revised (IBQ-R) (Gartstein & Rothbart, 2003) was completed by mothers at 3 and 6 months postnatal. Gartstein and Rothbart (2003) reported three factors in the IBQ-R: Negative Emotionality, Surgency-Extraversion, and Regulation (*low regulation* was interpreted as *high dysregulation* in our study) (Gartstein, personal communication, May 15, 2012). The Regulation factor included five subscales (Smiling/Laughter, Low-Intensity Pleasure, Cuddliness/Affiliation, Duration of Orienting, and Soothability) standardized and aggregated to create dysregulation scores at 3 and 6 months. Given that the dysregulation factor was composed of multiple subscales, testing the factor score reduced multiple testing and the chance of Type 1 error.

Early childhood dysregulation at 18 and 36 months

The Early Childhood Behavior Questionnaire (ECBQ) (Putnam et al., 2006) is the upward extension of the IBQ-R and was completed by mothers at 18 and 36 months postnatal. Putnam et al. (2006) found that the ECBQ leads to the same three factors as the IBQ-R (i.e., Negative Emotionality, Surgency-Extraversion, and Regulation). Again, we only used the Regulation factor, which included eight subscales (Attention Shifting, Low-Intensity Pleasure, Cuddliness, Attention Focusing, Inhibitory Control, Perceptual Sensitivity, Sociability, and Soothability) standardized and aggregated to create dysregulation scores at 18 and 36 months. Again, testing the factor score reduced multiple testing and chance of Type 1 error. For more information on our use of the IBQ-R and ECBQ, please refer to Babineau et al. (2015).

Childhood dysregulation at 48 and 60 months

The Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2000), a measure of child behavior and symptomatology, was completed by mothers when their children were 48 and 60 months of age. The CBCL—Dysregulation Profile (CBCL-DP) (Althoff et al., 2010), based on three subscales (Attention Problems, Anxious/Depressed, and Aggressive Behavior), was standardized and aggregated to create dysregulation scores at 48 and 60 months.

2.2.4 | Covariates

Information for covariates was obtained from the Health and Well Being of Mothers and their Newborns (Kramer et al., 2009) questionnaire completed at 24–26 weeks' gestation. Potential confounds were chosen a priori from the literature, regardless of the findings from our univariate analysis, and included maternal age, self-reported race and ethnicity, partnership status, education, family income, postnatal depression symptoms and smoking, and infant birth weight and biological sex. When associated with both maternal prenatal depression symptoms and dysregulation using a threshold of $p < .05$, we adjusted for confounders as covariates. The covariates that were retained were infant biological sex, maternal education, and maternal postnatal depression symptoms. Maternal education was dichotomized as "mid/low education" (i.e., ≤high school, some college/trade, and college/trade graduate) and "high education" (≥university graduate), given that the sample was evenly split between these two groups (see Table 1). Maternal depression symptoms were self-reported on the CES-D at 12 months postnatal and assessed as a continuous variable.

The population structure of the MAVAN was evaluated using principal component analysis of all autosomal SNPs that passed quality control (Price et al., 2006; Silveira et al., 2017). The first three principal components derived were used as covariates in the PRS analyses, including self-reported race and ethnicity, as these were proven to be the most informative of the population structure underlying the MAVAN cohort (Silveira et al., 2017).

2.3 | Statistical analyses

2.3.1 | Latent class analysis for dysregulation trajectories

Six time points of dysregulation (i.e., 3, 6, 18, 36, 48, and 60 months) were examined in a correlation matrix. Possible latent classes, referred to as *trajectories* (i.e., groups), were based on measures of dysregulation from 3 to 60 months ($N = 582$) and fitted with the Extended Mixed Models Using Latent Classes and Latent Processes (LCMM) (Proust-Lima et al., 2017) package in R (R Core Team, 2017). The model fit was compared across two, three, or four trajectories and the model with lowest Bayesian Information Criteria (BIC) was chosen (Schwarz, 1978). We tested for a linear, quadratic, or cubic model (i.e., dysregulation over time was allowed to change linearly, quadratically, or cubically). We also conducted a Chi-square test of independence to explore any group differences by biological sex.

