Research Article

Mediating the Impact of Prenatal Cannabis Exposure on Neurobehavioral Disinhibition: The Role of Delayed Developmental Milestone Attainment

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Objective: Environmental perturbations such as prenatal cannabis exposure (PCE) during critical periods may lead to disruptions in biological systems that have downstream consequences on behavior and development. Developmental milestones have served as a measure of normative development that allows providers and parents to identify areas for intervention. However, little is known about the direct impacts of PCE on development milestone attainment and whether failures to attain development milestones mediate later disruptions in executive functioning and behavioral disinhibition. **Method:** Data from the Adolescent Brain Cognitive Development (ABCD) study were used to examine prenatal cannabis effects on development while using a propensity score approach to control for familial and environmental characteristics. **Results:** PCE was not significantly associated with any delays in gross motor or language attainment; however, after accounting for confounders via propensity score for PCE (pPCE), PCE was significantly associated with delays in 'saying his/her first word' (Odds Ratio = 1.51, 95% Confidence Interval: [1.08, 2.10]). Upon examining the mediating effects, there were no significant total direct or total indirect effects on executive functioning. However, pPCE was associated with behavioral disinhibition and a significant mediation of PCE on behavioral disinhibition via delays in saying his/her first word were observed. **Conclusions:** This study suggests that delays in saying his/her first word serves as a risk factor for later behavioral disinhibition/externalizing problems. Importantly, the current study didn't examine language development, rather delays in saying his/her first word can provide insight into the possible impacts prenatal cannabis exposure has on developmental milestone attainment.

Key words: = prenatal; cannabis; developmental milestones; executive functioning; externalizing

Developmental milestones are a set of goals/markers of a child's development from infancy to childhood used to assess five categories of development: social/emotional and behavioral, gross motor, fine motor, language, and cognitive (Misirliyan & Huynh, 2022). Late identification of delays in development are associated with increased risk of developing later emotional, social, and academic difficulties (Lipkin et al., 2020). Previous literature suggests that developmental milestones are sensitive to environmental perturbations (Sliwowska et al., 2016), including prenatal substance exposure. However, less is known about the impact of

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prenatal cannabis exposure on these milestones. Overall, results suggesting a negative association between the acquisition of developmental milestones and prenatal substance exposure are mixed, have largely been conducted in rodent models, and primarily focus on prenatal alcohol or nicotine (Brys et al., 2014; Christensen et al., 2016). For example, preclinical and clinical studies have demonstrated deficits in grip strength, increased locomotor behavior, deficits in attention (Brys et al., 2014), and intellectual delays and delayed milestone attainment (Daugaard et al., 2020) in a rodent model of prenatal alcohol exposure and clinical study of prenatal valproate exposure, respectively. In addition, poorer gross motor and fine motor development has been observed among children with prenatal alcohol exposure, with evidence of dose-dependent effects and the greatest impairments among children diagnosed with Fetal Alcohol Syndrome (Bay & Kesmodel, 2011; Doney et al., 2014). In contrast, other studies have reported that low-level alcohol exposure (Hutchinson et al., 2019) or any alcohol exposure (Richardson et al., 1995) is not significantly associated with disruptions in either mental or motor development.

Human clinical studies of prenatal cannabis exposure suggest that heavy use, particularly during the third trimester, is associated with delayed motor development at 9 months of age, with impairments persisting through 3 years (Fried & Watkinson, 1990; Richardson et al., 1995). In contrast, no differences in gross motor development have been observed among 3-year-old children with low to moderate first trimester exposure, as assessed using the Gross Motor Scale developed at the University of Oregon Medical School (Gesell, 1947) and the Bayley Scales of Infant Development, nor among children assessed at 12 and 24 months with heavy exposure (>5 joints/week) using the Bayley Scales (Fried & Watkinson, 1988). More recent work similarly found no associations between prenatal cannabis exposure and gross motor outcomes across childhood (Avalos et al., 2024). Although Fried and Watkinson (1988) and Avalos and colleagues (2024) reported null findings, changes in cannabis potency over time, differences in sample demographics representative of the United States population, and the use of alternative assessment measures may clarify past mixed results. Preclinical studies have examined the impact of prenatal cannabis exposure on motor development during the early stages of pregnancy (first and second trimester) as well as the third trimester. Sprague Dawley rats prenatally exposed to delta-9-tetrahydrocannabinol (THC) during the human equivalent of the first and second trimester exhibited delayed early sensorimotor development as well as continued impaired motor coordination in early adolescence (Breit et al., 2022). Similarly, zebrafish embryos exposed to THC during the first trimester exhibited alterations in motor neuron morphology and locomotor responses to stimuli (Ahmed et al., 2018). In contrast, Sprague Dawley rats exposed to THC during the human third trimester equivalent displayed advanced early sensorimotor development and no long-lasting consequences to motor coordination in early adolescence (Breit et al., 2019). Overall, results from the preclinical models suggest exposure during the first and second trimesters results in atypical motor development, while evidence from clinical studies suggest heavy and third trimester exposure to disrupt motor development.

Attainment of developmental milestones is informative for the later diagnoses of neurodevelopmental disorders such as Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorder (Gurevitz et al., 2014; Hannigan et al., 2021; Havmoeller et al., 2019; Johnson et al., 2015). The current project focuses on gross motor and language development, as these are the most commonly studied milestones in relation to prenatal substance exposure. In addition, gross motor development has been shown to be predictive of broader cognitive development and aspects of executive functioning. As measured by the Peabody Developmental Motor Scales- 2nd Edition, gross motor development was positively associated with cognitive development scaled scores on the Bayley Scales of Infant and Toddler Development- 3rd edition (Veldman et al., 2019), suggesting that the early development of gross motor skills may support cognitive development. This is consistent with other reports of an indirect influence of early gross motor behavior on cognitive ability and executive functioning related domains, such as working memory and inhibitory control (Wu et al., 2017). Further, research suggests that delays in language attainment (expressive and receptive

delays) are a risk factor for socio-emotional behavioral problems and more pervasive developmental delays (Tervo, 2007). Children with language delays may also experience difficulties with frustration, become more withdrawn, suffer low self-esteem, or experience social rejection, which could further exacerbate or contribute to the behavioral problems later in life (Botting & Conti-Ramsden, 2000; Tervo, 2007). Therefore, it is necessary to examine not only the potential impacts of prenatal cannabis exposure on milestone attainment but also the persistent effects on later neurobehavioral development.

The role of the endocannabinoid receptor system in critical regulatory processes during early gestation and in neural development is well documented. Disruptions in endocannabinoid signaling have been associated with cell death, abnormal oviductal embryo transport, and dysregulated implantation (Ezechukwu et al., 2020; Maccarrone, 2008; Wang, 2006). It can be posited that cannabis use during the preimplantation phase would increase activation of CB1 and CB2 receptors, leading to possible deleterious consequences by increasing anandamide levels during this critical period. By 14 weeks of gestation, the endocannabinoid receptor system has matured in the fetal brain, and, by 17-18 weeks gestation, mature adult-like receptor levels can be measured in areas of the brain like the globus pallidus (Biegon & Kerman, 2001). These receptors continue to increase in density in the frontal cortex, basal ganglia, cerebellum, and hippocampus from gestation to adulthood (Mato et al., 2003). It is likely, given the presence of CB1 and CB2 receptors in areas of the fetal brain involved in motor development, emotion regulation, and cognitive development, that the endocannabinoid receptor system plays a crucial role in behaviors such as developmental milestone attainment, executive functioning, and behavioral disinhibition. However, the effects of exposure to cannabis during gestation on these processes are largely unknown.

Based on the literature, the current study aimed to 1) characterize developmental milestone attainment from 3 months- 2 years of age among children with prenatal cannabis exposure compared to unexposed children within the Adolescent Brain Cognitive Development Study; and 2) evaluate milestone attainment as a mediator linking prenatal cannabis exposure and neurobehavioral disinhibition. *Hypothesis:* Children prenatally exposed to cannabis would demonstrate delays in their developmental milestone attainment relative to unexposed children, and that these delays would mediate the effect of prenatal exposure and neurobehavioral disinhibition. Specifically, prenatal cannabis exposure will be associated with delays in gross motor and language milestones, including but not limited to sitting without assistance, walking without assistance, and saying his or her first word.

