HHS Public Access

Author manuscript

Child Dev. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

Child Dev. 2023 ; 94(6): 1595–1609. doi:10.1111/cdev.13938.

Association of Gestational Diabetes Mellitus and Perinatal Maternal Depression with Early Childhood Behavioral Problems: An Environmental Influences on Child Health Outcomes (ECHO) Study

Lauren C. Shuffrey, PhD[1], **Santiago Morales**[2], **Melanie H. Jacobson**[3], **Michelle Bosquet Enlow**[4,5], **Akhgar Ghassabian**[6], **Amy E. Margolis**[1], **Maristella Lucchini**[1], **Kecia N. Carroll**[7], **Rosa M. Crum**[8], **Dana Dabelea**[9], **Arielle Deutsch**[10], **William P. Fifer**[1,11], **Brandon Goldson**[7], **Christine W. Hockett**[10,12], **W. Alex Mason**[13], **Lisette T. Jacobson**[14], **Thomas G O'Connor**[15], **Nicolò Pini**[1], **Yael Rayport**[1], **Ayesha Sania**[1], **Leonardo Trasande**[16], **Rosalind J. Wright**[7], **Seonjoo Lee**[17], **Catherine Monk**[1,18,19,*] **on behalf of program collaborators for Environmental influences on Child Health Outcomes**

[1]Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, USA

[2]Department of Psychology, University of Southern California, Los Angeles, California, USA

[3]Department of Pediatrics, Division of Environmental Pediatrics, New York University School of Medicine, New York, New York, USA

[4]Department of Psychiatry and Behavioral Sciences, Boston Children's Hospital, Boston, Massachusetts, USA

[5]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA

[6]Department of Pediatrics, New York University School of Medicine, New York, New York, USA

[7]Icahn School of Medicine at Mount Sinai, New York, New York, USA

[8]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

[9]Lifecourse Epidemiology of Adiposity and Diabetes (LEAD) Center, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

[10]Avera Research Institute; Sioux Falls, South Dakota, USA

[11]Division of Developmental Neuroscience, New York State Psychiatric Institute

[12]Department of Pediatrics, University of South Dakota School of Medicine, Sioux Falls, South Dakota, USA

Correspondence: Lauren C. Shuffrey, PhD, Pardes Rm 4932, 1051 Riverside Drive, New York, NY 10032, lcg2129@cumc.columbia.edu.

*See Acknowledgments for full listing of collaborators

Analytic Code: The analytic code necessary to reproduce the analyses presented in this paper is not publicly accessible. Requests to access the analytic code should be directed to the ECHO Data Analysis Center, ECHO-DAC@rti.org.

Preregistration: The analyses presented here were not publicly preregistered.

[13]Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, Tennessee, USA

[14]Department of Population Health, Department of Obstetrics & Gynecology, University of Kansas School of Medicine, Wichita, Kansas, USA

[15]Departments of Psychiatry, Psychology, Neuroscience, and Obstetrics and Gynecology, University of Rochester, Rochester, New York, USA

[16]Department of Pediatrics, New York University Grossman School of Medicine, New York, New York, USA

[17]Mailman School of Public Health, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, USA

[18]Departments of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, New York, USA

[19]Division of Behavioral Medicine, New York State Psychiatric Institute, New York, New York, USA

Abstract

This study examined the association of gestational diabetes mellitus (GDM) and prenatal and postnatal maternal depressive symptoms with externalizing, internalizing, and autism spectrum problems on the Preschool Child Behavior Checklist (CBCL 1½−5) in 2,379 children aged 4.12±0.60 (48.4% female; 46.8% White; 22.8% Hispanic) in the National Institutes of Health Environmental influences on Child Health Outcomes (ECHO) Program. CBCL data were collected between 2009 and 2021. GDM (n=216) and prenatal and postnatal maternal depressive symptoms were each associated with increased child externalizing and internalizing problems. GDM was associated with increased autism behaviors only among children exposed to perinatal maternal depressive symptoms above the median level. Sex stratified analyses revealed an effect of GDM on child behavioral outcomes in males only.

A robust literature under the Developmental Origins of Health and Disease (DOHaD) framework has demonstrated the role of environmental exposures in shaping offspring life course neurodevelopmental outcomes through fetal programming mechanisms. Gestational diabetes mellitus (GDM), defined as diabetes that was not clearly present prior to pregnancy, but develops during gestation (American Diabetes, 2021), has been linked to both adverse perinatal maternal mental health and child neurodevelopmental outcomes (Cai et al., 2016; S. Chen, Zhao, Dalman, Karlsson, & Gardner, 2021; Delanerolle et al., 2021; Rowland & Wilson, 2021; Wilson et al., 2020). Prior research suggests an association between GDM with perinatal maternal depression (Delanerolle et al., 2021; Wilson et al., 2020). GDM and prenatal depression affect approximately 10% and 13% of women in the United States (U.S.), respectively. Each diagnosis is associated with an increased risk for neurodevelopmental sequalae in offspring mediated through independent or overlapping fetal programming mechanisms (Burlina, Dalfra, & Lapolla, 2019; Fraser & Lawlor, 2014; Shuffrey & Fifer, 2020). Additionally, maternal postpartum depression (PPD) is associated with behavioral dysregulation in offspring through postnatal maternal stress or caregiving related pathways (S. Chen et al., 2021; Goodman, 2019; Rowland & Wilson, 2021). Despite

the public health relevance, the impact of comorbid GDM and prenatal maternal depression or the potentially moderating role of postnatal maternal depression on child neurobehavioral outcomes has not been examined in a unified framework nor using a prospective cohort design.

Several large maternal cohort studies and subsequent meta-analyses have identified associations between *in utero* exposure to GDM and an increased risk for specific neurodevelopmental disorders (NDDs) in children. For example, *in utero* exposure to GDM has been associated with child autism spectrum disorder (ASD), with a pooled odds ratio (OR) of 1.42 (95% CI 1.22, 1.65) across 18 studies (Rowland & Wilson, 2021). However, results have been mixed when examining associations between *in utero* exposure to GDM and the prevalence of attention-deficit/hyperactivity disorder (ADHD) (S. Chen et al., 2021; Rowland & Wilson, 2021). In addition to specific NDDs, *in utero* exposure to GDM has been associated with variation in several other neurodevelopmental outcomes, including deficits or delays in auditory attention (Cai et al., 2016), explicit and recognition memory (DeBoer, Wewerka, Bauer, Georgieff, & Nelson, 2005; Nelson et al., 2000; Nelson, Wewerka, Borscheid, Deregnier, & Georgieff, 2003; Riggins, Miller, Bauer, Georgieff, & Nelson, 2009), sensorimotor systems (Ghassabian et al., 2016; Ornoy, Ratzon, Greenbaum, Wolf, & Dulitzky, 2001), and social processes (Krzeczkowski et al., 2019). Research focused on identifying biological pathways between GDM and neurodevelopmental sequalae in offspring has suggested epigenetic changes, altered maternal immune or hypothalamic-pituitary-adrenal (HPA) axis function, placental dysregulation, hormonal changes, or pathologic levels of glucose, lipids, or amino acids as possible fetal programming mechanisms (Edalat et al., 2013; Kong, Chen, Gissler, & Lavebratt, 2020; Money et al., 2018; Pantham, Aye, & Powell, 2015; Richardson & Carpenter, 2007).

GDM is also a risk factor for perinatal maternal depression, which can affect child neurobehavioral development through independent or overlapping fetal programming mechanisms *in utero* and altered caregiving behaviors in the postpartum. A recent meta-analysis reported that GDM was associated with increased depressive symptoms around the time of a GDM diagnosis (OR 2.08; 95% CI 1.42, 3.05), following a GDM diagnosis (OR 1.41; 95% CI 0.88, 2.25), and in the postpartum period (OR 1.59; 95% CI 1.26, 2.00) (Wilson et al., 2020). Other large, diverse cohort studies in the U.S. have identified comorbid GDM and prenatal maternal depression are associated with increased risk for postpartum depression (Shuffrey et al., 2022). Prenatal maternal depression is also associated with an increased risk for child ASD, ADHD (L. C. Chen et al., 2020; Rai et al., 2013; Wiggins et al., 2019), deficits in social processes (Leis, Heron, Stuart, & Mendelson, 2014; Madigan et al., 2018), and psychopathology (O'Donnell, Glover, Barker, & O'Connor, 2014). Similar to GDM, studies examining potential biological pathways underlying the associations between prenatal maternal depression and child neurobehavioral outcomes have demonstrated epigenetic changes and altered maternal immune system and HPA axis function as possible fetal programming mechanisms (Christian, Franco, Glaser, & Iams, 2009; Coussons-Read, Okun, & Nettles, 2007; Edalat et al., 2013; Money et al., 2018; Pantham et al., 2015; Richardson & Carpenter, 2007; Rogers et al., 2020). In the postpartum period, maternal depression can potentiate the effects of *in utero* exposure to GDM and depression through altered maternal parenting behaviors, impaired maternal-infant bonding,

or other postnatal pathways, potentially acting as an effect modifier (Goodman, 2019). For example, maternal major depressive disorder in the first year postpartum is associated with increased child behavior problems between 1.5 and 12 years of age (Bagner, Pettit, Lewinsohn, & Seeley, 2010).

GDM and perinatal maternal depression are frequently co-morbid, yet prior studies have not examined the interactive effects of these exposures on child neurobehavioral outcomes. Externalizing and internalizing behaviors are cross-cutting dimensions of several neurodevelopmental disorders. Externalizing behaviors are characterized by disruptive conduct, aggression, hyperactivity, and attentional problems whereas internalizing behaviors are characterized by depressive and anxiety symptoms, social withdrawal, and somatic complaints (Achenbach, Ivanova, Rescorla, Turner, & Althoff, 2016). One prior study has examined the role of GDM and postnatal maternal depression on child externalizing and internalizing outcomes. A study of 815 mother-child dyads examined the association between maternal metabolic disorders (GDM n = 60, overweight/obese n = 342) and externalizing and internalizing behaviors at 2 years of age operationalized by the parent-report Preschool Child Behavior Checklist (CBCL 1½−5) (Krzeczkowski et al., 2019). GDM and higher pre-pregnancy body mass index (BMI) were associated with increased externalizing and internalizing problems (Krzeczkowski et al., 2019). After adjusting for maternal PPD and socioeconomic status (SES), only gestational diet, though not maternal PPD, was associated with externalizing and internalizing problems. This suggests maternal PPD may be a mediator on the causal pathway between GDM, prenatal depression, and behavioral outcomes or a postnatal effect modifier (Krzeczkowski et al., 2019). However, this study did not include measurements of prenatal maternal depressive symptoms.