To further validate dysregulation trajectories extracted from three instruments, we created an Item Response Theory trajectory of dysregulation (Dysregulation-IRT). Dysregulation-IRT included items from the IBQ-R, ECBQ, and CBCL-DP that were most comparable across

TABLE 1 Descriptive statistics for MAVAN mother and child ($N = 582$ pairs)

	M (*SD*)	%
Maternal age at delivery	30.58 (5)	
In a partnership at delivery		94.8
Prenatal depression symptoms	12.44 (9.7)	
Prenatal CES-D ≥16		28.5
Education		
≤High school		10.7
Some college/trade		9
College/trade graduate		31.1
≥University graduate		49.2
Annual household income (CAD)		
<$15,000		6.8
$15,000 to <$30,000		12.6
$30,000 to <$50,000		20
$50,000 to <$80,000		24.2
≥80,000		36.4
Self-reported race and ethnicity		
Black or African American		4.4
East Indian		0.8
Hispanic		2.5
Non-Hispanic White		83.1
Other or more than one race		9.2
Infant biological sex—Female		46.2

Note: Maternal prenatal depression symptoms were measured on the Center for Epidemiologic Studies Depression Scale (CES-D).
Abbreviation: CAD, Canadian dollar.

measures (see Supplemental Table S2). A graduate student (Babineau, V.) and postdoctoral fellow (Szekely, E.) independently selected items that were similar across two or more instruments. Concordance was 74% and consensus was reached in cases of discordance. Good concordance between the original model and the Dysregulation-IRT model was established by correlation analyses, Chi-square tests, paired *t*-tests, and weighted Cohen's kappa (see Supplemental Material and Table S3).

2.3.2 | Regression analysis

We chose a categorical classification of dysregulation for our primary analysis based on previous studies that have also employed group- and trajectory-based models of dysregulation (Winsper & Wolke, 2014), contributing to research that characterizes a clinical range of dysregulation (Althoff et al., 2010; Kim et al., 2012).

Associations with a greater likelihood of being in the high dysregulation group (i.e., a group derived in our latent class analysis, see Section 3.1) were modeled from potential main effects of, and interactions between, prenatal depression symptoms and child PRS using the Latent Environmental and Genetic InTeraction (LEGIT) package in R (Jolicoeur-Martineau, Belsky, et al., 2019; Jolicoeur-Martineau, Wazana, et al., 2019). LEGIT was used to consider latent variables G and E within a G × E regression or logistic model. G was a weighted sum of genetic variants (i.e., PRS) and E was prenatal depression symptoms. For each LEGIT model that included a PRS variable, all *p*-value thresholds were tested. Testing was done by regressing each PRS with the outcome in a linear regression, while adjusting for covariates. The MDD and Cross Disorder PRS were evaluated at nine different *p*-value thresholds (.0001, .001, .01, .05, .1, .2, .3, .4, and .5) and the ADHD and Total Problems PRS were evaluated at seven different *p*-value thresholds (.0001, .001, .01, .05, .1, .2, and .5) (Silveira et al., 2017). For each PRS, the threshold that led to the highest log-likelihood was chosen.

As a first step, four logistic regression models were created to test for potential interactions between maternal prenatal depression symptoms and each of the PRS (i.e., MDD PRS, ADHD PRS, Cross Disorder PRS, and Total Problems PRS), in association with a greater probability of being in the high dysregulation group. As a second step, all four PRS (i.e., the MDD, ADHD, Cross Disorder, and Total Problems PRS) were included at their optimal threshold (i.e., the threshold initially found when only including an individual PRS). Variable selection was used to determine which of the four PRS to retain. The specific type of variable selection used was Least Absolute Shrinkage and Selection Operator (LASSO) (Kukreja et al., 2006). This allowed for a more nuanced understanding of the separate contribution of each PRS in association with dysregulation, and a more powerful model given the inclusion of multiple PRS in the same model. In each logistic regression model, effect sizes were calculated using area under the curve (AUC), and in the regression models, effect sizes were calculated using coefficient of determination (R^2). The same procedures were repeated to validate our findings with the Dysregulation-IRT trajectories (see Supplemental Material).

2.3.3 | Post hoc regression analysis

Given the small sample size for the high dysregulation group determined by our latent class analysis (i.e., 6% of $N = 232$ was $n = 14$ mother–child pairs), we conducted a complementary post hoc regression analysis testing associations with dysregulation scores from 3 to 60 months as a single overall outcome variable that reflected the entire group of participants, that is, the full range of lowest to highest dysregulation scores. We followed the same regression methodology as previously described, including the first and second step in the regression analysis. The same procedures were repeated with Dysregulation-IRT (see Supplemental Material).