METHODS

Participants

Data are from the Adolescent Brain Cognitive Development (ABCD) Study (release 5.0), an ongoing single-cohort prospective longitudinal study focusing on brain development and child and adolescent health outcomes (Jernigan et al., 2018). ABCD includes 21 research sites across the U.S. and has recruited a total of 11,868 children weighted to be representative of the U.S. population. Among the 11,868 ABCD participants, 7,894 were singletons, 1,810 were nontwin siblings, 2,134 were twins, and 30 were triplets. The sample for the current analyses consisted of mothers [n = 9,876; ages 13-60, mean (M) = 29.40, standard deviation (SD) = 6.27] and their children (n = 11,868). Study participants were recruited using a stratified random sample with the intention of following the participants for 10 years post recruitment. Ages of the children are as follows: baseline [ages 9-11 (M = 9.92, SD = 0.62)], 1- year follow up [10-12 (M = 10.92, SD = 0.64)], 2- year follow up [11-14 (M = 12.03, SD = 0.67)], and 3- year follow up [11-15 (M = 12.91, SD = 0.65)]. Table 1 provides ABCD sample characteristics for the current analyses.

Measures

Data were analyzed by age (ages 9-13); therefore data collected at baseline, 1- year follow up, 2- year follow up, and 3- year follow up were used. Additional measures utilized to test the previously defined hypotheses are outlined below.

Prenatal cannabis exposure. Prenatal cannabis exposure (PCE) was assessed via the Developmental History Questionnaire (DHQ). The

DHQ was adapted from the National Comorbidity Survey- Adolescent study, a federally funded project of ~10,000 adolescents (Kessler, Avenevoli, Costello, et al., 2009; Kessler, Avenevoli, Green, et al., 2009; Merikangas et al., 2009). PCE was based on parent or caregiver retrospective self-report taken at baseline of "before knowing of pregnancy. Marijuana" and "knowing of pregnancy. Marijuana." Participant responses on this question were restricted to yes/no responses, however parents or caregivers were not asked about the timeframe in which they used cannabis (i.e., before conception, at recognition, etc.). This operationalization of PCE is in line with other reports (Terplan, 2022) and includes exposure before and after knowledge of pregnancy. Specifically, two groups were created based on responses: no PCE (n = 10,824) and PCE (n = 696). This is important because, for example, in 2019, among the pregnancies in United States, approximately 42% were unplanned (Rossen, 2023). Crucially, the development of the fetal central nervous system occurs before most women know they are pregnant. Thus, we aimed to capture the most accurate timing data (i.e. likelihood of exposure) as possible in this secondary data analysis. Table S1 provides the percentages of the ABCD sample that make up the following categories: cannabis use before knowing of pregnancy, cannabis use after knowing of pregnancy, and cannabis use before or after knowing of pregnancy.

Familial confounders. Familial/maternal confounders are risk factors known to be associated with cannabis use during pregnancy, as well as prenatal and behavioral outcomes (Brown et al., 2019; De Genna et al., 2015; El Marroun et al., 2008; Mark et al., 2016; Young-Wolff et al., 2020). The familial/maternal confounders included were selected based on a review of the literature primarily from findings drawn from three widely cited longitudinal studies of maternal cannabis effects on birth and behavioral outcomes: the Maternal Health Practices and Child Development Project (MHPCD; Day & Richardson, 1991), the Ottawa Prenatal Prospective Study (OPPS; Fried, 1995), and Generation R (Jaddoe et al., 2006). Familial/maternal confounders related to prenatal and postnatal behavior and family history of substance use, as well as psychopathology, were measured using the DHQ. Parents/caregivers retrospectively reported at baseline on family alcohol use, drug use, and depression psychopathology history. The current analyses only used information related to immediate family members (mother and father) and grandparents. Perceived neighborhood safety was measured using the Neighborhood Safety Protocol of the PhenX Toolkit, which was derived from the Safety from Crime items assessing neighborhood qualities (Echeverria, 2004; Mujahid et al., 2007). Parent or caregiver reports on three items assessing feelings of safety and presence of crime within their respective neighborhoods were used, with higher scores indicating greater/positive perceived neighborhood safety (Hamilton et al., 2011). Parental externalizing traits, specifically rule breaking behavior and ADHD were assessed using the Parent Adult Self Report (ASR) questionnaire, an assessment designed to measure adaptive and maladaptive functioning (Achenbach, 2006; Guerrero et al., 2020).

Developmental milestone attainment. The DHQ provided information on developmental milestone attainment. A parent/caregiver retrospectively reported at baseline on the age at which developmental milestones were achieved. Specifically, parents/caregivers reported on the age at which the child rolled over, sat without assistance, walked without assistance, said his/her first word, and stopped wetting the bed. The use of the developmental milestone questions derived from the DHQ is the standard that is used to evaluate key milestones in infancy and childhood within other published ABCD studies (Zhuo et al., 2022). While some suggest that parents or caregivers may not be able to provide objective observations of their infant's development, research has suggested that maternal retrospective reports of key developmental milestones, specifically developmental delays, are reliable and have been used in other studies (Langendonk et al., 2007; Majewska et al., 2013). Delayed developmental milestone attainment was determined based on the distribution of the sample. The following were used as cutoffs to indicate relative delays in rolling over (5 months of age [>90th percentile]), sitting without assistance (10 months of age [>95th percentile]), walking without assistance (18 months of age [>90th percentile]), speaking first word (13 months of age [>90th percentile]), and

wetting the bed (12 years of age [>90th percentile]). Notably, the 95th percentile was used for sitting without assistance because the 75th and 90th percentile were equivalent. We also modeled developmental milestone attainment as delays in 2 or more gross motor milestones with or without a language delay (i.e., rolling over, sitting without assistance, walking without assistance with or without speaking first words; Zhuo et al., 2022). Comparatively, the Center for Disease Control and Prevention (CDC) classifies normative age of developmental milestone attainment as 4 months (rolling over), 9 months (sitting without assistance), 18 months (walking without assistance), and 12 months (saying first word; (Centers for Disease Control and Prevention [CDC], 2024). The CDC's classification of the average age for walking without assistance aligns with the 90th percentile cutoff in ABCD, underscoring the importance of using the ABCD sample's distribution—and its skewness—to more accurately identify delayed motor development within the present study.

Neurobehavioral Disinhibition Measures

Early Adolescent Temperament Questionnaire- Parent Report. Parents/caregivers completed 6 items on the Early Adolescent Temperament Questionnaire- Parent Report (EATQ) designed to assess two distinct emotion regulation strategies: cognitive reappraisal and expressive suppression (Gross & John, 1998, 2003). Higher scores on items comprising the two subscales indicated higher/more consistent use of the emotion regulation strategies.

Child Behavior Checklist (CBCL)- Parent Report. Parents/caregivers reported on observed externalizing behaviors using the CBCL. Broad-spectrum externalizing behaviors in the CBCL include delinquent and aggressive behaviors. Standardized T-scores were used to create a 9-13 years of age score that accounted for externalizing scores between those ages. T-scores are standardized for sex and age, with higher scores indicating more problems (Achenbach, 1991). The use of broad spectrum externalizing T-scores is supported by recent reports of a bi-factor and higher order models within ABCD (Clark et al., 2021).

Difficulty in Emotion Regulation Questionnaire- Parent Report. The Difficulty in Emotion Regulation Questionnaire- Parent Report (DERS) is a 29-item questionnaire used to assess emotional dysregulation. Specifically, the DERS has six subscales that emerge as the following four dimensions of emotion regulation: (1) awareness and understanding of emotions, (2) acceptance of emotions, (3) the ability to engage in goal directed behavior and inhibit impulsive behavior even when experiencing negative emotionality and (4) effective implementation of emotion regulation strategies (Gratz & Roemer, 2004). These DERS subscales demonstrate adequate internal consistency (Bunford et al., 2020; Gratz & Roemer, 2004), with higher scores indicating greater emotional dysregulation.