Together, this evidence underscores a gap in knowledge surrounding the possible joint roles of GDM and prenatal maternal depressive symptoms in shaping early childhood behavioral development through potentially interactive fetal programming mechanisms. Additionally, postnatal maternal depressive symptoms may moderate the effects of adverse *in utero* exposures. The objective of this analysis was to examine the independent and joint effects of *in utero* exposure to GDM and prenatal maternal depressive symptoms on behavioral problems during early childhood as measured by the Preschool CBCL (internalizing, externalizing, and autism spectrum problems). We hypothesized that *in utero* exposure to comorbid GDM and higher levels of prenatal maternal depressive symptoms would be associated with increased child externalizing and autism spectrum problems. We also hypothesized that increased postnatal maternal depressive symptoms would moderate the association between GDM, increased prenatal maternal depressive symptoms, and increased child externalizing and autism spectrum problems. Although not the primary focus of the current analyses, we additionally hypothesized that prenatal and postnatal maternal depressive symptoms would be associated with increased internalizing problems. Finally, although several sex differences have been noted in developmental programming models (Aiken & Ozanne, 2013), few studies have systematically investigated these differences. Leveraging the relatively large sample size, we explored potential sexually dimorphic effects in all models.

METHOD

Study Design and Participants

Data for this analysis were collected through the National Institutes of Health's (NIH) Environmental influences on Child Health Outcomes (ECHO) Program, which consists of longitudinal birth cohort studies across the United States and Puerto Rico. The goal of the ECHO Program is to investigate how early-life environmental exposures affect child health and development across five primary domains: pre-, peri-, and postnatal outcomes; upper and lower airway conditions; obesity; neurodevelopment; and positive health (Blaisdell et al., 2021; Forrest, Blackwell, & Camargo, 2018; Gillman & Blaisdell, 2018). The ECHO-wide protocol can be found at: https://echochildren.org/echo-program-protocol/. ECHO-wide analyses are pre-registered through the ECHO program via a two-step analysis proposal process. Access to ECHO-wide de-identified data is not granted until after an analysis proposal is approved.

Current study: Participants in the current analysis included children enrolled in an ECHO cohort between 2 and < 6 years of age with available data on the CBCL 1½−5 which was collected between 2009 and 2021. Additional inclusion criteria included information regarding prenatal maternal GDM status, a minimum of one self-reported prenatal maternal depressive symptom assessment, and a minimum of one self-reported postnatal maternal depressive symptom assessment collected during the first postpartum year (n = 2500). Exclusion criteria included participants in an ECHO cohort contributing fewer than 25 participants to the analysis or contributing to less than 1% of the total sample size (n = 30 participants from several cohorts) or missing information regarding the enrollment ECHO cohort (n = 91, 3.6%). After exclusions, a total of 2,379 child participants across five ECHO cohorts enrolled from five U.S. states (Colorado, Massachusetts, New York, Pennsylvania, and Tennessee) met the inclusion criteria and were included in the current analysis. All participants consented to participate in their local ECHO cohort and share their information with the ECHO consortia. Both a central and cohort-specific Institutional Review Board monitored human subject activities at each cohort site and the centralized ECHO Data Analysis Center. Written informed consent and parent's/guardian's permission was obtained along with child assent as appropriate, for ECHO-wide Cohort Data Collection Protocol participation. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.

Gestational Diabetes Mellitus

Information regarding GDM was harmonized across ECHO cohorts based on either the mother's gestational diabetes diagnosis from self-report using ECHO case report forms or maternal medical record abstraction.

NIH Patient-Reported Outcomes Measurement Information System Depression Scale

(PROMIS®-D). The PROMIS-D scale (Cella et al., 2010) was utilized by the NIH ECHO Program to harmonize different self-report depression symptom instruments used by individual ECHO cohorts into one common scale. This enables researchers interested in aggregating data across studies which use the Edinburgh Prenatal/Postnatal

Depression Scale (EPDS), the Adult Self-Report (ASR) Achenbach System Depression Problems Syndrome Scale, the Brief Symptom Inventory-18 item (BSI-18), the Center for Epidemiological Studies Depression Scale (CES-D), the Patient Health Questionnaire-9 (PHQ-9), Beck Depression Inventory, the SF-36 Health Survey Mental Health Summary, or the Kessler 6 Mental Health Scale. By placing all scores on the same PROMIS-D T-score metric, scores can be compared and used in combined analyses that span multiple studies. Since PROMIS-D allows for a comparison of depressive symptoms across ECHO cohorts, data from the original depression instruments were not available for this analysis. PROMIS-D T-scores are referenced to a mean of 50 and standard deviation of 10 with respect to the general adult U.S. population, such that individuals with T-scores of 50 have depressive symptom severity equal to the mean in the general adult U.S. population. In the current analysis, prenatal maternal depressive symptoms were originally measured using the Brief Symptom Inventory-18 item (BSI-18) (40%), the Edinburgh Prenatal/Postnatal Depression Scale (EPDS) (30%), and the Patient Health Questionnaire-9 (PHQ-9) (30%) assessments prior to being harmonized to the PROMIS-D. All participants were administered the EPDS (100%) for assessment of postnatal depressive symptoms up to one year postpartum. Both prenatal and postnatal maternal depressive symptoms were harmonized from the original assessment scales described above to PROMIS-D T scores by the ECHO Data Analysis Center (DAC).

Preschool Child Behavior Checklist 1½−5 (CBCL 1½−5)

The CBCL is one of the most widely used parental report measures of child social, emotional, and behavioral concerns. The Preschool CBCL consists of 100 items that describe children's behaviors such as "*doesn't get along well with other children*" where parents are asked to describe their child's behavior now or within the past 2 months on a Likert scale where 0 = Not True (as far as you know), 1 = Somewhat or Sometimes True, and 3 = Very True or Often True. The original factor analysis of the CBCL revealed seven first-order factors (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behaviors) and two second-order factors (externalizing problems and internalizing problems) (Achenbach & Rescorla, 2000). The CBCL also includes Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented scales that map on to diagnostic constructs, including the autism spectrum problems subscale (Achenbach, Dumenci, & Rescorla, 2003). A study examining the utility of the autism spectrum problems subscale as an ASD screening tool demonstrated that a receiver operating characteristic analyses (ROC) with a cut point of a T-score ≥ 60 yielded a sensitivity of 77% and a specificity of 97% - 99% in predicting ASD in a cohort of children with and without familial risk for ASD (Rescorla, Winder-Patel, et al., 2019). A separate study demonstrated that the autism spectrum problems subscale indicated good measurement invariance for configural and metric invariance through confirmatory factor analysis in a sample of 20,000 participants across multiple societies (Rescorla, Adams, Ivanova, & International, 2020) and that items from the autism spectrum problems subscale were stable over time (Rescorla, Ghassabian, et al., 2019).

Maternal and Child Sociodemographic and Medical History

Maternal race, ethnicity, pre-pregnancy weight, age at delivery, delivery mode, child sex assigned at birth, gestational age, and age at CBCL administration were harmonized across ECHO cohorts. Sociodemographic and medical history data were assessed via maternal self-report using ECHO case report forms or through maternal-infant medical record abstraction.

Statistical Analyses

All statistical analyses were conducted in R version 4.1.0 in a secure virtual private network platform hosted by the Research Triangle Institute (RTI) using de-identified data. Sociodemographic characteristics of mothers with and without GDM and their children with and without *in utero* exposure to GDM were compared using one-way analyses of variance (ANOVAs), the chi-squared test, or Fisher's exact test. Primary analyses consisted of a series of linear regression models to estimate the interaction terms (two-way and three way) and simple main effects and of maternal GDM (binary), prenatal maternal depressive symptoms (continuous PROMIS T-score), and postnatal maternal depressive symptoms (continuous PROMIS T-score) in the same model with each of the following CBCL 1½−5 domains (separately): externalizing problems T-score, internalizing problems T-score, and autism spectrum problems T-score. Unadjusted models were restricted to GDM, prenatal maternal depressive symptoms, and postnatal maternal depressive symptoms as predictors with the original depression instrument (BSI-18, EPDS, or PHQ-9) coded as a nominal covariate. Adjusted models additionally included maternal race, ethnicity, age at delivery, pre-pregnancy BMI category (underweight or normal weight vs. overweight or obese), child assigned sex at birth, gestational age category (preterm vs. term), and age at CBCL 1½−5 assessment. Missing covariate data are reported in Table 1. Missing data were handled using the missing-indicator method. Significant main effects and interactions were probed through secondary stratified analyses. We observed a main effect of child assigned sex at birth in our planned analyses, therefore *post-hoc* analyses consisted of repeating linear regression models stratified by child assigned sex at birth. For all models, we report the regression coefficients (β) and the standard error of estimates for each main effect and the significant interaction term. Finally, secondary analyses consisted of logistic regression analyses to estimate the interaction terms and simple main effects of *in utero* exposure to GDM and prenatal and postnatal maternal depressive symptoms with clinically relevant scores on the CBCL: externalizing problems (T-score ≥ 64), internalizing problems (T-score ≥ 64), and autism spectrum problems (T-score ≥ 70). Logistic regression analyses were estimated for both univariate models (e.g., GDM only, prenatal maternal depressive symptoms only, and postnatal maternal depressive symptoms only) and adjusted models. We report unadjusted and adjusted odds ratios (ORs) and the 95% confidence intervals (CIs) of the ORs.

