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Contextualized Effects of Maternal Cannabis During Pregnancy on Postnatal Outcomes and Childhood Alcohol Sipping in the Adolescent Brain Cognitive Development Project

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Abstract

Contextualized Effects of Maternal Cannabis During Pregnancy on Postnatal Outcomes and Childhood Alcohol Sipping in the Adolescent Brain Cognitive Development Project

By Ami S. Ikeda

It is suspected that prenatal cannabis exposure might interfere with fetal development and pose a significant risk for several negative postnatal outcomes, early initiation of substances of abuse, and behavioral disruptions, including delinquent and aggressive behaviors. Taken together, this is concerning as early substance initiation has been linked with being diagnosed with an alcohol use disorder or other substance use disorder in adulthood as well as several secondary problems. Few studies have examined the prospective effect of prenatal cannabis exposure on postnatal outcomes and alcohol sipping in the context of known maternal and familial confounders. The current study addressed this question using 11,878 children and their mothers from the Adolescent Brain Cognitive Development (ABCD) Study. Maternal and familial confounders were accounted for using propensity scores and together with maternal reporting of cannabis use during pregnancy were used as predictors of rare birth outcomes and alcohol sipping in childhood. Logistic regression models using 15 maternal risk factors robustly classified mothers who 'did smoke' versus 'did not smoke' during pregnancy. Additionally, mothers reporting of maternal cannabis use during pregnancy was associated with increased risk of alcohol sipping in children. However, this association did not survive correction for maternal and familial confounders. Interestingly, propensity for prenatal cannabis exposure was associated with not breathing at birth. Despite no direct effect of prenatal cannabis exposure on alcohol sipping, mediation analysis indicated significant indirect effects of cannabis use during pregnancy and propensity for maternal cannabis use during pregnancy on childhood alcohol sipping via childhood externalizing behaviors. *In utero* cannabis exposure may play a role in alcohol sipping behavior in childhood as well as some understudied birth outcomes however, these effects may be better attributed to maternal/familial behaviors and a broader set of child-level externalizing behaviors.

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Contextualized Effects of Maternal Cannabis During Pregnancy on Postnatal Outcomes and Childhood Alcohol Sipping in the Adolescent Brain Cognitive Development Project

Introduction

Cannabis is used both recreationally and medicinally. Recently, randomized controlled trials have supported medicinal cannabis use in alleviating chronic pain, nausea induced from chemotherapy, and spasticity associated with multiple sclerosis (Abrams, 2018). Despite, the therapeutic benefits of cannabis in clinical samples, cannabis is a teratogen. Like alcohol and tobacco, cannabis can interfere with prenatal development and has been associated with various negative postnatal outcomes. However, there is a paucity of studies examining the effects of cannabis use during pregnancy despite the increasing rates of cannabis use amongst pregnant women. The 2019 National Survey on Drug Use and Health (NSDUH) reported that within the past month, 5.4% of women reported using cannabis while pregnant with 9.1% using within the first trimester and 3.3% using within the third trimester (Center for Behavioral Health Statistics and Quality, 2020). Moreover, these prevalence estimates are likely underreported given the high rates of unplanned pregnancies, stigma associated with substance use during pregnancy, shifts in legalization, and increased prevalence estimates of cannabis use among women of childbearing age. In 2019, 17.5% of women of childbearing age reported using cannabis within the past year and 11.4% within the past month (Center for Behavioral Health Statistics and Quality, 2020).

These prevalence estimates are especially concerning as delta^{9} -tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, is a lipid soluble substance that readily passes through the placental membrane (Jaques et al., 2014). Preclinical data has shed important light on the rate of cannabis metabolism between mother and fetus. In a non-human primate study, plasma levels reached peak at 3 minutes within the mother and 15 minutes within the fetus post-infusion and plasma THC levels became equal within both the mother and fetus at 3 hours