National Institutes of Health (NIH) Toolbox. To assess dimensions of executive function, brief standardized tests from the National Institutes of Health (NIH) Toolbox in the areas of attention, inhibition, cognitive flexibility, and working memory were used. The NIH Toolbox is an iPad-based lab-administered set of lab tasks normed for assessment in individuals between the ages of 3-85 (Luciana et al., 2018). The List Sorting Working Memory Test is a picture number sequencing test and demonstrates good test-retest reliability (ICC = 0.86) and convergent validity with similar assessment batteries (Tulsky et al., 2013). The Flanker Inhibitory Control and Attention Test measures the degree to which participants can quickly and accurately determine if the target stimuli are congruent or incongruent with the surrounding stimuli. Finally, the Dimensional Change Card Sort Test, a measure of cognitive flexibility, asks participants to determine, out of a set of stimuli, which stimulus matched the target stimuli by a given dimension (i.e., shape or color). The test involves 40 pseudorandom trials. For both the Flanker Inhibitory Control and Attention Test as well as the Dimensional Change Card Sort Test, a participants score is based on accuracy and reaction time/speed. Both tests demonstrate strong test-retest reliability, ICC = 0.92 and 0.92, respectively, as well as convergent validity with similar assessments (Zelazo et al., 2014; Zelazo et al., 2013). The three tasks from the NIH Toolbox were selected to measure executive function and are consistent with other published ABCD studies (Rozzell-Voss et al., 2024).

Data Analysis

Propensity for prenatal cannabis exposure. Propensity score analysis was used to control for maternal/familial level confounding while examining the effect of PCE on developmental milestones and neurobehavioral disinhibition. Propensity scores were derived using a logistic regression model conducted in SAS (version 9.4; SAS, 2013) using data from 11,520 caregiver reports on prenatal cannabis use. Model fit was assessed using the receiver operating characteristic (ROC) curve (Swets, 1986), where values closer to 1.00 indicated better classification of using cannabis during pregnancy and values close to 0.5 indicated chance. Propensity scores for PCE (pPCE) were created using 23 maternal/familial risk factors, and missingness was accounted on each risk variable by including a dummy variable category. These 23 risk variables included: biological mother, maternal age, paternal age, parental education, partner education, planned pregnancy, prenatal vitamins, birth weight, nausea, prenatal care (i.e., number of doctor's visits), number of months breastfed, maternal and paternal immediate family alcohol use, maternal and paternal immediate family drug use, maternal and paternal family history of depression, prenatal alcohol use, prenatal tobacco use, maternal externalizing behaviors (i.e., ADHD and Rule-Breaking T-scores), and neighborhood safety. Parental race (simple effect coded for White, Black, Mixed, Asian, Alaska/ Native American, Pacific Islander, Hispanic, and Other) was included as a covariate, and all models were fit and clustered by site id, as well as familial structure, and included a weight variable that accounted for the representativeness of the ABCD sample.

Neurobehavioral disinhibition within the Adolescent Brain Cognitive Development Study. Exploratory factor analysis was used to ensure that the available measures held together as hypothesized to capture neurobehavioral disinhibition as a single latent factor. In addition to testing model fit for the broader neurobehavioral disinhibition construct, exploratory factor analysis was also used on the DERS to identify the appropriate factor structure for the present sample.

Effects of PCE on developmental milestones and neurobehavioral disinhibition. A set of logistic regression models were used to examine the prospective effect of PCE on the developmental outcomes. Models examined the unique contribution of PCE over and above covariates and expanded the model further to examine the effect of PCE on the developmental outcomes while accounting for child's familial propensity for PCE. Path analyses were conducted using MPlus (version 8; Muthén, 2017) to examine the direct and indirect effect of PCE and pPCE on neurobehavioral disinhibition (executive function and behavioral disinhibition) via significantly delayed developmental milestones. Confidence intervals for the direct and indirect effects were estimated using bootstrapping (10,000 iterations) and all models included sex and race as covariates.

All outlined analyses accounted for correlated observations within families caused by the presence of twins, triplets, and siblings, using the sandwich estimator to adjust the standard errors (Zhang et al., 2011; Zhang et al., 2019). We visually examined the distribution of missing data across models to ensure that missingness was not systematically skewed. To control for multiple comparisons, *p*-values were adjusted using the Benjamini-Hochberg procedure to maintain the false discovery rate at q = 0.05. *P*-values were compared to their corresponding false discovery rate (FDR) thresholds.

RESULTS

Sample Descriptives

Maternal and child/adolescent level sample characteristics are described in Table 1. The observed prevalence of familial factors assessed in relation to propensity for cannabis use during pregnancy are shown in Table 2. Sensitivity analyses were conducted on a subset of the sample (biological mother versus non biological mother; for prevalence estimates and observed effects see Table S2 and Table S3).

Propensity for Prenatal Cannabis Use in Mothers

Among 11,520 caregivers with reports of prenatal cannabis use, 6.07% (N = 696) endorsed using cannabis either before or after knowing of their pregnancy. The results from the logistic regression analysis using 23 maternal and familial risk factors to predict PCE are summarized in Table 3. The model demonstrated

strong predictive accuracy with an area under the ROC curve (AUC) of 0.90 (Figure 1), indicating the model robustly classified mothers who used cannabis during their pregnancy and those that did not. Risk factors significantly associated with greater odds of PCE included younger maternal age, unplanned pregnancy, maternal immediate family drug use, paternal immediate family drug use, prenatal alcohol use, prenatal tobacco use, non-biological mothers, lower perceived neighborhood safety, lower ADHD T-scores, and higher rule breaking T-scores. Importantly, consistent with propensity score approaches, all 23 risk factors were included in subsequent analyses, not just the risk factors significantly associated with propensity for PCE. Additional analyses focusing exclusively on biological parent responses (AUC = 0.89), as well as using non-biological mothers only (i.e., excluding parent; AUC = 0.96), yielded similar results, see Figures 2 and 3 and Tables 6 and 7. Given, the consistency of prenatal cannabis reports, regardless of reporter as demonstrated by the AUC, all subsequent analyses leveraged data from all reporters (parent, caregiver, etc.).

Effects of Prenatal Cannabis Exposure on Developmental Milestones

The means and standard deviations for the individual developmental milestones in children with PCE and no PCE are presented in Table 4. Developmental milestone models were evaluated in a stepwise manner, initially assessing the main effect of PCE alone (Model a), followed by the inclusion of propensity for PCE (Model b). Logistic regression model results are presented in Table 5. PCE alone was not significantly associated with any of the developmental milestones. However, adding propensity for PCE (pPCE) to all models increased the PCE logistic regression model parameter estimates. Interestingly, after accounting for familial/maternal confounders via the propensity score, PCE was significantly associated with delays in 'saying his/her first word' (Model 4b). Specifically, children prenatally exposed to cannabis were at increased odds of delayed first word (OR = 1.51, 95% CI [1.08, 2.10]) compared to non-exposed children. These effects remained statistically significant after controlling for FDR (q = 0.05) using the Bejamini-Hochberg procedure, with significance retained at the third-ranked threshold ($p \leq 0.021$).

Characterizing Neurobehavioral Disinhibition

Exploratory factor analysis (EFA) using *geomin* rotation was conducted to explore the dimensionality of the 29 item DERS questionnaire. The variance accounted for by the solution, the variance accounted for by each individual factor, and the interpretability of the factors were all evaluated to determine the initial plausibility of the factor structure. Consistent with previous literature (Bunford et al., 2020; Gratz & Roemer, 2004), six factors were identified (nonacceptance, goals, impulse, awareness, strategies, and clarity); see Table 6 for the items composing the 6 factor model. A six factor DERS model was then tested using confirmatory factor analysis (CFA). The six latent variables were as follows: (1) Nonacceptance of Emotional Response, (2) Difficulties Engaging in Goal-Direct Behavior, (3) Impulse Control Difficulties, (4) Lack of Emotional Awareness, (5) Limited Access to Emotion Regulation Strategies, and (6) Lack of Emotional Clarity. All standardized factor loadings were generally large (> 0.4 threshold) and statistically significant (p's < .001) across all 6 latent factors, see Table 7 for factor loadings. The 6-factor model fit well descriptively [Comparative Fit Index (CFI) = .877, Root Mean Square Error of Approximation (RMSEA) = .057, Standardized Root Mean Square Residual (SRMR) = .051], see Table 8. Next, a single neurobehavioral disinhibition factor model was tested using EFA; however, a one-factor model did not fit well statistically. Instead, a one-factor executive function and a one-factor behavioral disinhibition model were independently tested using confirmatory factor analysis. The executive function model was indicated by 3 observed variables and fit well descriptively (CFI = .995, RMSEA = .013, SRMR = .008), see Table 9 for factor loadings and Table 10 for fit statistics. In comparison, the behavioral disinhibition model was indicated by 13 observed variables and 4 latent factors with moderate model fit (CFI = .617, RMSEA = .159, SRMR = .109), see Table 11 for factor loadings and Table 12 for fit statistics. All subsequent analyses and interpretations will examine executive function and behavioral disinhibition as independent latent constructs

rather than as a single neurobehavioral disinhibition latent construct. See Figure S3 for a factor model of executive function and behavioral disinhibition.