RESULTS

Sample Characteristics

The final sample consisted of 2,379 children, with 216 exposed *in utero* to GDM and 2,163 not exposed (Table 1). Compared with the non-GDM group, a greater proportion of mothers with GDM self-identified as Asian ($X^2 = 8.97$, $p = .0028$), Black ($X^2 = 22.78$, $p < .0001$), mixed race ($X^2 = 7.17$, $p = .0074$), or Hispanic/Latina ($X^2 = 22.99$, $p < .0001$).

No significant differences were observed in the proportion of mothers who self-identified as White between the GDM and non-GDM groups. We were unable to examine demographic differences in the proportion of mothers who self-identified as American Indian or Alaskan Native and Native Hawaiian or Other Pacific Islander between the GDM and non-GDM groups due to small cell sizes. Women with GDM were more likely to be overweight or obese prior to pregnancy compared with women without GDM ($X^2 = 27.88$, $p < .0001$). Women with GDM had increased prenatal maternal depressive symptoms, as measured by PROMIS-D T-scores, compared with women without GDM ($F(1, 2377) = 7.66$, $p = .006$). No significant differences were observed in postnatal maternal depressive symptoms between women with and without GDM ($p>0.05$). In addition, no significant differences were detected in the birth mode between children with and without *in utero* exposure to GDM. Children with *in utero* exposure to GDM were more likely to be born preterm (<37 weeks' gestation) ($X^2 = 4.34$, $p < .05$) and were older at the CBCL assessment ($F(1, 1420) = 41.79$, $p < .0001$). Child sex did not differ by *in utero* exposure to GDM.

Associations of GDM and prenatal and postnatal maternal depressive symptoms with child externalizing problems

Linear regression models showed no significant two or three-way interaction effect of GDM and prenatal and postnatal maternal depressive symptoms on child externalizing problems. Simple main effects of GDM and prenatal and postnatal maternal depressive symptoms on child externalizing problems were observed in the adjusted model ($F(15, 2363) = 16.99$, $p < .0001$, adj. $R^2 = 0.09$). GDM ($\beta = 1.86 \pm 0.69$), prenatal maternal depressive symptoms ($\beta = 0.19 \pm 0.03$), and postnatal maternal depressive symptoms ($\beta = 0.21 \pm 0.03$) were each independently associated with increased child externalizing problems (Figure 1A). Significant covariates in the adjusted models included child age at CBCL assessment ($\beta = -0.86 \pm 0.33$) and female sex ($\beta = -1.64 \pm 0.39$). Due to the significant effect of child assigned sex at birth on externalizing problems, *post-hoc* analyses were conducted.

Associations of GDM and prenatal and postnatal maternal depressive symptoms with child externalizing problems stratified by sex

Post-hoc analyses stratified by child sex revealed an association between *in utero* exposure to GDM and externalizing problems in male children ($\beta = 2.29 \pm 0.94$), but not female children ($\beta = 0.59 \pm 1.07$) (Figure 1B). Prenatal and postnatal maternal depressive symptoms remained predictors of externalizing problems in both male and female children.

Associations of GDM and prenatal and postnatal maternal depressive symptoms with child internalizing problems

Linear regression models showed no two or three-way interaction effect of GDM and prenatal and postnatal maternal depressive symptoms on child internalizing problems. Main effects of GDM and prenatal and postnatal maternal depressive symptoms on child internalizing problems were observed in the adjusted model ($F(15, 2363) = 27.48$, $p < .0001$, adj. $R^2 = 0.14$). GDM ($\beta = 1.50 \pm 0.71$), prenatal maternal depressive symptoms ($\beta = 0.22 \pm 0.03$), and postnatal maternal depressive symptoms ($\beta = 0.22 \pm 0.03$) were each independently associated with increased child internalizing problems (Figure 1A). Significant covariates in the adjusted models included child age at CBCL assessment ($\beta =$

0.67 ± 0.33) and maternal age at delivery (β = −0.71 ± 0.38). Child assigned sex at birth was not a significant predictor of internalizing problems. However, due to analyses revealing an effect of GDM on externalizing problems in male children only, *post-hoc* analyses stratified by child assigned sex at birth were conducted to understand the potential role of sex in the association between GDM and child internalizing problems.

Associations of GDM and prenatal and postnatal maternal depressive symptoms with child internalizing problems stratified by sex

Post-hoc analyses stratified by child sex revealed an association between *in utero* exposure to GDM and internalizing problems in male children (β = 1.89 ± 0.94), but not female children (β = 0.99 ± 1.10) (Figure 1B). Prenatal and postnatal maternal depressive symptoms remained predictors of internalizing problems in both male and female children.

Associations of GDM and prenatal and postnatal maternal depressive symptoms with child autism spectrum problems

Linear regression models showed a three-way interaction effect of GDM and prenatal and postnatal maternal depressive symptoms on child autism spectrum problems in the adjusted model (F(19, 2359) = 12.21, p < .0001, adj. R^2 = 0.08). To better interpret the three-way interaction effect of GDM and prenatal and postnatal maternal depressive symptoms on child autism spectrum problems, we stratified by maternal postnatal depressive symptoms.

Association of GDM and prenatal maternal depressive symptoms with child autism spectrum problems stratified by postnatal maternal depressive symptoms.—We were not adequately powered to run stratified analyses based on a clinically relevant cutoff for maternal postnatal depressive symptoms, therefore we examined the two-way interaction effect and main effects of GDM and prenatal maternal depressive symptoms at lower levels of postnatal depressive symptoms and higher levels of postnatal depressive symptoms based on a median split (Median = 43.7). Stratified analyses within the lower postnatal maternal depressive symptoms group (N = 1,007) revealed no significant two-way interaction effect of GDM and prenatal maternal depression on child autism spectrum problems. Within the lower postnatal maternal depressive symptoms group, there was a main effect of prenatal maternal depressive symptoms (β = 0.09 ± 0.02), but not GDM status (β = 0.58 ± 0.62), on child autism spectrum problems (F(13, 993) = 5.35, p < .0001, adj. R^2 = 0.05). Similarly, stratified analyses within the higher postnatal maternal depressive symptoms group (N = 1,372) revealed no significant two-way interaction effect of GDM and prenatal maternal depression on child autism spectrum problems. However, within the higher postnatal maternal depressive symptoms group there was a main effect of both GDM status (β = 1.21 ± 0.57) and prenatal maternal depressive symptoms (β = 0.11 ± 0.03) on child autism spectrum problems (F(13, 1358) = 10.43, p < .0001, adj. R^2 = 0.08) (Figure 2A).

Association of GDM and postnatal maternal depressive symptoms with child autism spectrum problems stratified by prenatal maternal depressive symptoms.—We conducted a sensitivity analysis to determine if the association between GDM and autism problems was similarly moderated by prenatal maternal depressive

symptoms. We examined the two-way interaction effect and main effects of GDM and postnatal maternal depressive symptoms at lower levels of prenatal depressive symptoms and higher levels of prenatal depressive symptoms based on a median split (Median = 45.9). Stratified analyses within the lower prenatal maternal depressive symptoms group (N = 1,167) revealed no significant two-way interaction effect of GDM and postnatal maternal depression on child autism spectrum problems. Within the lower prenatal maternal depressive symptoms group, there was a main effect of postnatal maternal depressive symptoms (β = 0.12 ± 0.02), but not GDM status (β = −0.30 ± 0.02), on child autism spectrum problems ($F(11, 1155) = 5.19$, $p < .0001$, adj. $R^2 = 0.04$). Similarly, stratified analyses within the higher prenatal maternal depressive symptoms group (N = 1,212) revealed no significant two-way interaction effect of GDM and postnatal maternal depression on child autism spectrum problems. However, within the higher prenatal maternal depressive symptoms group there was a main effect of both GDM status (β = 1.38 ± 0.58) and postnatal maternal depressive symptoms (β = 0.08 ± 0.02) on child autism spectrum problems ($F(11, 1200) = 8.68$, $p < .0001$, adj. $R^2 = 0.06$) (Figure 2B).

Associations of GDM and prenatal and postnatal maternal depressive symptoms with child autism spectrum problems stratified by sex

Due to analyses revealing an effect of GDM on externalizing and internalizing problems in male children only, *post-hoc* analyses stratified by child assigned sex at birth were conducted to understand the potential role of sex in the association between GDM and child autism spectrum problems. *Post-hoc* linear regression models showed no three-way interaction effect of GDM and prenatal and postnatal maternal depressive symptoms on child autism spectrum problems in sex stratified models. *Post-hoc* analyses stratified by child sex revealed a similar, but non-significant, two-way interaction effect of GDM and prenatal maternal depressive symptoms on child autism spectrum problems in both sexes. We therefore examined main effects in sex stratified analyses. In the adjusted models stratified by male sex, we observed a significant main effect of GDM (β = 1.30 ± 0.59), prenatal maternal depressive symptoms (β = 0.12 ± 0.03), and postnatal maternal depressive symptoms (β = 0.09 ± 0.02) with increased autism spectrum problems (Figure 1B). In the adjusted models stratified by female sex, no main effect of GDM on child autism spectrum problems was observed (Figure 1B). However, in the adjusted models stratified by female sex, we observed significant main effects of both prenatal maternal depressive symptoms (β = 0.05 ± 0.02) and postnatal maternal depressive symptoms (β = 0.07 ± 0.02) with increased child autism spectrum problems (Figure 1B).

Associations of GDM and prenatal and postnatal maternal depressive symptoms with child clinically relevant symptoms

Logistic regression models showed no significant two or three-way interaction effects of GDM and prenatal and postnatal maternal depressive symptoms on any of the symptom scales when dichotomized into non-clinical versus clinically elevated symptoms (Table 2; Figure 3). In the fully adjusted models, GDM was associated with clinical levels of autism spectrum problems (OR 2.88; 95% CI 1.54, 5.17) (Figure 3). *Post-hoc* analyses stratified by child sex revealed an association between GDM and clinical levels of autism spectrum problems in male children only (OR 3.26; 95% CI 1.58, 6.41). GDM was not associated

with clinical levels of externalizing or internalizing problems. In the fully adjusted models, prenatal maternal depressive symptoms were associated with clinical levels of internalizing problems (OR 1.04; 95% CI 1.01, 1.07), but not with clinical levels of externalizing problems or autism spectrum problems. Finally, postnatal maternal depressive symptoms were associated with clinical levels of externalizing problems (OR 1.06; 95% CI 1.03, 1.09), internalizing problems (OR 1.04; 95% CI 1.01, 1.06), and autism spectrum problems (OR 1.05; 95% CI 1.02, 1.08).