post dose (Bailey, 1987). More importantly, THC levels were observed in the fetal brain, fetal liver and placenta 180 minutes post last dose (Bailey, 1987). Additionally, the variability in cannabis metabolism differs based off of the route of administration with clinical studies demonstrating peak THC plasma levels after 3 minutes when smoking and 60 to 90 minutes after oral consumption of 20mg THC (Ohlsson et al., 1980). More so, changes in smoking behavior (i.e., number of puffs, hold time, inhalation length, and paraphernalia used) may have important impacts to bioavailability and cannabis metabolism (Chayasirisobhon, 2020; Grotenhermen, 2003; Lindgren et al., 1981). This is of important consequence as the endocannabinoid receptor system, involving two well studied cannabinoid receptors: cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) are widely distributed throughout the central nervous system and are even found in some peripheral tissues (Matsuda et al., 1990) and immune cells (Munro et al., 1993). Furthermore, the maturation of the endocannabinoid receptor system in the brain occurs by 14 weeks of gestation (Biegon & Kerman, 2001). These findings illustrate the need to elucidate the developmental consequences associated with prenatal cannabis exposure. Of particular importance to the current study is disentangling the direct consequences of maternal cannabis during pregnancy from the maternal confounders on two important offspring outcomes, rare birth outcomes and childhood alcohol sipping behavior.

The Importance of Maternal Confounders in Prenatal Exposure Studies

There are 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). However, results across these studies are mixed due to methodological differences as well as, confounding in effect size estimates as a result of

maternal and familial variables associated with maternal substance use. Maternal confounders are risk factors known to be associated with cannabis use during pregnancy, as well as prenatal and behavioral outcomes; these include: concurrent alcohol or tobacco use (Brown et al., 2019; De Genna et al., 2015; Mark et al., 2016; Peadon et al., 2011; Young-Wolff et al., 2020), younger maternal age (Brown et al., 2019; De Genna et al., 2015; Mark et al., 2016; Van Gelder et al., 2010; Young-Wolff et al., 2020), unplanned pregnancies (Young-Wolff et al., 2020), lower education (El Marroun et al., 2008; Mark et al., 2016; Passey et al., 2014; Van Gelder et al., 2010), lower socioeconomic status, less prenatal care, presence of depressed mood, and paternal cannabis use (Brown et al., 2019; El Marroun et al., 2008). Additional maternal confounders include a history of childhood maltreatment or history of sexual or physical abuse (El Marroun et al., 2008; Mark et al., 2016) and increased delinquent behavior (El Marroun et al., 2008). Additionally, in a population based study between 1997-2004, it was reported that mothers who used cannabis during their pregnancy were underweight (BMI $<18.5 kg/m^2$) and were more likely to gain more weight during their pregnancy compared to women who did not report using cannabis or other illicit drugs of abuse (Van Gelder et al., 2010). However, one study reported no association between maternal cannabis use and maternal age, psychopathology, or perceived stress (El Marroun et al., 2008).

As evidenced by previous research, there are a cluster of demographic features that may put mothers at an increased risk for using cannabis during their pregnancy, although findings are mixed. Specifically, women between the ages of 16-24 report higher cannabis use both before and during pregnancy compared to women between the ages of 25-45 (Young-Wolff et al., 2020). Additionally, lower education appears to be associated with continued maternal cannabis use, using before and during pregnancy (El Marroun et al., 2008). In addition to specific

demographic features, co-occurring mood-related disorders and substance use disorders may also act as risk factors. The presence of depressive symptoms appears to be an important risk factor for maternal cannabis use during pregnancy and the length of depressive symptoms may even influence chronicity of cannabis use (De Genna et al., 2015). Persistent depressive symptoms were significantly associated with increasing/chronic cannabis use compared to mothers who stopped using cannabis (De Genna et al., 2015). More broadly, women with depressive symptoms were at a three times greater risk of using cannabis during pregnancy compared to women without depressive symptoms (Brown et al., 2019; Goodwin et al., 2020). Finally, mothers that had a history of a cannabis use disorder were at a 2.77 times increased risk of using cannabis during their pregnancy and were likely to continue to use cannabis during their pregnancy compared to mothers with no such history (El Marroun et al., 2008). More so, maternal cannabis use during pregnancy was linked with daily/weekly use, while women who only used cannabis before pregnancy were more likely to be monthly users (El Marroun et al., 2008). This is especially concerning as a previous study suggests, that mothers with a cannabis use disorder were also more likely to present with depressive symptoms, anxiety, and nausea/vomiting disorders (Meinhofer et al., 2022). Overall, there are several risk factors or maternal confounders that need to be accounted for but rarely are. It is an essential step in disentangling the relationship between maternal cannabis during pregnancy and important childhood level outcomes. Studies in the prenatal alcohol and tobacco literature (Källén, 2012; Palmer et al., 2016; Walpole et al., 1989) have repeatedly demonstrated that ignoring these maternal confounders leads to biased patterns of association and misinterpretation of the consequences of *in utero* drug exposure.