In both the primary and post hoc analyses, we used a repeated measure of dysregulation, meaning we had six measures of dysregulation including time points 3, 6, 18, 36, 48, and 60 months; to account for lon-

TABLE 2 Correlations of dysregulation at 3, 6, 18, 36, 48, and 60 months of age ($N = 582$)

	IBQ-R 3 months	IBQ-R 6 months	ECBQ 18 months	ECBQ 36 months	CBCL-DP 48 months	CBCL-DP 60 months
IBQ-R 3 months						
IBQ-R 6 months	.56***					
ECBQ 18 months	.40***	.40***				
ECBQ 36 months	.30***	.33***	.57***			
CBCL-DP 48 months	.06	.17***	.25***	.36***		
CBCL-DP 60 months	.02	.13*	.25***	.27***	.61***	

Abbreviations: ECBQ, Early Childhood Behavior Questionnaire; CBCL-DP, Child Behavior Checklist—Dysregulation Profile; IBQ-R, Infant Behavior Questionnaire—Revised.
*$p < .05$; **$p < .01$; ***$p < .001$.

gitudinality, we reshaped the data into long-form so that we had only one dysregulation score per child, a time variable that indicated what time point the score was from. Each dysregulation score referred to dysregulation in the long-form dataset. As prenatal depression was a continuous variable, all cases were used when PRS was also available. The post hoc analysis that relied on dysregulation as a continuous variable enabled us to better support findings from our primary analysis with the smaller sample size comprising the dysregulation group (6%).

3 | RESULTS

The participants' characteristics are presented in Table 1.

3.1 | Dysregulation trajectories

The dysregulation trajectory results include 582 children. Dysregulation scores were normally distributed across measures from 3 to 18 months and became gradually more skewed to the right from 36 to 60 months ($p < .01$). The correlation matrix revealed that 6-month dysregulation correlated with all subsequent time points, whereas 3-month dysregulation only correlated with measures up to and including 36-month dysregulation (see Table 2). The correlations were stronger between measures of dysregulation that were closer in time (e.g., 3 and 6 months) than distant (e.g., 6 and 60 months). The latent class analysis revealed a two-class model as the best fit (BIC: 4201.17, 4208.82, and 4222.36 for two-, three-, and four-class models, respectively; see Figure 1). Children labeled as being in the *low dysregulation* group (94%) remained persistently low on dysregulation over time. In contrast, those labeled as being in the *high dysregulation* group (6%) were initially low and became increasingly high on dysregulation over time. The dysregulation groups could be differentiated as of 18 months. More males than females (i.e., $n = 23$ vs. $n = 12$) were found in the high dysregulation group ($\chi^2(1) = 7.72$, $p < .01$). The Dysregulation-IRT trajectory analysis identified a similar two-class model (see Supplemental Figure S1).

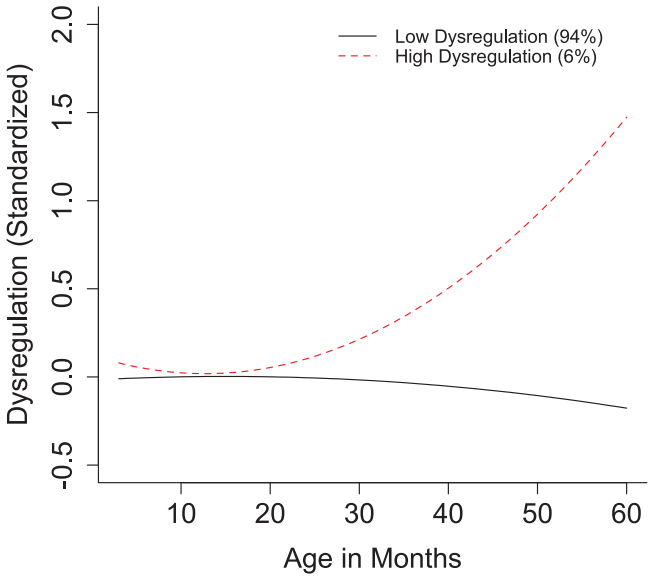


FIGURE 1 Trajectories of dysregulation from 3 to 60 months.