DISCUSSION

The present study is the first to examine the interaction effects of GDM and prenatal and postnatal maternal depressive symptoms on behavioral outcomes during early childhood. Additionally, this study is the first to control for pre- and postnatal maternal depressive symptoms when examining associations between GDM and child autism related outcomes.

When examining the interactive and main effects of GDM and prenatal and postnatal maternal depressive symptoms on child externalizing and internalizing behaviors, we demonstrated an association of GDM and prenatal and postnatal maternal depressive symptoms with both increased externalizing and internalizing problems. *Post-hoc* analyses revealed an association of GDM with child externalizing and internalizing problems for male children only, whereas pre- and postnatal maternal depressive symptoms were similarly linked to child externalizing and internalizing problems in both sexes. Although several prior studies have identified associations between pre- and postnatal maternal depression with child behavioral problems (Bagner et al., 2010; Leis et al., 2014; Madigan et al., 2018; O'Donnell et al., 2014), to our knowledge, this is the first study to identify links between GDM and child behavioral outcomes when controlling for both pre- and postnatal maternal depression. One prior report demonstrated an association between GDM and pre-pregnancy BMI with increased child externalizing and internalizing problems (Krzeczkowski et al., 2019). However, this study also found that maternal PPD and SES were postnatal effect modifiers (Krzeczkowski et al., 2019). Although we did not have data on household SES to include in the present report, postnatal maternal depressive symptoms were not an effect modifier in our analyses examining child externalizing or internalizing outcomes.

We additionally examined the interactive and main effects of GDM and prenatal and postnatal maternal depressive symptoms with child autism spectrum problems derived from the CBCL DSM-oriented scales. We demonstrated a significant three-way interaction effect between GDM and prenatal and postnatal maternal depressive symptoms with child autism spectrum problems. To further interpret this three-way interaction, we stratified by lower and higher levels of perinatal maternal depressive symptoms, based on a median split, in follow-up analyses. In children of mothers with either lower levels of prenatal or postnatal depressive symptoms, GDM status was not associated with increased child autism spectrum problems. In children of mothers with higher levels of prenatal or postnatal maternal depressive symptoms, both GDM status and maternal depressive symptoms were each associated with increased autism spectrum problems. Since we only observed an association between GDM and child autism behaviors at higher levels of prenatal or postnatal maternal depressive symptoms, our findings suggest perinatal maternal depressive symptoms acted

as an effect moderator such that lower levels of perinatal maternal depressive symptoms were protective and higher levels of perinatal maternal depressive symptoms potentiated the effects of *in utero* exposure to GDM on child autism problems.

Research under the DOHaD framework postulates that exposure to an adverse *in utero* environment is associated with an increased risk for adverse physical health, developmental, or psychiatric outcomes through fetal programming mechanisms. Our findings linking GDM and prenatal maternal depression to increased autism spectrum problems are supported by animal studies that have demonstrated associations between increased maternal inflammation and HPA axis upregulation during pregnancy with behavioral changes in offspring (Money et al., 2018; Salari, Fatehi-Gharehlar, Motayagheni, & Homberg, 2016). Other studies have demonstrated intergenerational transmission of maternal stress based on transgenerational epigenetic alterations (Yehuda & Lehrner, 2018). In a two-hit animal model of prenatal maternal stress that was used to examine the interaction of prenatal psychological and immune stress, results revealed increased adverse maternal pregnancy outcomes, increased gestational length variation, and upregulation of uterine mRNA expression (Verstraeten, McCreary, Weyers, Metz, & Olson, 2019). A separate two-hit animal model of prenatal maternal stress demonstrated sex-specific consequences on offspring adult behavior (Verstraeten, McCreary, Falkenberg, et al., 2019).

Several developmental programming studies have demonstrated adverse *in utero* exposures result in different phenotypes for male and female offspring (Aiken & Ozanne, 2013). In the current analysis, GDM was linked to behavioral outcomes only in males, whereas pre- and postnatal maternal depressive symptoms similarly impacted both sexes. Although ASD, externalizing problems, and diagnoses associated with externalizing problems, such as ADHD, are all more prevalent among males (Santos, Ferreira, Martins, Goncalves, & Castelo-Branco, 2022), it is also possible that GDM affects child neurobehavior in a sexually dimorphic manner. Animal models of GDM have demonstrated male, but not female, offspring display increased repetitive behaviors, but no differences in sociability (Aviel-Shekler et al., 2020), significantly increased HPA axis stress responses and impaired sensorimotor gating (Bronson, Chan, & Bale, 2017), and memory impairment (Zou et al., 2021). While not directly comparable, an animal model of prenatal maternal overweight or obesity demonstrated maternal high-fat diet resulted in decreased fetal and adult brain serotonin (5-HT) availability in males only via a feedback loop where increased inflammation dependent on macrophage Toll-like receptor 4 signaling resulted in excess microglial phagocytosis of 5-HT neurons in the dorsal raphe nucleus of males only (Ceasrine et al., 2022).

Recent clinical research studies have also demonstrated the presence of sexual dimorphism in the association between *in utero* exposure to GDM and child health outcomes, although none related to neurobehavioral outcomes. Three studies reported a sexually dimorphic association between GDM and increased risk for being overweight during early childhood, adolescence, and adulthood for males only (Le Moullec et al., 2018) (Li et al., 2017; Regnault, Gillman, Rifas-Shiman, Eggleston, & Oken, 2013) and one study reported an association for females only (Tam et al., 2017). Prior research reporting on the association between GDM and offspring neurocognitive, neurobehavior, or language development have

not examined potential sex-specific effects through stratified analyses (Cai et al., 2016; Camprubi Robles et al., 2015; DeBoer et al., 2005; Dionne, Boivin, Seguin, Perusse, & Tremblay, 2008; Fraser, Nelson, Macdonald-Wallis, & Lawlor, 2012; Ghassabian et al., 2016; Krzeczkowski et al., 2019; Nelson et al., 2000). Therefore, future studies examining effects of GDM on child neurodevelopmental outcomes should consider sex stratified analyses.

We also observed perinatal maternal depressive symptoms moderated the association between GDM and child autism behaviors. Several prior studies have reported associations between GDM and perinatal maternal depression (Delanerolle et al., 2021; Wilson et al., 2020). However to our knowledge this is the first study to report perinatal maternal depressive symptoms as a moderator in the association between GDM and child autism behaviors. Our findings are in part supported by a study which reported an association of adverse maternal experiences including prior experiences of trauma with postnatal maternal depressive symptoms and child social emotional problems, only among mothers with diabetes during pregnancy (Rayport et al., 2022). ASD is estimated to be 40–80% heritable; however, both genetic and non-genetic factors can modulate the penetrance of autism risk genes, which results in a highly heterogeneous ASD phenotype (Rylaarsdam & Guemez-Gamboa, 2019). In the present study, we utilized the CBCL autism problem scale, which is not a diagnostic measure, but rather a measure of autism behaviors. ASD is hypothesized to originate *in utero*, likely to due to interactive prenatal environmental exposures and genetic influences. As previously discussed, GDM and prenatal maternal depression may have overlapping biological mechanisms such as increased prenatal maternal inflammation and/or HPA axis upregulation. However, the association between GDM and child autism behaviors moderated via postnatal maternal depression may have independent pathways. A recent Japanese study identified an association between mothers' broader autism phenotype (BAP) with both increased risk of postpartum depression and insecure maternal attachment (Hirokawa et al., 2019). Data from the same cohort reported an association between maternal BAP and reduced consumption of folate, vitamin C, vitamin D, and Omega−3 fatty acids during pregnancy (Hirokawa et al., 2020). Although we did not have measures of maternal BAP in this study, it is possible maternal BAP accounted for some of the variance in the association between GDM and child autism problems moderated by higher levels of maternal perinatal depressive symptoms.

Finally, we examined associations of GDM and prenatal and postnatal maternal depressive symptoms with clinical levels of child externalizing, internalizing, and autism spectrum problems via logistic regression analyses. Multivariate analyses revealed that GDM was not associated with clinical levels of externalizing or internalizing problems. The strongest association observed in our analyses was between GDM and autism spectrum problems (OR 2.99; 95% CI 1.54, 5.17), even when controlling for pre- and postnatal maternal depressive symptoms. In the present analysis, we reported a higher OR than prior studies that have examined the association between GDM and the prevalence of ASD. For example, the most recently published systematic review and meta-analysis estimated that GDM was associated with an increased prevalence of ASD with a pooled OR of 1.42 (95% CI 1.22, 1.65) (Rowland & Wilson, 2021). A separate recent Swedish population-based cohort study corroborated these findings (OR 1.42; 95% CI 1.32, 1.56) (S. Chen et al., 2021). However,

this study also reported significant associations between GDM and the prevalence of ADHD (OR 1.13; 95% CI 1.05, 1.22), comorbid ASD and ADHD (OR 1.26; 95% CI 1.09, 1.44), and intellectual disability without ASD (OR 1.62; 95% CI 1.40, 1.88) (S. Chen et al., 2021). Our increased OR is expected, as the clinical cutoff point for autism spectrum problems on the CBCL is not equivalent and more liberal than criteria for an ASD diagnosis.

Strengths and Limitations

The strengths of our analysis include leveraging the ECHO study to have a large sample size, which included participant representation from five U.S. states; enrolling a diverse participant population, with more than half of maternal participants self-identifying as being from an underrepresented minority group; and having both prenatal and postnatal assessments of maternal depressive symptoms and child behavioral outcomes for over 2,000 participants. However, several limitations must be taken into consideration when interpreting our findings.