Cannabis Effects on Postnatal Outcomes

An area of interest is the associated negative postnatal outcomes. Unlike the Fetal Alcohol Spectrum Disorder field that has developed a teratogenic profile that can be used in the identification and diagnoses of children prenatally exposed to alcohol (Hoyme et al., 2016; Jones et al., 1973; Mattson et al., 2011; Riley et al., 2011; Wozniak et al., 2019), the consequences of prenatal cannabis exposure are not well understood. A review of the literature found mixed support for associations between cannabis use during pregnancy and birth and infant outcomes with some studies reporting no differences or only small differences in birth weight (Conner et al., 2016; Mark et al., 2016; Paul et al., 2020; Van Gelder et al., 2010) and no other negative growth effects between newborns with or without fetal exposure (Fried & O'Connell, 1987). Similarly, other studies have found only somewhat reduced birthweights between children with exposure versus no exposure (Klebanoff et al., 2020). On the contrary, there is also a body of evidence that suggest that greater cannabis use during pregnancy may be associated with more negative birth outcomes (Reece & Hulse, 2019). Specifically, researchers find that cannabis use during pregnancy is associated with lower birth weight, smaller head circumference, restricted growth (Crume et al., 2018; El Marroun et al., 2009; Rodriguez et al., 2019; Shi et al., 2021), increased risk of preterm birth (Bandoli et al., 2021; Corsi et al., 2019; Hayatbakhsh et al., 2012; Shi et al., 2021), and higher rates of being placed in the neonatal intensive care unit (Corsi et al., 2019; Gunn et al., 2016; Hayatbakhsh et al., 2012). Further, greater cannabis use during pregnancy has been linked to increased rates of chromosomal anomalies, microcephalus, trisomy 21, anencephalous (Reece & Hulse, 2019), cardiovascular deficits, and orofacial clefts (Reece & Hulse, 2020). Maternal cannabis during pregnancy has been associated with various motor deficits including increased tremors, startle reactions and decreased response to visual stimuli (Fried, 1980; Fried & Makin, 1987). Additionally, a recent study found that combined prenatal

cannabis and tobacco exposure was associated with infants decreased self-regulation, deficits in response to visual stimuli, and decreased motor activity compared to non-exposed newborns (Stroud et al., 2018). Despite the mixed findings, animal studies appear to corroborate, findings that are reported in human studies, of reductions in birth liver and brain weights (Natale et al., 2020). Also, the relationship between prenatal cannabis exposure and rare birth outcomes is limited and mixed. For the purpose of the current study, rare birth outcomes include being born blue at birth, having a slow heart rate at birth, not breathing at birth, experiencing convulsions, jaundice, requiring oxygen, requiring a blood transfusion, or Rh incompatibility. First, being born blue at birth or "blue baby syndrome" or infant methemoglobinemia occurs when hemoglobin is unable to carry oxygen or carbon dioxide (Curry, 1982). Methemoglobinemia can be hereditary, usually occurring due to cytochrome b5 (NADH-MetHb) reductase deficiency or the presence of abnormal Hemoglobin M molecules (Curry, 1982). This condition can also occur after exposure to chemicals including pharmaceuticals however, the mechanisms in which this occurs is not well understood (Curry, 1982). Overall, infants may be born blue at birth due to a lack of oxygen in the blood however, no studies to date have examined the association between prenatal drug exposure, including prenatal cannabis exposure, and being born blue at birth.