Direct and Indirect PCE and Propensity for PCE effects on Developmental Milestones, Executive Function, and Behavioral Disinhibition

Results examining the main effects between PCE, executive function and behavioral disinhibition are presented in Table 13. Maternal reports of PCE alone (Model 1a) were not associated with executive functioning. However, PCE was associated with behavioral disinhibition (Model 2a), specifically higher PCE was associated with greater behavioral disinhibition (ß = 0.15, 95% CI [0.10, 0.18]). Upon accounting for risk of PCE (i.e., pPCE) in all models (i.e., Model a vs. Model b), PCE parameter estimates generally decreased in magnitude suggesting confounding. Model 2b indicated that pPCE is associated with behavioral disinhibition. In particular, greater pPCE was positively associated with behavioral disinhibition (0.22, [0.18, 0.25]). Figure S3 and S4 show models examining the effect of PCE and pPCE on executive function and behavioral disinhibition via delays in saying first word. Two independent models were tested, one model examining the indirect and direct effects of PCE and pPCE on executive functioning via delayed first word and a model testing the same for behavioral disinhibition via delayed first word. There were no significant direct or indirect effects on executive functioning. In the second independent model tested, there were significant direct and indirect effects (j' and fh path) on behavioral disinhibition. See Table 14 and Table 15 for a summary of the mediation parameters and a summary of the direct and indirect effects, respectively. In particular, pPCE was associated with behavioral disinhibition (path j'). Tests of the indirect effect using bootstrapped confidence interval indicated significant mediation of PCE on behavioral disinhibition (path fh).

Finally, in order to understand which of the familial and environmental factors may be driving the association between pPCE and behavioral disinhibition an exploratory post hoc analysis was conducted. For a detailed breakdown of indicators of propensity for cannabis exposure and behavioral disinhibition see Table S6.

DISCUSSION

Delays in saying his or her first word, while not representative of expressive or receptive language ability, can inform possible delays in these language domains in later development. These findings are consistent with a previous study examining developmental milestone attainment in ABCD (Zhuo et al., 2022); however, Zhuo et al. did not examine milestone attainment in a sample of children prenatally exposed to cannabis. Instead, the study controlled for various perinatal risk factors and maternal characteristics. Interestingly, the present study did not observe delays in any of the motor milestones that Zhuo et al. reported, which could be informative of the targeted impact of prenatal cannabis exposure on specific regions of the brain or nervous system that are involved in language production/development. One possible explanation is that repeated activation of CB1 receptors during critical periods of central nervous system development may produce long-lasting alterations in the expression and functioning of multiple neurotransmitter systems, including dopaminergic and GABAergic pathways, which are implicated in higher-order cognitive processes (Grant et al., 2018). Moreover, brain regions involved in auditory and verbal processing—such as the hippocampus, cerebellum, and basal ganglia—have a high density of CB1 receptors (Herkenham et al., 1991; Takahashi & Linden, 2000) and may be impacted by *in utero* cannabis exposure. Findings from prenatal alcohol exposure studies have identified brain volume reductions in the frontal, temporal, and parietal lobes in children with heavy prenatal alcohol exposure (Glass et al., 2014; Sowell, 2002), which may inform potential shared neurodevelopmental pathways that may also be impacted in children with prenatal cannabis exposure.

Our initial model (i.e., without propensity scores) suggested no significant association between PCE and delayed developmental milestone attainment. However, after accounting for several familial and environmental confounders via the propensity score adjustment, PCE was significantly associated with delays in

saying first word. This pattern is consistent with a suppression (negative confounding) effect, whereby confounding variables included in the propensity score attenuated the unadjusted association. For instance, several confounders included within the propensity score are independently associated with both higher likelihood of PCE and delayed developmental milestone attainment. When these shared risk factors are not adequately controlled for, they can mask the unique association between PCE and language development. Therefore, the propensity score adjustment reduces this confounding, allowing the association between PCE and delayed first word to emerge more clearly. However, our results are inconsistent with previous findings that infants exposed to cannabis later in pregnancy perform better on expressive and receptive language assessment measures compared to infants with no exposure (Talavera-Barber et al., 2023) and other studies reporting no clinically significant delays in development (Avalos et al., 2024). As previously mentioned, these differences could be explained by the difficulties of isolating the effects of the exposure itself. Additionally, our dichotomous prenatal cannabis exposure variable does not account for timing of exposure, dose, potency, or frequency which impact the bioavailability and drug metabolism in the fetus.

Furthermore, developmental milestone attainment norms can vary largely by ethnic, cultural, genetic, and environmental factors (Gerber et al., 2010), which may limit the generalizability to other populations. Nevertheless, the present study accounted for the familial structure of ABCD as well as socioenvironmental confounders via the propensity score that could additionally account for variation in milestone attainment.

Several other prenatal and postnatal factors have been associated with attainment of developmental milestones. Such factors include parity (higher birth order), greater paternal age, younger gestational age and low birth weight predicting slower milestones attainment (Flensborg-Madsen & Mortensen, 2017). Of course, an individual's genetic background cannot be ignored and was not accounted for in the present study. A recent meta-analysis that systematically examined a pooled sample of 79,044 monozygotic and dizygotic twin samples reported high heritability estimates for developmental milestone attainment of psychomotor functioning (pooled h^2, 0.59; 95% CI, [0.25-0.79]), attention (pooled h^2, 0.48; 95% CI, [0.17-0.71]), and behavioral functioning (pooled h^2, 0.44; 95% CI, [0.15-0.75]), suggesting that individual observed differences in these domains in infancy may be explained, in part, by genetic factors (Austerberry et al., 2022). While there are inherent limitations to evaluating developmental milestones, as described, they continue to serve as important markers for providers and researchers.

Finally, the results suggest that the relationship between PCE and behavioral disinhibition is mediated by delays in saying his/her first word. It is possible that delays in saying his/her first word serves as a risk factor for later externalizing problems. Previous studies have reported that broader language ability, both expressive and receptive language, is associated with externalizing traits including conduct problems and increased aggression. Mechanistically, the association between broader language ability and externalizing traits is driven by the mediation of poor social skills (Petersen et al., 2013). Importantly, other studies have found that expressive language delays at 18 months of age were weakly associated with externalizing scores on the CBCL (Henrichs et al., 2013), and persistent expressive language delays were associated with increased externalizing scores at 36 months of age (Henrichs et al., 2013). These findings are consistent with other reports that persistent poor receptive language performance is associated with greater behavioral and psychosocial problems later in life (Schoon et al., 2010). Notably, although the indirect effect of delayed first word on behavioral disinhibition was statistically significant, its magnitude was small ($\beta = 0.01$). This suggests that delayed first word is likely a minor developmental pathway linking PCE to later behavioral outcomes. Small indirect effects are common in longitudinal developmental models, particularly when distal outcomes are influenced by additional interacting biological, social, and environmental processes over time. Additionally, our study did not examine receptive or expressive language development. Thus, it would be important to investigate whether delays in saying his/her first word persist and are predictive of later delayed language development.