First, data were not originally collected with the intention of the proposed analyses. Since the current study was observational and included participants with available longitudinal data, results may not be representative. Secondly, information about how maternal GDM status was ascertained (maternal report vs. medical record abstraction) was not available for this analysis. An additional limitation was our reliance on parental report of child behavior and the wide age range in which children were assessed on the CBCL (2 – 5 years of age). Recent research suggests small magnitudes of associations between maternal psychopathology and biases in reporting on child emotional and behavioral problems (Olino, Michelini, Mennies, Kotov, & Klein, 2021), however it is possible that maternal reporting of child behaviors was influenced by maternal depression. Future studies should also consider developing standardized objective measures of child externalizing or internalizing behaviors. Child externalizing, internalizing, and autism-related behaviors can vary greatly across development but show increasing stability during the toddler period. For example, more than 50% of children with disruptive behaviors at three to four years of age will continue to demonstrate these behaviors when entering school (Maheswari & Samundeeswari, 2018). In the present analysis, age at CBCL assessment was not distributed evenly across age bins. The majority of children were between 4 and 5 years of age at the time of CBCL assessment (N = 1816). Therefore, we were unable to examine developmental implications related to timing of CBCL assessment.

Our greatest limitation was the inability to stratify by clinically relevant levels of prenatal or postnatal maternal depression. Due to small cell sizes in the cross-tabulation between GDM and clinically relevant symptoms, we could not conduct secondary analyses to probe the interaction effect between GDM, prenatal, and postnatal maternal depression based on clinically relevant cutoffs with child autism spectrum problems. We therefore stratified by lower and higher levels of prenatal and postnatal maternal depressive symptoms based on a median split. It is noteworthy that median prenatal and postnatal depressive symptoms in the present analysis do not reflect a clinically relevant cutoff and are lower than the PROMIS-D T-score metric with a mean of 50 and standard deviation of 10 in the U.S. general population. One possible explanation for the lower observed levels of maternal

perinatal depressive symptoms is that maternal depressive symptoms were measured using the EPDS, BSI-18, or PHQ-9 and these scores were later harmonized to PROMIS-D T scores. Finally, although we examined clinically relevant outcomes on the CBCL, we were likely underpowered to examine interactions in these analyses.

Several potential unobserved confounders should be explored in further analyses. For example, we did not include data on household socioeconomic information or maternal educational attainment, as these data were not available for all participants in the current analyses. Due to some participants having multiple assessments of depressive symptoms in the prenatal or postnatal period, we averaged assessments within the prenatal period and postnatal period separately. We additionally did not have information on the gestational week of a GDM diagnosis, GDM severity or treatment, GDM management, other medical comorbidities, or perinatal depression treatment, which are all potential unobserved confounders. Finally, it is possible that prenatal and postnatal maternal perceived stress or anxiety are associated with child behavior, and these measures were not available for all participants in the current analyses.

Conclusions

In summary, pre- and postnatal maternal depressive symptoms were associated with externalizing and internalizing problems in both sexes, whereas GDM was associated with externalizing and internalizing problems in male children only. Additionally, we observed a three-way interaction between GDM, prenatal maternal depressive symptoms, and postnatal maternal depressive symptoms with autism spectrum problems. Stratified analyses revealed an association between GDM and child autism spectrum problems in children of mothers with higher levels of perinatal maternal depressive symptoms only. Finally, analyses stratified by sex revealed links between GDM and autism spectrum problems in male children only. Our findings have important research and clinical implications. They suggest sexually dimorphic effects of GDM on child behavioral outcomes. Future studies should attempt to identify biological mechanisms underlying resiliency in females exposed to GDM *in utero* due to the lack of associations with subsequent behavioral problems in the current analyses. Additionally, since both GDM and prenatal maternal depression are associated with epigenetic changes, increased inflammatory processes, and HPA-axis upregulation during pregnancy (Christian et al., 2009; Coussons-Read et al., 2007; Edalat et al., 2013; Money et al., 2018; Pantham et al., 2015; Richardson & Carpenter, 2007), identification of the interactions among underlying biological mechanisms is needed to mitigate adverse neurobehavioral outcomes. Further understanding of mechanisms may inform prophylactic programs during pregnancy with the potential to be translated into strategies that improve long-term child behavioral outcomes.

Acknowledgments:

The authors wish to thank our ECHO colleagues; the medical, nursing, and program staff; and the children and families participating in the ECHO cohorts. We also acknowledge the contribution of the following ECHO program collaborators: ECHO Components—Coordinating Center: Duke Clinical Research Institute, Durham, North Carolina: Smith PB, Newby KL.

Funding information:

Research reported in this publication was supported by the Environmental influences on Child Health Outcomes (ECHO) program, Office of the Director, National Institutes of Health, under Award Numbers U2COD023375 (Coordinating Center), U24OD023382 (Data Analysis Center), U24OD023319 (PRO Core), UH3 OD023248 (DABELEA), UH3 OD023271 (KARR), UH3 OD023349 (O'CONNOR), UH3 OD023305 (TRASANDE), UH3 OD023337 (WRIGHT), UH3 OD023328 (MONK), and UH3 OD023279 (ELLIOTT). Dr. Lauren Shuffrey is supported by K99HD103910 issued by the Eunice Kennedy Shriver National Institute of Child Health & Human Development. Dr. Ayesha Sania is supported by UH3OD023279–05S1, re-entry supplement from Office of the Director, NIH, and Office of Research on Women Health (ORWH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability:

De-identified data from the ECHO Program are available through NICHD's Data and Specimen Hub (DASH). DASH is a centralized resource that allows researchers to access data from various studies via a controlled-access mechanism. Researchers can now request access to these data by creating a DASH account and submitting a Data Request Form. The NICHD DASH Data Access Committee will review the request and provide a response in approximately two to three weeks. Once granted access, researchers will be able to use the data for three years. See the DASH Tutorial for more detailed information on the process.

REFERENCES

Achenbach TM, Dumenci L, & Rescorla LA (2003). DSM-oriented and empirically based approaches to constructing scales from the same item pools. J Clin Child Adolesc Psychol, 32(3), 328–340. doi:10.1207/S15374424JCCP3203_02 [PubMed: 12881022]

Achenbach TM, Ivanova MY, Rescorla LA, Turner LV, & Althoff RR (2016). Internalizing/Externalizing Problems: Review and Recommendations for Clinical and Research Applications. J Am Acad Child Adolesc Psychiatry, 55(8), 647–656. doi:10.1016/j.jaac.2016.05.012 [PubMed: 27453078]

Achenbach TM, & Rescorla LA (2000). Manual for the ASEBA preschool forms and profiles. Retrieved from

Aiken CE, & Ozanne SE (2013). Sex differences in developmental programming models. Reproduction, 145(1), R1–13. doi:10.1530/REP-11-0489 [PubMed: 23081892]

American Diabetes, A. (2021). Standards of Medical Care in Diabetes-2021 Abridged for Primary Care Providers. Clin Diabetes, 39(1), 14–43. doi:10.2337/cd21-as01 [PubMed: 33551551]

Aviel-Shekler K, Hamshawi Y, Sirhan W, Getselter D, Srikanth KD, Malka A, … Elliott E (2020). Gestational diabetes induces behavioral and brain gene transcription dysregulation in adult offspring. Transl Psychiatry, 10(1), 412. doi:10.1038/s41398-020-01096-7 [PubMed: 33239620]

Bagner DM, Pettit JW, Lewinsohn PM, & Seeley JR (2010). Effect of maternal depression on child behavior: a sensitive period? J Am Acad Child Adolesc Psychiatry, 49(7), 699–707. doi:10.1016/j.jaac.2010.03.012 [PubMed: 20610139]

Blaisdell CJ, Park C, Hanspal M, Roary M, Arteaga SS, Laessig S, … program collaborators for Environmental influences on Child Health, O. (2021). The NIH ECHO Program: investigating how early environmental influences affect child health. Pediatr Res. doi:10.1038/s41390-021-01574-8

Bronson SL, Chan JC, & Bale TL (2017). Sex-Specific Neurodevelopmental Programming by Placental Insulin Receptors on Stress Reactivity and Sensorimotor Gating. Biol Psychiatry, 82(2), 127–138. doi:10.1016/j.biopsych.2016.12.025 [PubMed: 28168960]

Burlina S, Dalfra MG, & Lapolla A (2019). Short- and long-term consequences for offspring exposed to maternal diabetes: a review. Journal of Maternal-Fetal & Neonatal Medicine, 32(4), 687–694. doi:10.1080/14767058.2017.1387893 [PubMed: 28969466]

Cai S, Qiu A, Broekman BF, Wong EQ, Gluckman PD, Godfrey KM, … group, G. s. (2016). The Influence of Gestational Diabetes on Neurodevelopment of Children in the First Two Years

of Life: A Prospective Study. PloS One, 11(9), e0162113. doi:10.1371/journal.pone.0162113 [PubMed: 27603522]

Camprubi Robles M, Campoy C, Garcia Fernandez L, Lopez-Pedrosa JM, Rueda R, & Martin MJ (2015). Maternal Diabetes and Cognitive Performance in the Offspring: A Systematic Review and Meta-Analysis. PLoS One, 10(11), e0142583. doi:10.1371/journal.pone.0142583 [PubMed: 26566144]

Ceasrine AM, Devlin BA, Bolton JL, Green LA, Jo YC, Huynh C, … Bilbo SD (2022). Maternal diet disrupts the placenta-brain axis in a sex-specific manner. Nat Metab. doi:10.1038/s42255-022-00693-8

Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, … Group, P. C. (2010). The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol, 63(11), 1179–1194. doi:10.1016/j.jclinepi.2010.04.011 [PubMed: 20685078]

Chen LC, Chen MH, Hsu JW, Huang KL, Bai YM, Chen TJ, … Su TP (2020). Association of parental depression with offspring attention deficit hyperactivity disorder and autism spectrum disorder: A nationwide birth cohort study. J Affect Disord, 277, 109–114. doi:10.1016/j.jad.2020.07.059 [PubMed: 32805586]

Chen S, Zhao S, Dalman C, Karlsson H, & Gardner R (2021). Association of maternal diabetes with neurodevelopmental disorders: autism spectrum disorders, attention-deficit/hyperactivity disorder and intellectual disability. Int J Epidemiol, 50(2), 459–474. doi:10.1093/ije/dyaa212 [PubMed: 33221916]