3.2 | Regression results—Probability of high dysregulation

The regression results include 232 pairs with available PRS data. Neither prenatal depression symptoms or PRS had a main effect on the probability of being in the high dysregulation group. Greater prenatal depression symptoms were associated with an increased probability of being in the high dysregulation group, moderated by higher Total Problems PRS (see Table 3; Figure 2). Prenatal depression symptoms did not interact with MDD, ADHD, or Cross Disorder PRS (see Table 3). Additionally, male sex was associated with an increased likelihood of being in the high dysregulation group (see Table 3). When comparing the separate contribution of the different PRS within the same model, only Total Problems PRS was associated with the probability of being in the high dysregulation group (see Table 3).

TABLE 3 Associations between maternal prenatal depression symptoms and probability of high dysregulation from 3 months to 5 years moderated by child PRS ($N = 232$)

	MDD PRS	ADHD PRS	Cross Disorder PRS	Total Problems PRS	Combined PRS
	ß	ß	ß	ß	ß
Intercept	−2.78	−2.84	−2.50	−3.16	−3.16
Covariates					
Sex—Male	0.67	0.68	0.73	1.16*	1.16*
Education—High	−1.36	−1.36	−1.42*	−1.21	−1.21
Postnatal depression	0.03	0.03	0.03	0.04	0.04
Predictors					
Genes (G)	0.80	−0.45	0.44	0.36	0.36
Prenatal depression (E)	0.03	0.03	0.30	0.07	0.07
G × E	−0.16	0.01	−0.07	0.65*	0.65*
AUC	.78	.77	.77	.82	.82

Note: The combined PRS model included all four PRS at their optimal thresholds, and only the Total Problems PRS was retained. Results reported are from regression models adjusted with covariates as follows: infant biological sex, maternal education, and maternal postnatal depression symptoms.
Abbreviations: ADHD, attention deficit hyperactivity disorder; AUC, area under the curve; MDD, major depressive disorder; PRS, polygenic risk scores.
*$p < .05$.

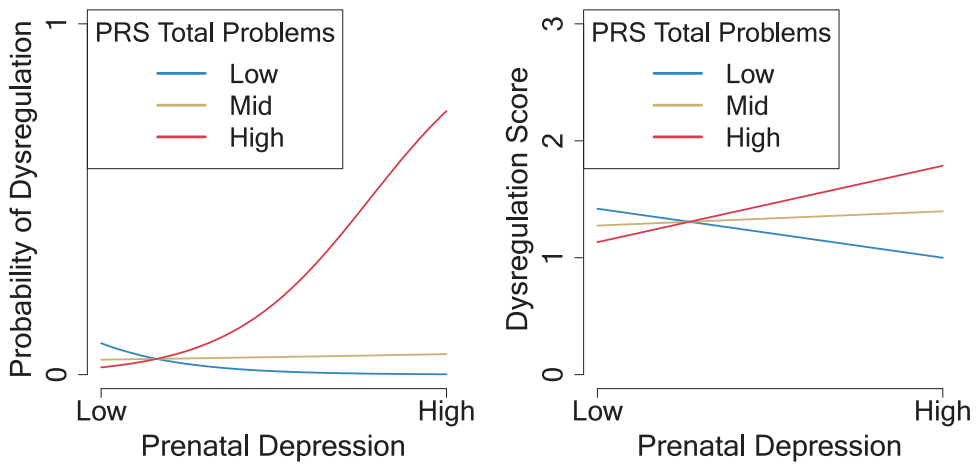


FIGURE 2 Associations between maternal prenatal depression and dysregulation from 3 months to 5 years of age moderated by child total problems polygenic risk scores. PRS, polygenic risk scores. Increased probability of being in the high dysregulation group is modeled on the left, and dysregulation in the overall sample is modeled on the right.

The results were only slightly different when predicting the probability of being in the high Dysregulation-IRT group (see Supplemental Material). Increased prenatal depression symptoms were associated with the increased likelihood of being in the high Dysregulation-IRT group, moderated by higher MDD PRS (i.e., not Total Problems PRS, as would have been expected) (see Supplemental Table S4). Otherwise, the results were similar to the initial dysregulation trajectory models (i.e., comparisons between Tables 3 and Supplemental Table S3). Additionally, there was only a 6% chance of being categorized into a different dysregulation trajectory when using Dysregulation-IRT items ($t(495) = 8.71, p < .001$) (see Supplemental Material).