Second, findings on slow heart rate, a possible consequence of congenital heart defects, have been mixed. In a preclinical study, zebrafish that were prenatally exposed to THC or CBD for 5 hours during gastrulation displayed a dose dependent reduction in heart rate compared to controls (Ahmed et al., 2018). These findings suggest that *in utero* exposure to THC and/or CBD may decrease heart rate and that greater exposure to THC and/or CBD may lead to further reductions in heart rate. This calls to the importance of understanding the developmental consequences of varying levels of THC and/or CBD exposure and the timing of exposure.

Additionally, Wistar rats were given an intraperitoneal injection of THC from gestational day 6 to 22 and echocardiograms were performed on the pups on postnatal day 1 and 21 (Lee et al., 2021). The findings support the teratogenic properties of cannabis, as smaller heart to body weight ratios were observed in exposed pups however, by three weeks (postnatal day 21) heart size relative to body weight became equal across control and experimental groups. Despite the growth catch-up, the cardiovascular function of the rats prenatally exposed to THC were reduced, with the experimental group exhibiting thicker anterior left ventricular wall thickness and decreased cardiac output (Lee et al., 2021). Importantly, this suggests long-term consequences of *in utero* cannabis exposure and increased risk for developing cardiovascular diseases over time. Additionally, findings associated with congenital heart defects are not limited to prenatal cannabis exposure. A population based case control study revealed that infants exposed to alcohol prenatally, less than once a week, were at a 1.3 times increased risk of developing a congenital heart defect and infants exposed once a week or more were at a 1.9 times increased risk of having a heart defect compared to infants with no exposure (Carmichael et al., 2003). However, a recent meta-analysis reported no link between prenatal alcohol exposure and overall congenital heart defects (Yang et al., 2015). For a comprehensive review on the associations between congenital heart anomalies and prenatal substance exposure see Feng et al. (Feng et al., 2014). Given the mixed findings it is not clear whether prenatal cannabis exposure could impact the development of peripheral tissues and organs such as the heart.

Third and as previously mentioned, much can be elucidated from the literature on fetal exposure to other drugs of abuse. Prenatal tobacco exposure while associated with a number of teratogenic consequences has also been linked with respiratory distress (Adibelli & Kirca, 2020). Similarly, a retrospective case-control study reported increased risk of respiratory distress

syndrome in infants prenatally exposed to cocaine (Ogunyemi & Hernández-Loera, 2004). Additionally, infants prenatally exposed to alcohol had a higher incidence of respiratory distress that required intervention such as, resuscitation or oxygen compared to infants with no alcohol exposure (Popova et al., 2021). More so, infants with prenatal alcohol exposure were at a 2.57 times increased risk of being diagnosed with "other respiration distress of newborn" and infants whose mothers engaged in binge drinking during pregnancy were at a 2.03 times increased risk of being diagnosed with "respiratory failure of a newborn" (Popova et al., 2021). Additionally, infants prenatally exposed to multiple substances of abuse displayed baseline differences in respiratory rate, minute ventilation, and end-tidal carbon dioxide in the supine sleeping position (back sleeping) compared to infants with no prenatal drug exposure (Rossor et al., 2018). However, findings are mixed with some studies reporting no association between prenatal drug exposure and respiratory distress (Beeram et al., 1994; Salihu et al., 2005). Results from animal studies also appear mixed, as some researchers report disruptions in respiration both with and without a stress, hypoxia, challenge (Lipton et al., 1996; Nettleton et al., 2008) and no baseline differences in respiration (Autret et al., 2002).

Fourth, research supports the relation between maternal cannabis during pregnancy and tremors (Fried, 1980; Fried & Makin, 1987). The occurrence of tremors/convulsions also appears in neonatal opioid withdrawal syndrome or neonatal abstinence syndrome, a consequence of *in utero* opioid exposure and other drugs of abuse (Conradt et al., 2019; Ko et al., 2017). However, it is important to note that the presentation of symptoms may vary based on the substance of abuse, quantity, frequency and duration of use (Tiroumourougane Serane & Kurian, 2008). Additionally, infants prenatally exposed to cocaine were at a two times increased risk of experiencing jitteriness/tremors compared to infants with no cocaine exposure (Bauer et al.,

2005). Despite clinical findings, Sprague-Dawley rats with prenatal ethanol exposure given a single intraperitoneal injection of either 30, 40, or 45 mg/kg of pentylenetetrazol (PTZ), a drug commonly used to induce convulsions in animals, took longer to convulse when given the PTZ compared to controls (Abel et al., 1993). However, it is important to note that this study was conducted in a group of Sprague-Dawley rats at postnatal day 35 and may not reflect risk for convulsions at birth or infancy.