Christian LM, Franco A, Glaser R, & Iams JD (2009). Depressive symptoms are associated with elevated serum proinflammatory cytokines among pregnant women. Brain Behav Immun, 23(6), 750–754. doi:10.1016/j.bbi.2009.02.012 [PubMed: 19258033]

Coussons-Read ME, Okun ML, & Nettles CD (2007). Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. Brain Behav Immun, 21(3), 343–350. doi:10.1016/j.bbi.2006.08.006 [PubMed: 17029703]

DeBoer T, Wewerka S, Bauer PJ, Georgieff MK, & Nelson CA (2005). Explicit memory performance in infants of diabetic mothers at 1 year of age. Dev Med Child Neurol, 47(8), 525–531. doi:10.1017/s0012162205001039 [PubMed: 16108452]

Delanerolle G, Phiri P, Zeng Y, Marston K, Tempest N, Busuulwa P, … Hapangama DK (2021). A systematic review and meta-analysis of gestational diabetes mellitus and mental health among BAME populations. EClinicalMedicine, 38, 101016. doi:10.1016/j.eclinm.2021.101016 [PubMed: 34308317]

Dionne G, Boivin M, Seguin JR, Perusse D, & Tremblay RE (2008). Gestational diabetes hinders language development in offspring. Pediatrics, 122(5), e1073–1079. doi:10.1542/peds.2007-3028 [PubMed: 18977957]

Edalat B, Sharifi F, Badamchizadeh Z, Hossein-Nezhad A, Larijani B, Mirarefin M, & Fakhrzadeh H (2013). Association of metabolic syndrome with inflammatory mediators in women with previous gestational diabetes mellitus. J Diabetes Metab Disord, 12(1), 8. doi:10.1186/2251-6581-12-8 [PubMed: 23497664]

Forrest CB, Blackwell CK, & Camargo CA Jr. (2018). Advancing the Science of Children's Positive Health in the National Institutes of Health Environmental Influences on Child Health Outcomes (ECHO) Research Program. J Pediatr, 196, 298–300. doi:10.1016/j.jpeds.2018.02.004 [PubMed: 29567045]

Fraser A, & Lawlor DA (2014). Long-term health outcomes in offspring born to women with diabetes in pregnancy. Current Diabetes Reports, 14(5), 489. doi:10.1007/s11892-014-0489-x [PubMed: 24664798]

Fraser A, Nelson SM, Macdonald-Wallis C, & Lawlor DA (2012). Associations of existing diabetes, gestational diabetes, and glycosuria with offspring IQ and educational attainment: the Avon Longitudinal Study of Parents and Children. Exp Diabetes Res, 2012, 963735. doi:10.1155/2012/963735 [PubMed: 22927834]

Ghassabian A, Sundaram R, Wylie A, Bell E, Bello SC, & Yeung E (2016). Maternal medical conditions during pregnancy and gross motor development up to age 24 months in the Upstate

KIDS study. Dev Med Child Neurol, 58(7), 728–734. doi:10.1111/dmcn.12947 [PubMed: 26502927]

Gillman MW, & Blaisdell CJ (2018). Environmental influences on Child Health Outcomes, a Research Program of the National Institutes of Health. Curr Opin Pediatr, 30(2), 260–262. doi:10.1097/MOP.0000000000000600 [PubMed: 29356702]

Goodman JH (2019). Perinatal depression and infant mental health. Arch Psychiatr Nurs, 33(3), 217–224. doi:10.1016/j.apnu.2019.01.010 [PubMed: 31227073]

Hirokawa K, Kimura T, Ikehara S, Honjo K, Sato T, Ueda K, … Children's Study, G. (2019). Associations between broader autism phenotype (BAP) and maternal attachment are moderated by maternal postpartum depression when infants are one month old: A prospective study of the Japan environment & children's study. J Affect Disord, 243, 485–493. doi:10.1016/j.jad.2018.09.060 [PubMed: 30273887]

Hirokawa K, Kimura T, Ikehara S, Honjo K, Ueda K, Sato T, … Children's Study, G. (2020). Associations Between Broader Autism Phenotype and Dietary Intake: A Cross-Sectional Study (Japan Environment & Children's Study). J Autism Dev Disord, 50(8), 2698–2709. doi:10.1007/s10803-020-04380-z [PubMed: 31997059]

Kong L, Chen X, Gissler M, & Lavebratt C (2020). Relationship of prenatal maternal obesity and diabetes to offspring neurodevelopmental and psychiatric disorders: a narrative review. Int J Obes (Lond), 44(10), 1981–2000. doi:10.1038/s41366-020-0609-4 [PubMed: 32494038]

Krzeczkowski JE, Lau A, Fitzpatrick J, Tamana S, Smithson L, de Souza R, … Investigators, C. S. (2019). Maternal Metabolic Complications in Pregnancy and Offspring Behavior Problems at 2 Years of Age. Matern Child Health J, 23(6), 746–755. doi:10.1007/s10995-018-2691-y [PubMed: 30600520]

Le Moullec N, Fianu A, Maillard O, Chazelle E, Naty N, Schneebeli C, … Favier F (2018). Sexual dimorphism in the association between gestational diabetes mellitus and overweight in offspring at 5–7 years: The OBEGEST cohort study. PLoS One, 13(4), e0195531. doi:10.1371/journal.pone.0195531 [PubMed: 29621322]

Leis JA, Heron J, Stuart EA, & Mendelson T (2014). Associations between maternal mental health and child emotional and behavioral problems: does prenatal mental health matter? J Abnorm Child Psychol, 42(1), 161–171. doi:10.1007/s10802-013-9766-4 [PubMed: 23748337]

Li S, Zhu Y, Yeung E, Chavarro JE, Yuan C, Field AE, … Zhang C (2017). Offspring risk of obesity in childhood, adolescence and adulthood in relation to gestational diabetes mellitus: a sex-specific association. Int J Epidemiol, 46(6), 2104. doi:10.1093/ije/dyx211 [PubMed: 29025133]

Madigan S, Oatley H, Racine N, Fearon RMP, Schumacher L, Akbari E, … Tarabulsy GM (2018). A Meta-Analysis of Maternal Prenatal Depression and Anxiety on Child Socioemotional Development. J Am Acad Child Adolesc Psychiatry, 57(9), 645–657 e648. doi:10.1016/j.jaac.2018.06.012 [PubMed: 30196868]

Maheswari K, & Samundeeswari A (2018). Prevalence of preschooler behavioural problems. Asian Pacific Journal of Health Sciences, 5(4), 129–135.

Money KM, Barke TL, Serezani A, Gannon M, Garbett KA, Aronoff DM, & Mirnics K (2018). Gestational diabetes exacerbates maternal immune activation effects in the developing brain. Molecular Psychiatry, 23(9), 1920–1928. doi:10.1038/mp.2017.191 [PubMed: 28948973]

Nelson CA, Wewerka S, Thomas KM, Tribby-Walbridge S, deRegnier R, & Georgieff M (2000). Neurocognitive sequelae of infants of diabetic mothers. Behav Neurosci, 114(5), 950–956. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11085609 [PubMed: 11085609]

Nelson CA, Wewerka SS, Borscheid AJ, Deregnier RA, & Georgieff MK (2003). Electrophysiologic evidence of impaired cross-modal recognition memory in 8-month-old infants of diabetic mothers. Journal of Pediatrics, 142(5), 575–582. doi:10.1067/mpd.2003.210 [PubMed: 12756394]

O'Donnell KJ, Glover V, Barker ED, & O'Connor TG (2014). The persisting effect of maternal mood in pregnancy on childhood psychopathology. Dev Psychopathol, 26(2), 393–403. doi:10.1017/S0954579414000029 [PubMed: 24621564]

Olino TM, Michelini G, Mennies RJ, Kotov R, & Klein DN (2021). Does maternal psychopathology bias reports of offspring symptoms? A study using moderated non-linear factor analysis. J Child Psychol Psychiatry, 62(10), 1195–1201. doi:10.1111/jcpp.13394 [PubMed: 33638150]

Ornoy A, Ratzon N, Greenbaum C, Wolf A, & Dulitzky M (2001). School-age children born to diabetic mothers and to mothers with gestational diabetes exhibit a high rate of inattention and fine and gross motor impairment. J Pediatr Endocrinol Metab, 14 Suppl 1, 681–689. doi:10.1515/jpem.2001.14.s1.681 [PubMed: 11393563]

Pantham P, Aye IL, & Powell TL (2015). Inflammation in maternal obesity and gestational diabetes mellitus. Placenta, 36(7), 709–715. doi:10.1016/j.placenta.2015.04.006 [PubMed: 25972077]

Rai D, Lee BK, Dalman C, Golding J, Lewis G, & Magnusson C (2013). Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. BMJ, 346, f2059. doi:10.1136/bmj.f2059 [PubMed: 23604083]

Rayport YK, Sania A, Lucchini M, du Plessis C, Potter M, Springer PE, … Shuffrey LC (2022). Associations of adverse maternal experiences and diabetes on postnatal maternal depression and child social-emotional outcomes in a South African community cohort. PLOS Global Public Health, 2(10). doi:10.1371/journal.pgph.0001124

Regnault N, Gillman MW, Rifas-Shiman SL, Eggleston E, & Oken E (2013). Sex-specific associations of gestational glucose tolerance with childhood body composition. Diabetes Care, 36(10), 3045–3053. doi:10.2337/dc13-0333 [PubMed: 23877978]

Rescorla LA, Adams A, Ivanova MY, & International AC (2020). The CBCL/1(1/2)-5's DSM-ASD Scale: Confirmatory Factor Analyses Across 24 Societies. J Autism Dev Disord, 50(9), 3326–3340. doi:10.1007/s10803-019-04189-5 [PubMed: 31559509]

Rescorla LA, Ghassabian A, Ivanova MY, Jaddoe VW, Verhulst FC, & Tiemeier H (2019). Structure, longitudinal invariance, and stability of the Child Behavior Checklist 1(1/2)-5's Diagnostic and Statistical Manual of Mental Disorders-Autism Spectrum Disorder scale: Findings from Generation R (Rotterdam). Autism, 23(1), 223–235. doi:10.1177/1362361317736201 [PubMed: 29143542]