Strengths and Limitations

To our knowledge, this study is the first to examine the impacts of prenatal cannabis exposure on developmental milestone attainment and subsequent mediating effects on executive functioning and behavioral disinhibition. However, due to limitations inherent in using pre-existing data, we were unable to examine several cannabis-related properties such as dose, strain, and timing of exposure (e.g., first, second or third trimester), which are necessary to understand the nuanced impact of PCE on development. Therefore, we used a conservative approach in characterizing and operationalizing PCE. Specifically, we used a broad, dichotomized definition of prenatal cannabis exposure that does not allow for a more detailed interpretation regarding frequency, timing, dose, or quantity of use because these details were not assessed in ABCD. However, there are several demographic and environmental factors that are additionally associated with increased propensity to use cannabis during pregnancy that may also impact subsequent offspring behavior and development. Therefore, the propensity score approach allowed for the controlling of these critical environmental, behavioral, and biological factors that may influence our outcomes of interest and allowed for an unbiased interpretation of our results. Furthermore, the assessment of developmental milestone attainment in the present study was limited. Specifically, age of milestone attainment was based on parent report derived from a single-item measure rather than a standardized developmental assessment (e.g., the Bayley Scales of Infant and Toddler Development). Accordingly, these findings should be interpreted with appropriate caution.

While the ABCD measure of prenatal use is based on retrospective report, the validity of which has been debated, we argue that this limitation is offset by the sample size, phenotyping, and representativeness afforded by the ABCD study. Further, there has been considerable work in the area of retrospective reporting of prenatal drug use. For example, previous studies report high concordance between self-report measures of prenatal substance use and biochemical assessments (Patrick et al., 1994; Skelton et al., 2022), as well as high consistency between retrospective maternal reports of smoking during pregnancy and cotinine sample results, which remained high after 15 years (Petitti et al., 1981; Pickett et al., 2009). Additionally, retrospective maternal reports of smoking during pregnancy were consistent with independent informant reports (Heath et al., 2003), birth record reports, and independent partner/father reports of mother's smoking during pregnancy (Knopik et al., 2016). Further, mothers were found to be accurate and consistent reporters of prenatal tobacco use as well as prenatal cannabis use at 6 months and 8 years post pregnancy, Cohen $\kappa = 0.65$ and 0.61, respectively (Ramos et al., 2020). Overall, these study results provide evidence that (i) mothers accurately report substance use during pregnancy; and (ii) mothers reports of substance use during pregnancy are accurate and remain consistent 8-15 years post pregnancy.

Additionally, while some suggest that parents or caregivers may not be able to provide objective observations of their infants development, research has suggested that maternal retrospective reports of key developmental milestones, specifically developmental delays, are reliable and have been used in other studies (Langendonk et al., 2007; Majewska et al., 2013). Comparisons between parent reports of developmental milestone attainment to independent home visit assessment reports yielded moderate agreement to almost perfect agreement (Cohen $\kappa = 0.54$ - 0.96; Bodnarchuk & Eaton, 2004).

The developmental lens we followed for this study allowed us to examine effects over time (3 months-2 yrs and 9-13 yrs), which adds to our limited knowledge of the long-term impacts of PCE. While previous longitudinal and cross-sectional studies have provided an abundance of knowledge, the cannabis landscape has changed substantially. Unfortunately, the dose, strain, timing of exposure, and potency could not be ascertained from the ABCD study, however, recruitment for the ABCD study occurred between 2016-2018, with estimated maternal pregnancy between 2007-2010. The cannabis availability, dose, laws, and regulations have significantly changed from when previous longitudinal studies recruited participants. Therefore, the current study, while not directly examine the impacts of dose or timing of exposure, can add to the growing literature of the impacts of PCE that is likely more

consistent with the cannabis products currently being sold.

Findings from the current study indicate that prenatal cannabis exposure, as opposed to social, environmental, and familial confounders, may better account for delays in saying his/her first word. Further, delays in saying his/her first word mediated the relationship between PCE and behavioral disinhibition between 9-13 years of age. Future studies should continue to parse apart these effects in order to understand the underlying changes in the biological or social mechanisms that uniquely impact individuals with *in utero* cannabis exposure that increases their risk for later behavioral disruptions. This work should include careful consideration of familial, social, and environmental confounders such as co-occurring substance use during pregnancy, which may represent important targets for prevention and intervention efforts. Importantly, future studies should also examine whether the delays in saying his/her first word persist, whether they are sex specific, and are predictive of more pervasive delays to language or speech development should also be investigated.

Table 1. *ABCD Study Sample Characteristics*

Maternal Variables	**No PCE (*N*= 10,824)**	**PCE (*N*= 696)**
Maternal Age, mean (*SD*)	29.71 (6.14)	25.32 (6.07)
Paternal Age, mean (*SD*)	32.06 (6.97)	28.24 (7.69)
Race/ethnicity		
White	7981(74%)	415 (60%)
Black	1601 (15%)	228 (33%)
Mixed	513 (5%)	29 (4%)
Asian	387 (4%)	5 (0.7%)
Hispanic	149 (1%)	6 (0.9%)
Alaska/Native American	29 (0.3%)	2 (0.3%)
Pacific Islander	11 (0.1%)	1 (0.1%)
Other	40 (0.4%)	6 (0.9%)
Child/ Adolescent Variables	**No PCE (*N*= 10,824)**	**PCE (*N*= 696)**
Baseline- Age, mean (*SD*)	9.92 (0.62)	9.87 (0.64)
1-Year- Age, mean (*SD*)	10.93 (0.64)	10.87 (0.65)
2-Year- Age, mean (*SD*)	12.03 (0.67)	11.99 (0.69)
3-Year- Age, mean (*SD*)	12.92 (0.65)	12.84 (0.65)
Race/ethnicity		
White	8198 (76%)	412 (59%)
Black	1652 (15%)	243 (35%)
Mixed	482 (4%)	24 (3%)
Asian	223 (2%)	4 (0.6%)
Hispanic	114 (1%)	3 (0.4%)
Alaska/Native American	33 (0.3%)	2 (0.3%)
Pacific Islander	10 (0.09%)	3 (0.4%)
Other	47 (0.4%)	4 (0.6%)
Sex		
Female	5156 (48%)	347 (50%)
Male	5668 (52%)	349 (50%)

Note. Study sample characteristics of mothers and children with prenatal cannabis exposure (PCE) and No PCE. Notation: proportion and percentages reported are relative to the total sample size for the given category for "No PCE" or "PCE." Variables were dummy coded in order to account for missingness.

Table 2. *Observed Prevalence (n[%]) of Familial Risk Factors/Confounders for Prenatal Cannabis Exposure (PCE)*

Familial Factors	No PCE (N= 10,824)	PCE (N= 696)
Biological Mom	9,512 (88%)	547 (79%)
Maternal Age, mean (*SD*)	29.71 (6.14)	25.32 (6.07)
Paternal Age, mean (*SD*)	32.06 (6.97)	28.24 (7.69)
Parental Education, mean (*SD*)[a]	17 (2.78)[a]	16 (2.49)[a]
Partner Education, mean (*SD*)[a]	16 (3.05)[a]	15 (2.76)[a]
Planned Pregnancy	6,867 (63%)	168 (24%)
Prenatal Vitamin	10,162 (94%)	586 (84%)
Birth Weight, mean (*SD*)	6.60 (1.48)	6.55 (1.44)
Nausea	1,471 (14%)	128 (18%)
Prenatal Care, mean (*SD*)	16 (7.52)	15 (6.47)
Months Breastfed, mean (*SD*)	8.04 (8.85)	4.90 (7.00)
Maternal Immediate Family Alcohol Use	1,822 (17%)	264 (38%)
Paternal Immediate Family Alcohol Use	2,188 (20%)	251 (36%)
Maternal Immediate Family Drug Use	806 (7.45%)	253 (36%)
Paternal Immediate Family Drug Use	1,092 (10%)	242 (35%)
Maternal Immediate History Depression	3,528 (33%)	348 (50%)
Paternal Immediate Family Depression	2,304 (21%)	184 (26%)
Alcohol Use During Pregnancy	2,426 (22%)	417 (60%)
Tobacco Use During Pregnancy	1,123 (10%)	415 (60%)
ADHD T-scores, mean (*SD*)	53.08 (5.39)	55.53 (7.18)
Rule Breaking T-scores, mean (*SD*)	52.30 (4.40)	56.06 (6.85)
Neighborhood Safety, mean (*SD*)[b]	3.93 (1.01)[b]	3.53 (1.18)[b]

Note. Characteristics of individuals from mothers with prenatal cannabis exposure (PCE). Notation: proportion and percentages reported are relative to the total sample size for the given category for "No PCE" or "PCE." Missingness was accounted for in the model through dummy coded variables. [a] Educational level values are equal to: 15 = Some College, 16 = Associate's Degree: Occupational, 17 = Associate's Degree: Academic Program [b] Neighborhood safety summary scores were calculated, original scores ranged from 1 (Strongly Disagree) to 5 (Strongly Agree) with higher scores indicating that they believe their neighborhoods are safe.