3.3 | Post hoc regression results

In a post hoc analysis, maternal prenatal depression symptoms and MDD, ADHD, and Total Problems PRS had main effects on overall dysregulation scores from 3 to 60 months (see Table 4). Consistent with our primary analyses, we found that greater prenatal depression symptoms, each in separate models, were associated with greater dysregulation scores from 3 to 60 months, moderated by higher MDD, ADHD, and Total Problems PRS (see Table 4; Figure 2). As covariates, exposure to greater postnatal depression was also associated with greater dysregulation, and being biologically male (see Table 4). In a

TABLE 4 Post hoc associations between maternal prenatal depression symptoms and dysregulation from 3 months to 5 years moderated by child PRS ($N = 232$)

	MDD PRS	ADHD PRS	Cross Disorder PRS	Total Problems PRS	Combined PRS
	ß	ß	ß	ß	ß
Intercept	1.87	1.87	1.88	1.84	1.88
Covariates					
Sex—Male	0.06*	0.06*	0.06*	0.08**	0.06*
Education—High	−0.07	−0.06	−0.07	−0.07	−0.07
Postnatal depression	0.01***	0.01***	0.01***	0.01***	0.01***
Predictors					
Genes (G)	0.07**	0.07**	−0.03	−0.08***	0.12***
Prenatal depression (E)	0.00*	0.00*	0.00	0.00*	0.00*
G × E	−0.00**	−0.01***	0.00	0.01***	−0.01**
PRS weights					
MDD PRS					0.66***
ADHD PRS					
Cross disorder PRS					−0.34*
Total problems PRS					
R^2	.82	.83	.82	.83	.82

Note: Results reported are from regression models adjusted with covariates as follows: infant biological sex, maternal education, and maternal postnatal depression symptoms.
Abbreviations: ADHD, attention deficit hyperactivity disorder; MDD, major depressive disorder; PRS, polygenic risk scores.
*$p < .05$; **$p < .01$; ***$p < .001$.

combined PRS model, increased prenatal depression symptoms were associated with greater dysregulation from 3 to 60 months, moderated by the Genetic factor (G) (see Table 4). In the best fit model, G was composed of the weighted sum of the MDD PRS (0.66) and the Cross Disorder PRS (−0.33). The results were similar when predicting *Dysregulation-IRT* as a continuous measure (i.e., comparisons between Tables 4 and Supplemental Table S5).

4 | DISCUSSION

This is a first study of the trajectory of early childhood dysregulation that includes measures as early as infancy. We validated the stability of our trajectories by demonstrating that they were associated with prenatal and genetic risk factors previously associated with the child's dysregulation and psychiatric comorbidity. Specifically, we demonstrated that the development of dysregulation over the first 5 years of life was associated with exposure to greater maternal prenatal depression, moderated by child polygenic risk for comorbid psychiatric problems. A dysregulation pattern became apparent and remained stable from 18 months to 5 years. Our findings are strengthened by complementary mother and child measures spanning the pre- to postnatal period, including repeat measures of dysregulation. These findings were corroborated by and extended our previous work (Babineau et al., 2015) in which we found that maternal prenatal depression interacted with child *5-HTTLPR* genotype in association with dysregulation from 3 months to 3 years of age. In the present study, we added a more complete characterization of genetic risk using multiple PRS, and measures of dysregulation extending up to 5 years of age.

We found two distinct developmental trajectories of dysregulation from 3 months to 5 years of age—children with stable low dysregulation, and children with stable increasingly high dysregulation. One interpretation is that children with low dysregulation might have better regulation skills than children with high dysregulation who are at increased risk for developing comorbid psychopathology. The children in the high dysregulation group accounted for 6% of the participants, which was consistent with previous estimates of dysregulation present in 4%–11% of children in community-based studies (Althoff et al., 2006; Kim et al., 2012). Our construct of dysregulation trajectories was further validated with item response theory and by a replication of the main findings in complementary analyses. Our findings are most consistent with Winsper and Wolke's (2014) findings with dysregulation trajectories from age 4 to 9.5 years, including one trajectory of high dysregulation scores (4% of children) compared to two trajectories demonstrating increased capacity to regulate (nearly 80% of children). Higher dysregulation scores strongly associated with regulatory problems that had first been observed in infancy (Winsper & Wolke, 2014). Our findings are also consistent with Wanless et al. (2016) who found two trajectories of child dysregulation between 3.5 and 6 years of age, although their results differed as one group demonstrated greater developmental gains across age and the second group remained dys-