Fifth, neonatal jaundice occurs when the infant has elevated bilirubin levels however, only one study has reported a relationship between prenatal opiate exposure and jaundice (Finnegan, 1985). Despite the absence of studies examining this relationship, it is plausible that maternal cannabis use disrupts the formation of peripheral tissues in the liver and warrants further investigation.

Finally, to our knowledge no studies have examined the association between prenatal cannabis exposure, and more broadly prenatal substance exposure, and the need for a blood transfusion at birth or Rh incompatibility. However, Rh incompatibility occurs when mother and fetus are Rh blood discordant (i.e., mother is Rh negative while the fetus is Rh positive). Thus, it is not clear if there are direct consequence to Rh blood compatibility and maternal cannabis exposure.

Effects of Maternal Cannabis During Pregnancy on Substance Use

Overall, there is a need to examine broader behavioral outcomes across development because the consequences associated with prenatal cannabis exposure do not appear to be limited to negative birth outcomes. Previous research has reported links between prenatal cannabis exposure and early cannabis initiation in adolescents, 14 years of age (Day et al., 2006; Porath & Fried, 2005). Prenatal cannabis exposure was also associated with increased frequency of use

(Day et al., 2006), continued use (Sonon et al., 2016), and increased "joints" smoked per week in males but not in females (Porath & Fried, 2005). Similarly, prenatal alcohol exposure appears to be a risk factor for early alcohol initiation in adolescence (Baer et al., 1998), continued use (Baer et al., 2003), and meeting criteria for a substance use and alcohol use disorder in young adulthood (Alati et al., 2006; Barr et al., 2006). Additionally, prenatal tobacco exposure appears to be linked with risk for tobacco dependence in adolescence as measured by the 6-item Fagerstrom Test for Nicotine Dependence questionnaire, with a score of 3 or higher indicating risk for nicotine dependence (De Genna et al., 2017). Prenatal tobacco exposure was also significantly linked with early initiation of alcohol, cannabis, and tobacco use in adolescence, 16 years of age (Goldschmidt et al., 2012). Taken together, it appears that prenatal substance exposure is a risk factor for early substance initiation. This is of particular concern as early substance initiation is linked with being diagnosed with a substance use disorder in adulthood (Grant & Dawson, 1997; Sonon et al., 2016) as well as many secondary problems, including increased suicidal ideations, suicidal attempts, suicidal completions, increased risky sexual behavior, and additional drug use (Windle et al., 2008).

Despite this, few studies have examined the association between low level substance use and prenatal substance exposure. Previous research reported a relationship between prenatal tobacco exposure and tobacco experimentation in children 10 years of age (Cornelius, 2000) and increased likelihood of endorsing alcohol sipping in children, between the ages of 9-11, with prenatal alcohol exposure (Lees et al., 2020). However, no studies have yet to examine the association between prenatal cannabis exposure and low-level drug use specifically, low level alcohol use. Alcohol use is important to examine as it is the most commonly used substance in individuals between 12-17 years of age. Data from the 2019 NSDUH revealed that in 2019, 9.4%

of individuals between 12-17 endorsed using alcohol within the past month, 21.2% within the past year, and 26.7% in their lifetime. Compared to 3.8%, 8.3%, 12.8% using tobacco within the past month, year and lifetime, respectively and 7.4%, 13.2%, 15.8% using cannabis within the past month, year, and lifetime, respectively (Center for Behavioral Health Statistics and Quality, 2020). Given, the high prevalence estimates it is essential to examine risk factors for alcohol sipping behavior as alcohol sipping is associated with poorer school engagement (Jackson, Colby, et al., 2015). More importantly, sipping alcohol by sixth grade was significantly associated with consuming a full drink by ninth grade, getting drunk, engaging in heavy episodic drinking, and using other substances of abuse compared to non-alcohol sippers (Jackson, Barnett, et al., 2015). Further, sipping alcohol by 10 years of age was significantly linked with early onset drinking (Donovan & Molina, 2011).