Rescorla LA, Winder-Patel BM, Paterson SJ, Pandey J, Wolff JJ, Schultz RT, & Piven J (2019). Autism spectrum disorder screening with the CBCL/1(1/2)-5: Findings for young children at high risk for autism spectrum disorder. Autism, 23(1), 29–38. doi:10.1177/1362361317718482 [PubMed: 28931307]

Richardson AC, & Carpenter MW (2007). Inflammatory mediators in gestational diabetes mellitus. Obstet Gynecol Clin North Am, 34(2), 213–224, viii. doi:10.1016/j.ogc.2007.04.001 [PubMed: 17572268]

Riggins T, Miller NC, Bauer PJ, Georgieff MK, & Nelson CA (2009). Consequences of low neonatal iron status due to maternal diabetes mellitus on explicit memory performance in childhood. Dev Neuropsychol, 34(6), 762–779. doi:10.1080/87565640903265145 [PubMed: 20183732]

Rogers A, Obst S, Teague SJ, Rossen L, Spry EA, Macdonald JA, … Hutchinson D (2020). Association Between Maternal Perinatal Depression and Anxiety and Child and Adolescent Development: A Meta-analysis. JAMA Pediatr, 174(11), 1082–1092. doi:10.1001/jamapediatrics.2020.2910 [PubMed: 32926075]

Rowland J, & Wilson CA (2021). The association between gestational diabetes and ASD and ADHD: a systematic review and meta-analysis. Sci Rep, 11(1), 5136. doi:10.1038/s41598-021-84573-3 [PubMed: 33664319]

Rylaarsdam L, & Guemez-Gamboa A (2019). Genetic Causes and Modifiers of Autism Spectrum Disorder. Front Cell Neurosci, 13, 385. doi:10.3389/fncel.2019.00385 [PubMed: 31481879]

Salari AA, Fatehi-Gharehlar L, Motayagheni N, & Homberg JR (2016). Fluoxetine normalizes the effects of prenatal maternal stress on depression- and anxiety-like behaviors in mouse dams and male offspring. Behav Brain Res, 311, 354–367. doi:10.1016/j.bbr.2016.05.062 [PubMed: 27263073]

Santos S, Ferreira H, Martins J, Goncalves J, & Castelo-Branco M (2022). Male sex bias in early and late onset neurodevelopmental disorders: Shared aspects and differences in Autism Spectrum Disorder, Attention Deficit/hyperactivity Disorder, and Schizophrenia. Neurosci Biobehav Rev, 135, 104577. doi:10.1016/j.neubiorev.2022.104577 [PubMed: 35167846]

Shuffrey LC, & Fifer WP (2020). Prenatal Risk Factors and Neurodevelopment. In Benson JB (Ed.), Encyclopedia of Infant and Early Childhood Development, Second Edition (2nd ed., pp. 608 – 620): Elsevier.

Shuffrey LC, Lucchini M, Morales S, Sania A, Hockett C, Barrett E, … program collaborators for Environmental influences on Child Health, O. (2022). Gestational diabetes mellitus, prenatal maternal depression, and risk for postpartum depression: an Environmental influences on Child Health Outcomes (ECHO) Study. BMC Pregnancy Childbirth, 22(1), 758. doi:10.1186/s12884-022-05049-4 [PubMed: 36209070]

Tam WH, Ma RCW, Ozaki R, Li AM, Chan MHM, Yuen LY, … Chan JCN (2017). In Utero Exposure to Maternal Hyperglycemia Increases Childhood Cardiometabolic Risk in Offspring. Diabetes Care, 40(5), 679–686. doi:10.2337/dc16-2397 [PubMed: 28279981]

Verstraeten BSE, McCreary JK, Falkenberg EA, Fang X, Weyers S, Metz GAS, & Olson DM (2019). Multiple prenatal stresses increase sexual dimorphism in adult offspring behavior. Psychoneuroendocrinology, 107, 251–260. doi:10.1016/j.psyneuen.2019.05.003 [PubMed: 31174163]

Verstraeten BSE, McCreary JK, Weyers S, Metz GAS, & Olson DM (2019). Prenatal two-hit stress affects maternal and offspring pregnancy outcomes and uterine gene expression in rats: match or mismatch? Biol Reprod, 100(1), 195–207. doi:10.1093/biolre/ioy166 [PubMed: 30084951]

Wiggins LD, Rubenstein E, Daniels J, DiGuiseppi C, Yeargin-Allsopp M, Schieve LA, … Levy SE (2019). A Phenotype of Childhood Autism Is Associated with Preexisting Maternal Anxiety and Depression. J Abnorm Child Psychol, 47(4), 731–740. doi:10.1007/s10802-018-0469-8 [PubMed: 30128718]

Wilson CA, Newham J, Rankin J, Ismail K, Simonoff E, Reynolds RM, … Howard LM (2020). Is there an increased risk of perinatal mental disorder in women with gestational diabetes? A systematic review and meta-analysis. Diabet Med, 37(4), 602–622. doi:10.1111/dme.14170 [PubMed: 31693201]

Yehuda R, & Lehrner A (2018). Intergenerational transmission of trauma effects: putative role of epigenetic mechanisms. World Psychiatry, 17(3), 243–257. doi:10.1002/wps.20568 [PubMed: 30192087]

Zou K, Ren J, Luo S, Zhang J, Zhou C, Tan C, … Ding G (2021). Intrauterine hyperglycemia impairs memory across two generations. Transl Psychiatry, 11(1), 434. doi:10.1038/s41398-021-01565-7 [PubMed: 34417446]

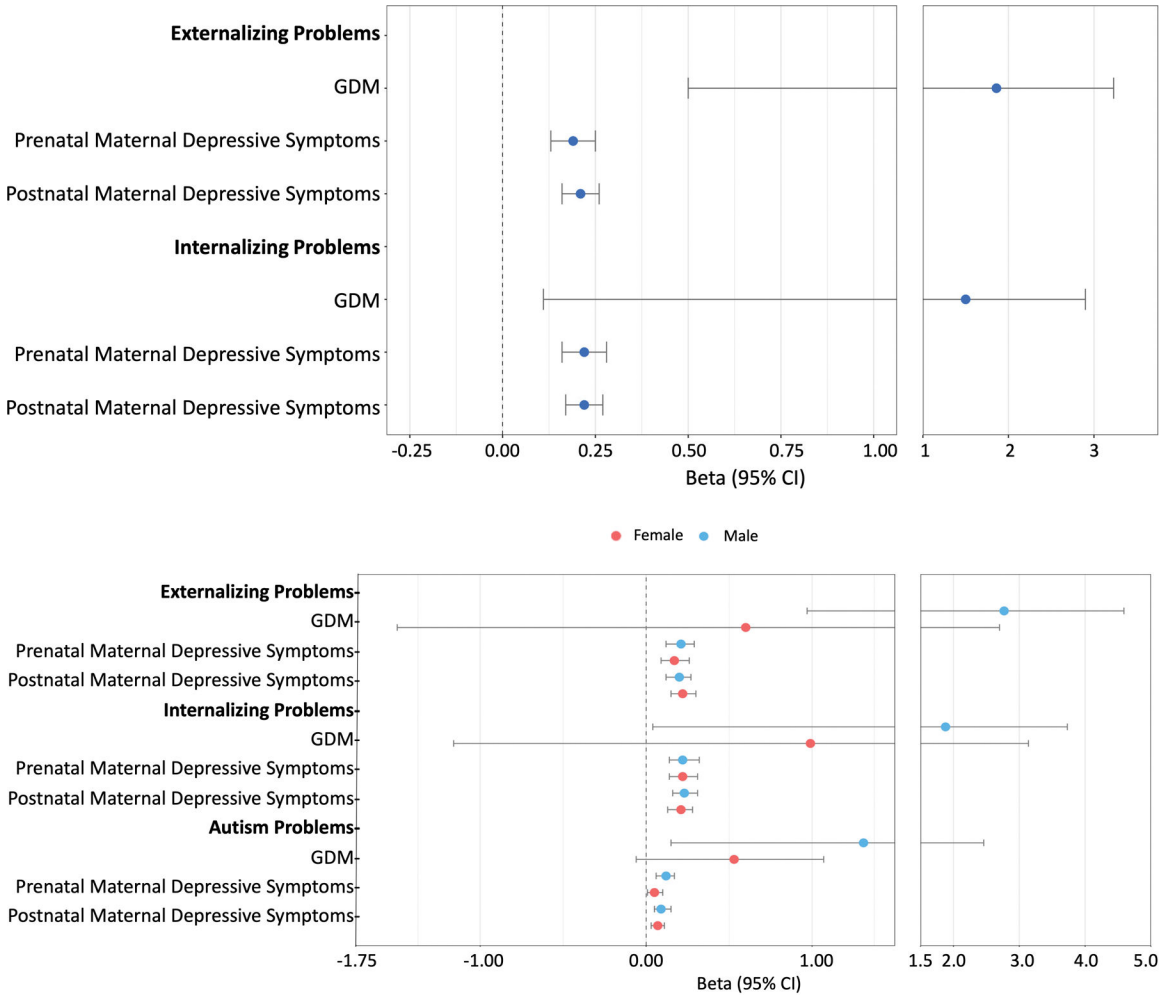

FIGURE 1.

Association between gestational diabetes mellitus (GDM) and prenatal and postnatal maternal depressive symptoms (*y*-axis) (a) with behavioral outcomes on the child behavior checklist (CBCL) (*x*-axis), (b) stratified by child's biological sex with behavioral outcomes on the Child Behavior Checklist (CBCL) (*x*-axis). Error bars reflect fully adjusted β coefficients with 95% confidence intervals (CIs).