regulated with slight gains in capacity to regulate over time. Similarly, Montroy et al. (2016) found that early childhood regulation, an opposite construct to dysregulation, either increased or remained the same over time from age 3 to 7 years (i.e., presumably low or decreasing dysregulation as they aged). Comparisons between our study and previous studies are limited, as trajectory studies of dysregulation have only been mapped as early as 3 years of age. Nevertheless, comparisons are still possible especially extending from 3 to 5 years of age, that is, the upper age limit of children in our study. Despite possible comparisons across studies, questions concerning the stability of early childhood regulation and dysregulation remain. For example, at what point, if any, in infancy to early childhood or throughout childhood might dysregulation be more likely to peak, remain stable, decrease, or fluctuate up and down within the same child. Any such questions must be considered with regard to multiple environmental factors including maternal postnatal mood and parenting quality (Hayes et al., 2013), and social determinants of health such as race, ethnicity, and socioeconomic status (Babineau et al., 2022).

The shape of our trajectories indicated that the two groups followed a similar course between 3 and 18 months of age, with marked differences emerging as of 18 months—different trajectory types may potentially have implications for intervention. A possible interpretation for trajectories diverging at 18 months is that this is the beginning or onset of the stability of a dysregulation profile. This is also supported in the weaker correlation of the dysregulation scores within the earliest time points assessed. Although dysregulation can present prior to 18 months in certain children, a distinct, stable, or more severe pattern might only emerge later in a small subset of children at increased risk for the development of comorbid psychopathology. This would also be consistent with evidence that infant temperament is relatively unstable over the first year of life, switching from "difficult to easy" or "easy to difficult" as a result of interactions with the primary caregiver (Washington et al., 1986). For example, infants with an initially difficult temperament may be more modestly dysregulated, or have an attuned and sensitive caregiver with whom the interaction can lead to an attenuation of dysregulation over time, whereas others may be too dysregulated or experience less downregulation from the caregiving match (Washington et al., 1986). Screening and identification of dysregulation assessed at this malleable period of development may be warranted to indicate the need for intervention focused on promoting early childhood self-regulation skills. Implications of two different trajectory types include opportunities for screening and focused interventions designed for the child or parent–child dyad, based on the presence of symptoms of dysregulation. Empirically supported for enhancing self-regulation in early childhood, Attachment and Biobehavioral Catch-up (ABC) (Dozier et al., 2011) is a brief parenting intervention designed to help parents of high-risk infants to increase children's ability to engage in self-regulation, with evidence for child outcomes including enhanced capacities in emotion expression, executive function, and inhibitory control. Outcomes enhanced by ABC reflect areas to be addressed in the dysregulation profile, including a combination of emotion, attention, and behavior problems (Holtmann et al., 2011; Meyer et al., 2009).

Our findings are informed by two complementary approaches to modeling the development of dysregulation. In the trajectory models, maternal prenatal depression symptoms were association with the high dysregulation group, moderated by the Total Problems PRS. In the post hoc analysis, greater maternal prenatal depression symptoms were associated with increased scores of dysregulation in the overall group of participants, moderated by MDD, ADHD, and Total Problems PRS in three separate models—these models did not specifically reflect those children who remained consistently dysregulated over time, but rather reflected all of the children including those with low, transient, and high dysregulation over time. One interpretation of these findings is that our primary trajectory models allowed us to identify specifically those children with more severe and enduring dysregulation, that is, the beginning of complex comorbid psychopathology more likely to persist over time. In comparison, the findings based on dysregulation in the overall group of participants may have more closely aligned with the beginning of less complex forms of dysregulation evident among those with ADHD and depression, with Total Problems PRS remaining significant as this group included all the participants and ranged from the lowest to highest scores of dysregulation. As for Cross Disorder PRS, we interpret the null findings in the context of the prominent inclusion of autism spectrum disorder, schizophrenia, and bipolar disorder, all conditions not commonly associated with our characterization of dysregulation that is likely better accounted for by Total Problems PRS with the inclusion of attention, anxiety, and depression problems. Furthermore, the Cross Disorder PRS was based on data from adults only, whereas the Total Problems PRS was based on data from children only. Overall, we interpret these findings as support for our hypothesis that the association between exposure to maternal prenatal depression symptoms and the development of childhood dysregulation over the first 5 years of life is moderated by child polygenic risk for comorbid psychiatric problems.