Additionally, childhood externalizing behaviors have been theorized as an intermediary phenotype linking prenatal cannabis and alcohol exposure to daily drug use later in life (De Genna et al., 2022). Relatedly, other studies propose that this relationship may be cyclical, as externalizing traits are positively associated with substance use but, results have also shown that use of substances of abuse may lead to increased externalizing behaviors (Miller & Spear, 2006; Obando et al., 2014). For a review on the associations between maternal cannabis during pregnancy on offspring development of externalizing behaviors and substance use please see Ikeda et al. (Ikeda et al., 2022). The purported indirect effect of externalizing behaviors on subsequent substance use may serve as a potential risk factor for early substance use initiation, thus warranting further investigation.

Study Goals

The current study aimed to extend our knowledge of risk factors of maternal cannabis during pregnancy (MCDP) and their developmental consequences with 3 aims. The first aim was to assess the familial risk factors associated with MCDP with parent/caregiver self- report measurements that captured the prenatal environment and accounts for maternal and familial confounders. The second aim of the current study was to evaluate the relationship between maternal reports of MCDP and propensity for MCDP (pMCDP) on postnatal infant outcomes. Finally, the third aim was to understand the link between maternal reports of MCDP, propensity for MCDP, and child alcohol sipping behavior using a child self-report measure. We hypothesized that children prenatally exposed to cannabis will be at greater risk for experiencing more birth complications and will endorse more alcohol sipping behavior compared to children with no prenatal cannabis exposure.

Methods

Participants

Data were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (release 3.0). ABCD is an ongoing single-cohort prospective longitudinal study focusing on brain development and child and adolescent health (Jernigan et al., 2018). The study includes 21 research sites across the United States which have recruited 11,878 children. In addition, the study included singletons (n = 7,900), nontwin siblings (n = 1,810), twins (n = 2,138), and triplets (n = 30). The overall samples used within the current analyses consisted of mothers [n = 11,614; ages 13-60 (mean (*M*) = 29.40, standard deviation (SD) = 6.27)] and their children (n = 11,878). The ABCD study has completed recruitment of their baseline sample [ages 9-11 (*M* = 9.92, SD = 0.63)] while employing a stratified random sample in anticipation of following the participants for 10 years. At the 1- year follow up participants were between 9 and 13 years of

age (*M* = 10.93, SD = 0.64) and at the 2- year follow up participants were between 10 and 14 years of age (*M* = 11.96, SD = 0.64). Table 1 provides ABCD Study sample characteristics that were included within the current analyses.

Measures

The current study employed several measures to test the aforementioned hypotheses. Only data collected at baseline were included within the analyses and evaluated.

Smoking During Pregnancy

Maternal cannabis during pregnancy (MCDP) was based on parent or caregiver retrospective self- report. Two groups were formed based off responses: no MCDP (n = 10,836; i.e., no cannabis use before or after knowing of pregnancy, and MCDP (n = 697; i.e., cannabis use either before or after knowing of pregnancy).

Family History

A parent or caregiver retrospectively reported on immediate and extended family alcohol and drug use history. Due to missingness as a result of unknown history, lack of biological relative that fit the descriptor category (i.e., uncle, aunt, etc.), or lack of administration of questions by the research assistant, only maternal immediate family and paternal immediate family (mother, father, and grandparents) alcohol and drug use were included within the analyses.

Neighborhood Safety

Parent reports of perceived neighborhood safety were 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). Measures incorporated within this study were selected from the PhenX Toolkit version February 14, 2022,

Ver 40.8. The original assessment consists of three items examining feelings of safety and presence of crime within their respective neighborhoods, with higher scores indicating greater/positive perceived neighborhood safety (Hamilton et al., 2011). Parents received all three items.

Birth Outcome Measures

A parent or caregiver retrospectively reported the child's birth outcomes which included premature size, blue at birth, slow heart rate, not breathing, convulsions, jaundice, requiring oxygen, requiring a blood transfusion, and Rh incompatibility.