Table 3. *Familial Risk Factors/Confounders Associated with Prenatal Cannabis Exposure (PCE)*

Familial Factors	**OR (SE)**	**95% Wald CI [Lower, Upper]**	***p***
Biological Mom	0.61 (0.16)	[0.44, 0.83]	.002**
Maternal Age	0.94 (0.01)	[0.92, 0.97]	<.0001***
Paternal Age	0.98 (0.01)	[0.96, 1.01]	.149
Parental Education	0.99 (0.02)	[0.94, 1.04]	.588
Partner Education	0.99 (0.02)	[0.95, 1.03]	.612
Planned Pregnancy	0.56 (0.14)	[0.43, 0.72]	<.0001***
Prenatal Vitamin	0.94 (0.23)	[0.60, 1.46]	.781
Birth Weight	1.05 (0.04)	[0.97, 1.15]	.220
Nausea	1.27 (0.15)	[0.95, 1.70]	.109
Prenatal Care	0.99 (0.01)	[0.97, 1.01]	.136
Months Breastfed	1.00 (0.01)	[0.98, 1.01]	.505
Maternal Immediate Family Alcohol Use	1.00 (0.14)	[0.76, 1.32]	.989
Paternal Immediate Family Alcohol Use	1.01 (0.14)	[0.77, 1.33]	.937
Maternal Immediate Family Drug Use	1.95 (0.16)	[1.43, 2.64]	<.0001***
Paternal Immediate Family Drug Use	1.70 (0.15)	[1.26, 2.30]	.0005**
Maternal Immediate History Depression	1.10 (0.14)	[0.84, 1.44]	.477
Paternal Immediate Family Depression	0.99 (0.15)	[0.74, 1.33]	.954
Alcohol Use During Pregnancy	3.88 (0.12)	[3.04, 4.95]	<.0001***
Tobacco Use During Pregnancy	4.86 (0.12)	[3.81, 6.19]	<.0001***
ADHD T-scores	0.98 (0.01)	[0.96, 1.00]	.025*
Rule Breaking T-scores	1.08 (0.01)	[1.06, 1.11]	<.0001***
Neighborhood Safety	0.86 (0.05)	[0.78, 0.95]	.002**
Race	1.14 (0.06)	[1.01, 1.27]	.028*

Note. * $p < .05$, ** $p < .01$, *** $p < .001$

Table 4. *Mean and Standard Deviations of Developmental Milestones*

Developmental Milestones	No PCE (N= 10,824)	PCE (N= 696)
Rollover, mean (SD)	4.02 (6.29)	3.85 (1.00)
Sit, mean (SD)	7.79 (13.26)	7.26 (1.66)
Walk, mean (SD)	13.76 (21.03)	12.92 (3.28)
First word, mean (SD)	11.12 (3.66)	10.82 (3.79)
Motor Development, mean (SD)[a]	1.63 (0.80)	1.58 (0.89)
Speech Development, mean (SD) [a]	1.72 (0.98)	1.70 (1.07)
Age Stopped Wetting Bed, mean (SD)*	5.99 (3.12)	6.39 (3.23)

Note. Prenatal cannabis exposure (PCE) *The mean and standard deviations for the developmental milestones are presented by age in months except for age stopped wetting the bed, which is presented in years. [a] To assess motor development and speech development, caretakers were asked 'would you say your child motor development (sitting, crawling, walking) was earlier, average, or later than most other children?' and 'would you say his/her speech development was earlier, average, or later than most other children?', respectively. Responses ranged from 1 (much earlier) to 5 (much later).

Table 5. *Developmental Milestones Associated with Prenatal Cannabis Exposure (PCE) and Propensity for Prenatal Cannabis Exposure (pPCE)*

Dependent Variable	Model	Independent Variable	OR (SE)	95% CI [Lower, Upper]	*p*
Rollover	Model 1a	PCE	1.02 (0.12)	[0.80, 1.29]	0.905
	Model 1b	PCE	1.17 (0.14)	[0.89, 1.55]	0.262
		Propensity Score	0.58 (0.31)	[0.32, 1.06]	0.077
Sit Without Assistance	Model 2a	PCE	0.92 (0.23)	[0.59, 1.45]	0.730
	Model 2b	PCE	0.79 (0.26)	[0.48, 1.32]	0.372
		Propensity Score	1.83 (0.46)	[0.75, 4.49]	0.185
Walk Without Assistance	Model 3a	PCE	0.79 (0.13)	[0.61, 1.03]	0.081
	Model 3b	PCE	0.83 (0.15)	[0.61, 1.12]	0.213
		Propensity Score	0.82 (0.33)	[0.43, 1.56]	0.541
Say His/Her First Word	Model 4a	PCE	1.27 (0.16)	[0.93, 1.73]	0.130
	Model 4b	PCE	1.51 (0.17)	[1.08, 2.10]	0.015*
		Propensity Score	0.53 (0.36)	[0.27, 1.07]	0.077
Stop Wetting the Bed	Model 5a	PCE	1.29 (0.16)	[0.93, 1.78]	0.124
	Model 5b	PCE	1.22 (0.20)	[0.82, 1.81]	0.320
		Propensity Score	1.30 (0.36)	[0.63, 2.65]	0.476
Gross Motor Delays With Language Delays	Model 6a	PCE	0.56 (0.42)	[0.25, 1.26]	0.161
	Model 6b	PCE	0.56 (0.46)	[0.23, 1.38]	0.209
		Propensity Score	1.00 (0.85)	[0.19, 5.31]	0.997
Gross Motor Delays Without Language Delays	Model 7a	PCE	0.99 (0.25)	[0.61, 1.60]	0.972
	Model 7b	PCE	1.32 (0.30)	[0.73, 2.40]	0.361
		Propensity Score	0.31 (0.71)	[0.08, 1.23]	0.096

Note. *$p < .05$, ** $p < .01$, *** $p < .0001$. covariate effects not shown. prenatal cannabis exposure (pce)

Table 6. *Items Composing the Six Difficulties in Emotion Regulation (DERS) Questionnaire Factors*

Factor	Item
1. Nonacceptance of Emotional Response (Nonacceptance)	11) When my child is upset, he/she becomes angry with him/herself for feeling that way. 12) When my child is upset, he/she becomes embarrassed for feeling that way 21) When my child is upset, he/she feels ashamed with him/herself for feeling that way. 25) When my child is upset, he/she feels guilty for feeling that way.
2. Difficulties Engaging in Goal-Directed Behavior (Goals)	18) When my child is upset, he/she has difficulty focusing on other things. 26) When my child is upset, he/she has difficulty concentrating. 33) When my child is upset, he/she has difficulty thinking about anything else.
3. Impulse Control Difficulties (Impulse)	3) My child experiences his/her emotions as overwhelming and out of control. 19) When my child is upset, he/she feels out of control. 14) When my child is upset, he/she becomes out of control. 27) When my child is upset, he/she has difficulty controlling his/her behaviors. 32) When my child is upset, he/she loses control over his/her behaviors.
4. Lack of Emotional Awareness (Awareness)	1) My child is clear about his/her feelings. 2) My child pays attention to how he/she feels. 6) My child is attentive to his/her feelings. 7) My child knows exactly how he/she is feeling. 8) My child cares about what he/she is feeling. 10) When my child is upset, he/she acknowledges his/her emotions.
5. Limited Access to Emotion Regulation Strategies (Strategies)	15) When my child is upset, he/she believes that he/she will remain that way for a long time. 16) When my child is upset, he/she believes that he/she will end up feeling very depressed. 23) When my child is upset, he/she feels like he/she is weak. 28) When my child is upset, he/she believes that there is nothing he/she can do to make him/ herself feel better. 29) When my child is upset, he/she becomes irritated with him/herself for feeling that way. 30) When my child is upset, he/she starts to feel very bad about him/herself. 35) When my child is upset, it takes him/her a long time to feel better. 36) When my child is upset, his/her emotions feel overwhelming.
6. Lack of Emotional Clarity (Clarity)	22) When my child is upset, he/she knows that he/she can find a way to eventually feel better. 24) When my child is upset, he/she feels like he/she can remain in control of his/her behaviors.