Maternal prenatal mood symptoms have consistently been associated with altered child neurodevelopment and increased risk for psychopathology (Babineau et al., 2022; Monk et al., 2019), and uncertainty remains regarding the biological mechanisms that lead to individual differences in children's response to prenatal distress (O'Donnell et al., 2017). Many potential pathways have been identified within and outside of the placenta, including the hypothalamic–pituitary–adrenal axis, immune system, and microbiome (Monk et al., 2019). Genetic and epigenetic mechanisms suggest a role for differential responses to stress by genotype (Abbott et al., 2018). In the current study, the influence of maternal prenatal depression symptoms in the early development of dysregulation was moderated by child polygenic risk for comorbid psychiatric problems. Altered development of neurobehavioral systems (e.g., autonomic nervous system) involved in emotion and behavior regulation are associated with functional changes in brain networks that modulate regulatory responses to stress, and may explain, in part, the outcome of increased risk for psychopathology (Booij et al., 2015). Longitudinal prenatal cohort studies with multiple genetic factors in interaction with the environment allow us to better characterize the role of the various systems involved in the development of psychiatric disorders (Booij et al., 2015). Our

findings add to the literature on developmental origins of health and disease (DOHaD) (Monk et al., 2019) by providing evidence for an association between maternal prenatal depression and the development of dysregulation, moderated by multiple genetic factors (i.e., Total Problems PRS), and suggest biological mechanisms of transmission programed in utero through genetic susceptibility.

The covariates we retained in our final models were child's biological sex, maternal education, and maternal postnatal depression symptoms. The children who were biologically male were at significantly greater risk of being in the high dysregulation group when exposed to prenatal depression symptoms. Concordantly, two thirds of the children in the high dysregulation group were biologically male. Our findings of biological sex differences can in part be interpreted alongside the evidence that males exposed to maternal stress in utero are at greater risk of developing neurodevelopmental disorders (Bale, 2016). Our findings are also consistent with Montroy et al. (2016) who found that females had more rapid beneficial gains along developmental trajectories that indicated the acquisition of regulation skills. They are additionally corroborated by the higher prevalence in males of ADHD (Arnett et al., 2015) and oppositional defiant disorder (Demmer et al., 2017), disorders that are significantly associated with dysregulation. Similarly, preschool irritability has been found to predict ADHD at 9 years of age, also in males (Dougherty et al., 2015).

Maternal postnatal depression symptoms were also a significant covariate, but only in the post hoc analyses. An association between maternal depression and child outcomes has been found throughout the life span (Murray et al., 2015), with exposure to prenatal depression possibly leading to increased susceptibility to postnatal depression (Hartman & Belsky, 2018). However, the mechanisms or pathways through which pre- and postnatal maternal depression exert influence on offspring outcomes are likely to differ (Pearson et al., 2013). Prenatal depression symptoms likely operate through biological mechanisms of transmission, as indicated by our main findings and post hoc analysis, and similar to and supported by extent DOHaD literature (Monk et al., 2019). Conversely, postnatal depression symptoms are more likely to operate through day-to-day interactions, such as maternal sensitivity and care, maternal modeling of mood and self-regulation, and dynamics between mother and child during interactions that lead to a shared mood (Pearson et al., 2013). In our post hoc models only, increased postnatal depression was a significant covariate in association with greater dysregulation in the overall group of children. In contrast, postnatal depression was not significant in our primary analyses, focused on a subset of children in the trajectory group of high dysregulation from 18 months to 5 years. We interpret these findings as indicating that both the main and post hoc analyses provide support for the influence of maternal prenatal depression moderated by child PRS in the development of early dysregulation, with in utero biological mechanisms at play. However, postnatal depression may play more of a role in the overall group of children that encompasses those with increased capacity to regulate, and a range of low to higher dysregulation.