Child Behavior Checklist (CBCL)

The CBCL was used to assess internalizing and externalizing behaviors according to parent report. The CBCL broad spectrum internalizing behaviors include withdrawal, somatic complaints, and anxious depressed scales while the externalizing behaviors include delinquent and aggressive behaviors. Standardized *T*-scores at baseline were used as opposed to creating a "life span score" that would account for externalizing and internalizing scores at baseline, 1 year follow up, and 2 year follow up. Table 25A and 26A provides results from the repeated measures ANOVA and group mean differences the support the inclusion of baseline internalizing and externalizing data only. *T*-scores are standardized for gender and age, with higher scores indicating more problems (Achenbach, 1991). Additionally, the decision was made to use broad spectrum internalizing and externalizing summary scores as recent reports support the bi-factor and higher order models within the ABCD study sample (Clark et al., 2021).

Substance Use Measures

The ABCD Youth Substance Use Interview included several substance use measures in order to assess lifetime and recent substance use patterns, peer group substance use, substance

use attitudes, subjective response to substance use and consequences of substance use. Within the current project, the Timeline Follow-back (TLFB) measure was used to evaluate low level alcohol use (alcohol sipping behavior; Sobell et al., 1996; Sobell, 1996).

Data Analysis

Propensity for MCDP

Propensity scores were used to control for confounding factors while examining the effect of MCDP on alcohol sipping, as well as MCDP and birth outcomes. This approach was selected as previous studies have used similar approaches to examine direct effects of maternal smoking during pregnancy and offspring substance use and externalizing traits across the risk distribution for maternal smoking during pregnancy that is inferred from a set of familial risk factors (Bidwell et al., 2016; Palmer et al., 2016). Additionally, this approach was selected over propensity score stratification or matching because our sample was limited to ~700 mothers, that self-reported using cannabis during their pregnancy, which would make stratifying across subjects into mutually exclusive "risk groups" based on their propensity scores difficult. Similarly, propensity score matching would require identifying matched pairs of individuals, which was not the intention of the ABCD project nor were sampling methods conducted to enable this matching. For further explanation of alternative propensity score methods please see Austin (Austin, 2011). Given the relatively low number of individuals nested within families (MCDP: N= 534 singletons, 89 sibling, 73 twins, and 1 triplet; Non MCDP: N= 7123 singletons, 1659 siblings, 2025 twins, and 26 triplets), all observations were treated as independent; propensity scores were unchanged (R^2=0.13) across the models ignoring and accounting for family structure. Additionally, missingness on each maternal risk variable was accounted for by including a dummy variable category. Model fit was assessed using the receiver operating

characteristic (ROC) curve (Swets, 1986), where values closer to 1.00 indicated better separation of using cannabis during pregnancy and values close to 0.5 indicated chance. Subsequent analyses were limited to a subset of mothers for whom complete information was available. Propensity scores were derived using a logistic regression model conducted in SAS [version 9.4] (SAS, 2013) using data on 11,434 mothers. MCDP was predicted using dummy coded versions of the fifteen maternal risk factor variables. Maternal covariates included race [White, Black, Mixed, Asian, Alaska/ Native American, Pacific Islander, Hispanic, and Other], maternal alcohol during pregnancy and maternal tobacco during pregnancy. Specific maternal variables included, biological mother, biological mothers age (left as a continuous variable), planned pregnancy, prenatal vitamins, nausea, number of prenatal care visits (left as a continuous variable), maternal education, maternal immediate family alcohol use, paternal immediate family alcohol use, maternal immediate family drug use, paternal immediate family drug use, and neighborhood safety (summary score was created). Models were fit and clustered by site id and included a weight variable that accounted for the representativeness of the ABCD sample.