Table 7. *Difficulties in Emotion Regulation (DERS) Questionnaire Items and Factor Loadings Following Confirmatory Factor Analysis*

OF[1]	OF[2]	Items (DERS)	Factor Loadings					
			1	2	3	4	5	6
6	3	1. My child is clear about his/her feelings				0.815		
4	3	2. My child pays attention to how he/she feels				0.887		
3	1	3. My child experiences his/her emotions as overwhelming and out of control			0.574			
6	-	4. My child has no idea how he/she is feeling	-	-	-	-	-	-
6	-	5. My child has difficulty making sense out of his/her feelings	-	-	-	-	-	-
4	3	6. My child is attentive to his/her feelings				0.812		
6	3	7. My child knows exactly how he/she is feeling				0.826		
4	3	8. My child cares about what he/she is feeling				0.812		
6	-	9. My child is confused about how he/she feels	-	-	-	-	-	-
4	3	10. When my child is upset, he/she acknowledges his/her emotions				0.750		
1	2	11. When my child is upset, he/she becomes angry with him/herself for feeling that way	0.659					
1	2	12. When my child is upset, he/she becomes embarrassed for feeling that way	0.701					
2	4	13. When my child is upset, he/she has difficulty getting work done		0.820				
3	1	14. When my child is upset, he/she becomes out of control			0.852			
5	1	15. When my child is upset, he/she believes that he/she will remain that way for a long time					0.757	
5	1	16. When my child is upset, he/she believes that he/she will end up feeling very depressed					0.717	
4	-	17. When my child is upset, he/she believes that his/her feelings are valid and important	-	-	-	-	-	-
2	4	18. When my child is upset, he/she has difficulty focused on other things		0.902				
3	1	19. When my child is upset, he/she feels out of control			0.864			
2	-	20. When my child is upset, he/she ca still get things done						
1	2	21. When my child is upset, he/she feels ashamed with him/herself for feeling that way	0.846					
5	1	22. When my child is upset, he/she knows that he/she can find a way to eventually feel better						0.798
1	2	23. When my child is upset, he/she feels like he/she is weak					0.632	
3	1	24. When my child is upset, he/she feels like he/she can remain in control of his/her behaviors						0.706
1	2	25. When my child is upset, he/she feels guilty for feeling that way	0.774					
2	4	26. When my child is upset, he/she has difficulty concentrating		0.876				
3	1	27. When my child is upset, he/she has difficulty controlling his/her behaviors			0.869			
5	1	28. When my child is upset, he/she believes that there is nothing he/she can do to make him/herself feel better					0.783	
1	2	29. When my child is upset, he/she becomes irritated with him/herself for feeling that way					0.754	

5	2	30. When my child is upset, he/she starts to feel very bad about him/herself							0.780		
5	-	31. When my child is upset, he/she believes that wallowing in it is all he/she can do	-	-	-	-	-	-			
3	1	32. When my child is upset, he/she loses control over his/her behaviors			0.886						
2	4	33. When my child is upset, he/she has difficulty thinking about anything else		0.848							
4	-	34. When my child is upset, he/she takes time to figure out what he/she is really feeling	-	-	-	-	-	-			
5	1	35. When my child is upset, it takes him/her a long time to feel better							0.776		
5	1	36. When my child is upset, his/her emotions feel overwhelming							0.792		

Note. Factors correspond to the following latent constructs: 1. Nonacceptance of Emotional Responses, 2. Goal Directed Behavior, 3. Impulse Control, 4. Emotional Awareness and Clarity, 5. Emotion Regulation Strategies, 6. Emotional Control. [1] Original factor (OF) 6 factor structure derived by Gratz and Roemer (Gratz & Roemer, 2004). [2] Original factor (OF) 4 factor structure derived by Bunford et al. (Bunford et al., 2020)

--- Items on the questionnaire were not available in the ABCD sample so the items were not included within the analyses

Table 8. *Model Fit Indices for 6 Factor Difficulties in Emotion Regulation (DERS) Questionnaire*

Factors I	n	RMSEA			CFI	TLI	SRMR
		Estimate	90% CI	*p*-value			
6 Factor DERS	9,524	0.057	[0.056-0.058]	<.0001	0.877	0.861	0.051

Table 9. *Executive Function Latent Factor Following Confirmatory Factor Analysis*

Lower Order Items	Description	Factor Loading (SE)
nih_flanker	NIH Toolbox Flanker Inhibitory Control and Attention Test Fully Corrected T-Score	0.651 (0.02)
nih_card	NIH Toolbox Dimensional Change Card Sort Test Fully Corrected T-Score	0.635 (0.02)
nih_list	NIH Toolbox List Sorting Working Memory Fully Corrected T-Score	0.338 (0.02)

Table 10. *Model Fit Indices for the Executive Function Latent Factor*

Factors	n	RMSEA			CFI	TLI	SRMR
		Estimate	90% CI	*p*-value			
Executive Function	11,531	0.013	[0.004-0.021]	1.000	0.995	0.988	0.008

Table 11. *Behavioral Disinhibition Latent Factor Following Confirmatory Factor Analysis*

Lower Order Items	Description	Factor Loading (SE)
temperament_depressive mood	sum(eatq_phenx_enjoy_p, eatq_phenx_cry_p, eatq_phenx_sad_p, eatq_phenx_hardly_sad_p, eatq_phenx_seems_sad_p)	0.463 (0.01)
temperament_frustration	sum(eatq_phenx_annoyed_p, eatq_phenx_irritated_crit_p, eatq_phenx_irritated_place_p, eatq_phenx_irritated_enjoy_p, eatq_phenx_disagree_p, eatq_phenx_frustrated_p)	0.525 (0.01)
temperament_aggression	sum(eatq_phenx_insult_p, eatq_phenx_angry_hit_p, eatq_phenx_rude_p, eatq_phenx_blame_p, eatq_phenx_doorslam_p, eatq_phenx_makes_fun_p, eatq_phenx_no_criticize_p)	0.623 (0.01)
cbcl_social	social syndrome scale t-score	0.734 (0.01)
cbcl_thought	thought syndrome scale t-score	0.713 (0.01)
cbcl_attention	attention syndrome scale t-score	0.739 (0.01)
cbcl_rulebreaking	rule breaking syndrome scale t-score	0.835 (0.01)
cbcl_aggression	aggressive syndrome scale t-score	0.937 (0.003)
cbcl_externalizing	externalizing syndrome scale t-score	0.919 (0.002)
cbcl_adhd	ADHD DSM5 scale t-score	0.763 (0.01)
cbcl_odd	Oppositional Defiant Disorder DSM5 scale t-score	0.908 (0.003)
cbcl_cd	Conduct Disorder DSM5 scale t-score	0.866 (0.01)
cbcl_stress	stress scale t-score	0.813 (0.01)
ders_nonacceptance	consists of 4 items- latent factor derived using CFA	0.330 (0.02)
ders_goals	consists of 3 items- latent factor derived using CFA	0.574 (0.01)
ders_impulse	consists of 5 items- latent factor derived using CFA	0.634 (0.01)
ders_strategy	consists of 8 items- latent factor derived using CFA	0.555 (0.01)

Table 12. *Model Fit Indices for the Behavioral Disinhibition Latent Factor*

Factors	n	RMSEA			CFI	TLI	SRMR
		Estimate	90% CI	*p*-value			
Behavioral Disinhibition	11,790	0.159	[0.158-0.160]	<.0001	0.617	0.568	0.109

Table 13. *Executive Function and Behavioral Disinhibition Associated with Prenatal Cannabis Exposure (PCE) and Propensity for Prenatal Cannabis Exposure (pPCE)*

Dependent Variable	Model	Independent Variable	β Est. (SE)	95% CI [Lower, Upper]	*p*
Executive Function	Model 1a	PCE	0.004 (0.02)	[-0.03, 0.04]	.851
	Model 1b	PCE	-0.03 (0.02)	[-0.04, 0.04]	.867
		Propensity Score	0.01 (0.02)	[-0.02, 0.05]	.414
Behavioral Disinhibition	Model 2a	PCE	0.15 (0.02)	[0.10, 0.18]	<.0001***
	Model 2b	PCE	0.04 (0.02)	[-0.001, 0.09]	.055
		Propensity Score	0.22 (0.02)	[0.18, 0.25]	<.0001***

Note. * $p < .05$, ** $p < .01$, *** $p < .0001$. Covariate effects not shown.