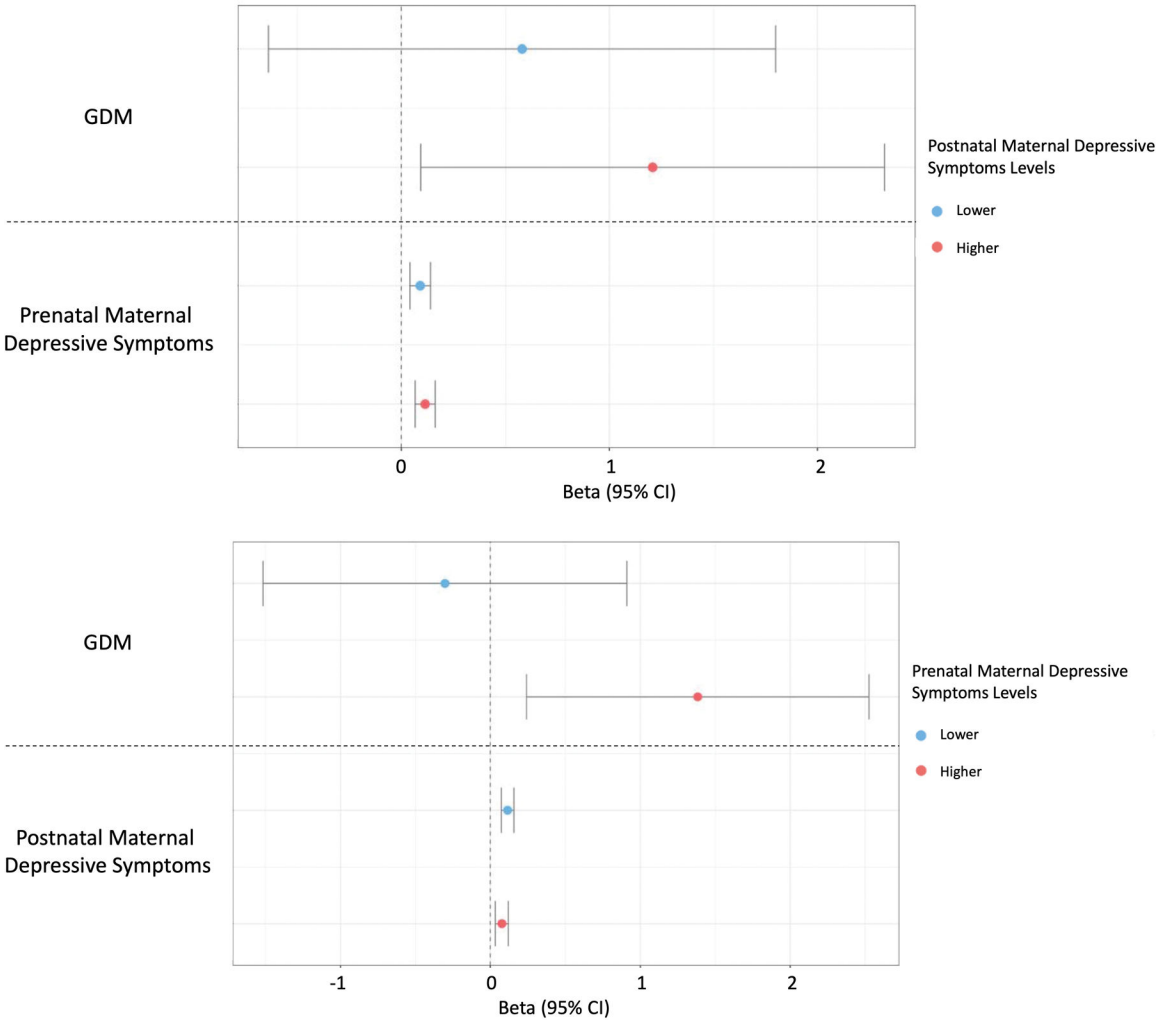

FIGURE 2.

Association between gestational diabetes mellitus (GDM) and (a) prenatal maternal, (b) postnatal maternal depressive symptoms (*y*-axis) with child autism problems on the DSM-oriented child behavior checklist (CBCL) scale (*x*-axis) stratified by lower and higher levels of postnatal maternal depressive symptoms. Error bars reflect univariate and fully adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

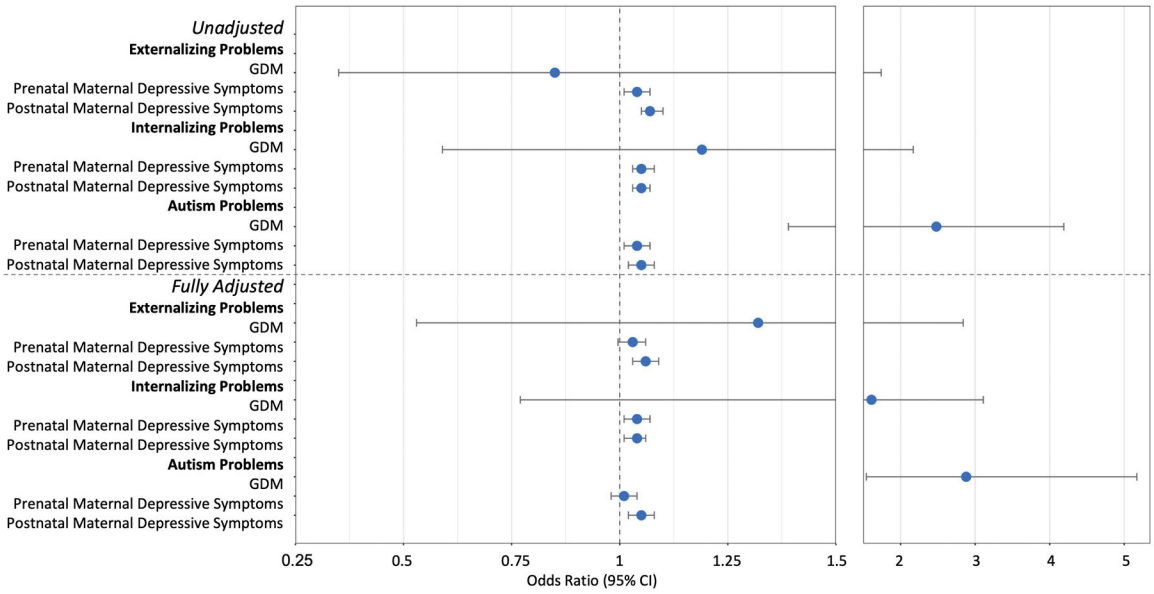

FIGURE 3.

Association between gestational diabetes mellitus (GDM) and prenatal and postnatal maternal depressive symptoms (*y*-axis) with clinical behavioral outcomes on the child behavior checklist (CBCL) (*x*-axis). Error bars reflect univariate and fully adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

TABLE 1

Participant Demographic Information

	GDM (n = 216)	Non-GDM (n = 2163)	Overall (n = 2379)
Maternal race			
American Indian or Alaskan Native	<5 (<1%)	<10 (<1%)	<15 (<2%)
Asian	18 (8.3%)	82 (3.8%)	100 (4.2%)
Black	37 (17.1%)	719 (33.2%)	756 (31.8%)
Mixed Race	46 (21.3%)	308 (14.2%)	354 (14.9%)
Native Hawaiian or Other Pacific Islander	<5 (<3%)	<15 (<1%)	<20 (<2%)
White	110 (50.9%)	1003 (46.4%)	1113 (46.8%)
Missing	<5 (<1%)	<35 (<2%)	<35 (<2%)
Maternal ethnicity			
Hispanic or Latino	78 (36.1%)	465 (21.5%)	543 (22.8%)
Non-Hispanic or Latino	138 (63.9%)	1692 (78.2%)	1830 (76.9%)
Missing	<5 (<1%)	<5 (<1%)	<5 (<5%)
Maternal age at delivery			
Mean (SD)	32.6 (5.66)	29.3 (5.89)	29.6 (5.95)
Median (min, max)	33.0 (18.0, 49.0)	29.0 (16.0, 50.0)	30.0 (16.0, 50.0)
Maternal pre-pregnancy BMI			
Underweight or normal weight	63 (29.2%)	990 (45.8%)	1053 (44.3%)
Overweight or obese	125 (57.9%)	1032 (47.7%)	1157 (48.6%)
Missing	28 (13.0%)	141 (6.5%)	169 (7.1%)
Birth mode			
Cesarean	81 (37.5%)	643 (29.7%)	724 (30.4%)
Vaginal	130 (60.2%)	1477 (68.3%)	1607 (67.5%)
Missing	<8 (<3%)	<45 (<3%)	<50 (<2.5%)
Gestational age category			
Preterm	22 (10.2%)	135 (6.2%)	157 (6.6%)
Term	194 (89.8%)	2028 (93.8%)	2222 (93.4%)
Child's biological sex at birth			
Male	126 (58.3%)	1102 (50.9%)	1228 (51.6%)
Female	90 (41.7%)	1061 (49.1%)	1151 (48.4%)
Child's age at CBCL assessment			
Mean (SD)	4.21 (0.582)	4.11 (0.606)	4.12 (0.604)
Median (min, max)	4.08 (2.00, 5.83)	4.00 (2.00, 5.92)	4.00 (2.00, 5.92)

Abbreviations: BMI, body mass index; CBCL, Child Behavior Checklist; GDM, gestational diabetes mellitus; SD, standard deviation

*The ECHO Program requires masking of cells with sample sizes <5.

TABLE 2

CBCL Clinical Thresholds

	GDM exposed (n = 216)	Non-GDM exposed (n = 2163)	Overall (n = 2379)
Externalizing problems			
Below clinical cutoff	< 210 (<97%)	< 2085 (<97 %)	< 2295 (< 97%)
Above clinical cutoff	< 10 (4%)	< 85 (5%)	< 90 (<4%)
Internalizing problems			
Below clinical cutoff	205 (94.9%)	2070 (95.7%)	2275 (95.6%)
Above clinical cutoff	11 (5.1%)	93 (4.3%)	104 (4.4%)
Autism spectrum problems			
Below clinical cutoff	199 (92.1%)	2091 (96.7%)	2290 (96.3%)
Above clinical cutoff	17 (7.9%)	72 (3.3%)	89 (3.7%)

Abbreviations: CBCL, Child Behavior Checklist; GDM, gestational diabetes mellitus