Our findings are to be interpreted within the context of certain limitations. While the ECBQ is the upward extension of the IBQ-R, both of which are measures of early childhood temperament, the CBCL is a separate measure of childhood behavioral problems (Kim et al., 2012). All three measures are strongly associated (Gartstein & Bateman, 2008; Gartstein et al., 2012) and share important characteristics, as they are parent reports, include similar questions on child behavior including observed frequency of behavior, and refer to behavior over a similar time period (i.e., the preceding weeks). Using different measures to assess the same construct at different ages is seen in cognitive and academic testing. For example, in determining a child's intellectual ability, subdomains and full scales can be compared from one test to another, and functioning can be assessed over time at different stages of development (Niileksela & Reynolds, 2019). Although we did not have the Childhood Behavior Questionnaire (CBQ) available (ages 3–7 years) (Rothbart et al., 2001), we suggest that the IBQ-R and ECBQ capture the early manifestation of dysregulation that is later measured by CBCL-DP. Dysregulation appears to shift from a reactive form in infancy to a more advanced cognitive–behavioral form in childhood that includes executive functions (Montroy et al., 2016; Winsper & Wolke, 2014), and the CBQ, SDQ, and CBCL were each developed to include developmentally appropriate items of regulation (Achenbach & Rescorla, 2000; Muris et al., 2003; Rothbart et al., 2001). We provide evidence that correlations over time among the IBQ-R, ECBQ, and CBCL-DP were stronger by age cluster, with the weakest correlations between the youngest (3 months) and oldest ages clusters (48 and 60 months). We additionally address this limitation with a model of the dysregulation trajectories that removed nonoverlapping items (Dysregulation-IRT model) (see Appendix S2) and is similarly associated with child polygenic risk factors and maternal prenatal depression symptoms.

Additional limitations of this study included our use of maternal report measures for dysregulation and perinatal mood, which could have led to shared method variance (Atella et al., 2003). Nevertheless, the questionnaires allowed for a longer observation period, multiple time points with repeated measures, and a reduction of bias given the recent occurring behaviors reported (Gartstein & Rothbart, 2003). The absence of additional caregiver reported measures, such as father report, is also an unfortunate limitation of our study design. We do not know whether all gestational parents identified as mothers as we did not ask them whether they had a preference in this regard nor did we ask them about gender identify. Another limitation is our modest number of participants. We used a recently developed statistical method (i.e., LEGIT) that enabled the simultaneous probing of interactions between multiple genes and environmental factors even within a relatively small number of participants, which reduced multiple testing and increased our detection power (Jolicoeur-Martineau, Belsky, et al., 2019; Jolicoeur-Martineau, Wazana, et al., 2019). A final limitation is that the finding that dysregulation diverged at 18 months of age may have been the consequence of a small number of participants and reliance on a low-risk community-based population. Although some children began to show dysregulation as early as 3 months of age, the divergence of the two groups was not apparent on average until 18 months. The use of a small low-risk population to study the early emergence of dysregulation may have obscured the average point in time at which certain children begin to develop a dysregulation profile,

which may have been better captured among children with clinical diagnoses.

Although measurement time points of the MAVAN extend throughout school age, the purpose of the current study was to investigate dysregulation from infancy to early childhood. Future investigations are underway to explore dysregulation throughout childhood with the use of additional measure such as interviewer-based psychiatric assessments to determine whether infant to early childhood dysregulation might then predict school age psychiatric symptoms and disorders.

4.1 | Implications

Our longitudinal study is a first attempt to identify the stability of dysregulation as early as infancy, and present findings support emerging stable dysregulation as of 18 months of age up to 5 years. We confirm that risk for dysregulation appears to stem from interactions between specific biological and early environmental influences (i.e., exposure to maternal prenatal stress and child polygenic risk for comorbid psychiatric problems). Effective treatments for reducing maternal prenatal depression symptoms include individual and group therapies based on principles from cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT) (Curry et al., 2019; Sona & Goodman, 2019), and treatments for enhancing infant and early childhood regulation abilities include ABC (Dozier et al., 2011). In accordance with previous reports on the association between childhood dysregulation and the development of lifelong comorbid psychopathology (Holtmann et al., 2011; Meyer et al., 2009), we support efforts for screening and early identification of dysregulation possible as early as 18 months, and clinical interventions to mitigate risk for the development of dysregulation beginning as early as the perinatal period.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data for this study are available from the corresponding author upon request.

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