Table 14. *Summary of Model Parameters*

Regression Paths for Executive Function	**ß Est. (SE)**	***p***	**95% CI [Lower, Upper]**
PCE -> Delayed First Word (a)	0.07 (0.03)	.008**	[0.02, 0.12]
Propensity Score -> Delayed First Word (b)	-0.04 (0.02)	.068	[-0.09, 0.002]
Delayed First Word-> Executive Function (c)	-0.06 (0.03)	.032*	[-0.13, -0.01]
PCE -> Executive Function (d')	0.008 (0.02)	.715	[-0.03, 0.05]
Propensity Score -> Executive Function (e')	0.01 (0.02)	.511	[-0.02, 0.05]
Regression Paths for Behavioral Disinhibition	**Est. (SE)**	***p***	**95% CI [Lower, Upper]**
PCE -> Delayed First Word (f)	0.07 (0.03)	.008**	[0.02, 0.12]
Propensity Score -> Delayed First Word (g)	-0.04 (0.02)	.070	[-0.09, 0.002]
Delayed First Word-> Behavioral Disinhibition (h)	0.14 (0.02)	<.0001***	[0.09, 0.17]
PCE -> Behavioral Disinhibition (i')	0.04 (0.02)	.140	[-0.01, 0.09]
Propensity Score -> Behavioral Disinhibition (j')	0.22 (0.02)	<.0001***	[0.18, 0.25]

Note. *$p < .05$, ** $p < .01$, *** $p < .0001$. See Figure X for a conceptual model of paths a, b, c, d', and e' and Figure X for a conceptual model of paths f, g, h, i', and j'. Covariates are included to adjust the effects of sex, income, and race. Covariate effects not shown. prenatal cannabis exposure (PCE), propensity for PCE (pPCE).

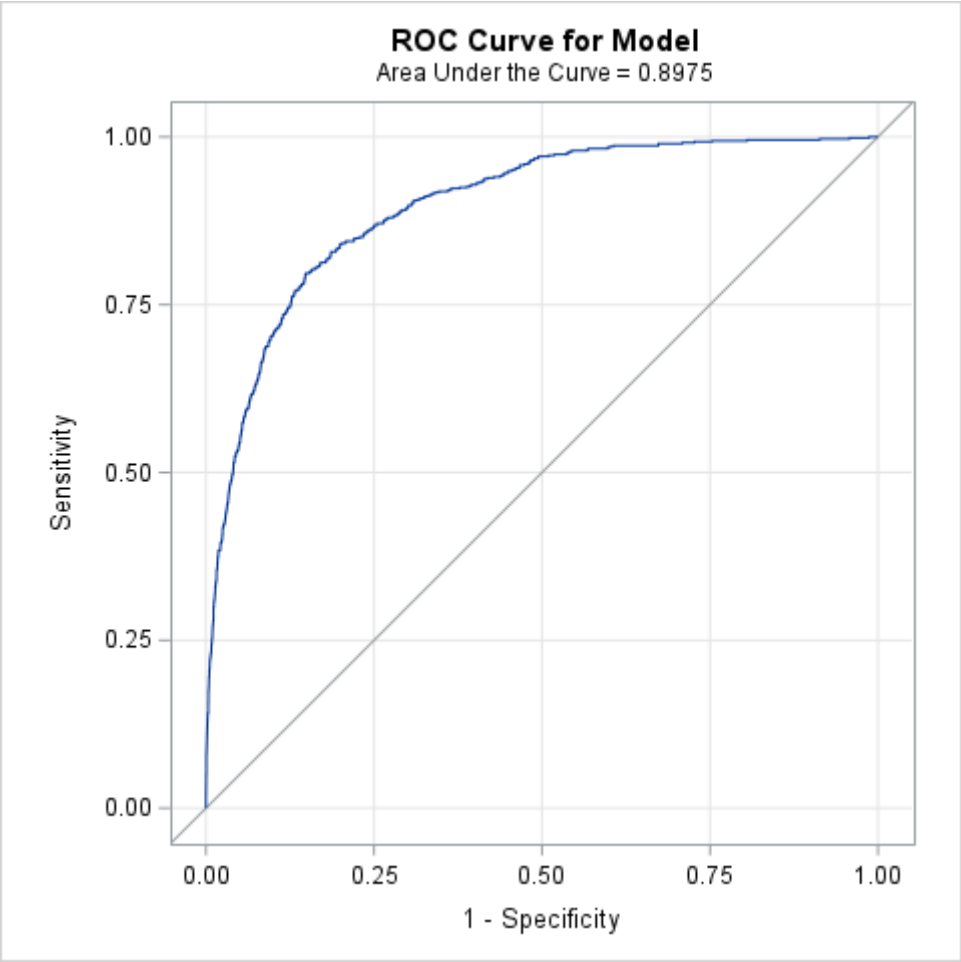
Table 15. *Summary Mediation Path Estimates and Corresponding 95% Bootstrapped Confidence Interval to Executive Function and Behavioral Disinhibition*

Effects from PCE to Executive Function	**ß Est. (SE)**	***p***	**95% CI [Lower, Upper]**
Total indirect effect via delayed first word (ac)	-0.004 (0.003)	.106	[-0.01, 0.000]
Total direct effect (d')	0.01 (0.02)	.715	[-0.03, 0.05]
Effects from Propensity Score to Executive Function	Est. (SE)	*p*	95% CI [Lower, Upper]
Total indirect effect via delayed first word (bc)	0.003 (0.002)	.132	[-0.05, -0.002]
Total direct effect (e')	0.01 (0.66)	.511	[-0.14, 0.20]

Effects from PCE to Behavioral Disinhibition	**Est. (SE)**	***p***	**95% CI [Lower, Upper]**
Total indirect effect via delayed first word (fh)	0.01 (0.003)	.006**	[0.003, 0.02]
Total direct effect (i')	0.04 (0.02)	.140	[-0.01, 0.09]
Effects from Propensity Score to Behavioral Disinhibition	Est. (SE)	*p*	95% CI [Lower, Upper]
Total indirect effect via delayed first word (gh)	-0.01 (0.003)	.090	[-0.01, 0.000]
Total direct effect (j')	0.22 (0.02)	<.0001***	[0.18, 0.25]

Note. *$p < .05$, ** $p < .01$, *** $p < .0001$. Results presented adjust for the effects of sex, race, and income. Covariate effects not shown. prenatal cannabis exposure (PCE), propensity for PCE (pPCE).

Figure 1. *ROC Curve of Model Predicting Prenatal Cannabis Exposure (PCE)*



Note. Logistic regression using 23 familial risk factors to predict PCE robustly captured mothers who 'did smoke' versus 'did not smoke' (area under the ROC curve = 0.90) younger maternal age, unplanned pregnancy, maternal immediate family drug use, paternal immediate family drug use, prenatal alcohol and tobacco use, non-biological mothers, lower neighborhood safety, lower ADHD T-scores, and higher rule breaking T-scores predicted greater odds of PCE.

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