Effects of MCDP on Birth Outcomes and Alcohol Sipping

We used a set of logistic regression models to examine the prospective effect of MCDP in children (N=11,429). First, we fitted a model examining covariate (age, sex, and race) effects (not shown). Second, we expanded the model to examine the unique contribution of MCDP over and above covariates (referred to in results tables as Model-1a thru 9a for birth outcomes and 1a for alcohol sipping). We then expanded the model further, by examining the effect of MCDP on all birth outcomes while accounting for differences in the child's familial propensity for MCDP (pMCDP; referred to in results tables as Model-1b thru 9b for birth outcomes and 1b for alcohol sipping). Given consistent evidence supporting a positive association between MCDP and

several childhood internalizing (INT) and externalizing (EXT) behaviors, which has downstream effects on future substance use, we examined the effect of MCDP on INT and EXT before and after accounting for pMCDP (Models -4 and -5, respectively). Finally, we used path analysis conducted in MPlus [version 8] (Muthén, 2017) to examine the direct and indirect of MCDP and pMCDP on alcohol sipping via its effect on EXT. All models included the following child-level covariates: age, sex, race, and income. Confidence intervals for the direct and indirect effects were estimated using bootstrapping (10,000 resamples).

Results

Sample Descriptives

Table 1 describes maternal- and child/adolescent- level sample characteristics. Table 2 shows the prevalence of familial factors assessed in relation to maternal cannabis during pregnancy. Additionally, secondary analyses were conducted on a subset of the sample (biological mother vs. non-biological mother) for prevalence estimates please see Table 12A. Approximately 25% of the entire sample (all time points completed) reported having sipped alcohol and 22% with missing 2-year follow-up reported having sipped alcohol. There was a significant difference between individuals who continued to participate at baseline, 1- year follow-up, and 2- year follow- up versus those who have yet to complete the 2-year follow-up χ^2 (1, N= 11,423) = 10.22, p= .001, indicating that individuals with all-time points collected are more likely to have reported sipping alcohol compared to those missing 2-year follow-up data.

Propensity for MCDP in Mothers

Amongst the 11,533 subjects with maternal reports of MCDP, 6.04% (N= 697) were exposed to cannabis at some point during their pregnancy. Table 3 describes the results of the logistic regression analysis using 15 maternal and familial characteristics to predict MCDP on

11,533 individuals from 8,660 families. The area under the ROC curve (AUC) was 0.88 (Figure 1). An area under the ROC curve of 0.88 indicates that the 15 maternal risk factors robustly classify mothers who ‘did smoke’ versus ‘did not smoke’ during pregnancy. Non-biological mothers, younger mothers, mothers with a lower education level, unplanned pregnancy, maternal family history of drug and alcohol use, paternal family history of alcohol use, prenatal alcohol and tobacco use, and lower neighborhood safety were associated with greater odds of MCDP. The analyses were also rerun using only non-biological mothers (i.e., excluding parent; AUC = 0.87) and using only parent responses (AUC = 0.95); results and conclusions remained the same, see Appendix Figures 3A and 4A and Tables 13A and 14A.

Effects of MCDP on Birth Outcomes

Table 4 presents the prevalence of birth outcomes in children with no MCDP and children with MCDP and Table 15A presents the prevalence of birth outcomes by biological mother vs. non-biological mother. Table 5 presents results from logistic regression models associated with birth outcomes and Tables 16A, 17A, and 18A presents the logistic regression results without covariates and within the sub-sample of biological mothers with and without covariates. For exploratory post-hoc analysis of birth outcomes in a biological mothers only sample see Table 21A. Mothers reporting of MCDP alone (Model a) was not significantly associated with being born premature, blue at birth, having a slow heart rate, not breathing, having convulsions, jaundice, requiring oxygen, or needing a blood transfusion. However, MCDP was significantly associated with Rh incompatibility. Interestingly, adding risk of MCDP to all models (i.e., Model a vs. Model b) reduced the MCDP logistic regression parameter estimates, suggesting confounding. Furthermore, Models-2b, 3b, and 4b suggests that the propensity for MCDP, as indicated by the set of confounders, is associated with babies ‘being

blue at birth', 'having a slow heart rate', and 'not breathing at birth'. In particular, for a one-unit change in the propensity for MCDP (pMCDP), the odds for being blue at birth increases by 4.07 (OR = 4.07(.60), 95% CI [1.18,14.10]). For a one-unit change in the pMCDP, the odds ratio for having a slow heart rate is expected to change by 2.77 (2.77 (.44), [1.10,6.93]). Similarly, a one-unit in pMCDP the odds for not breathing at birth is expected to change by 3.69 (3.69 (.44), [1.48,9.20]). Only the association for not breathing at birth remained significant after correcting for multiple comparisons. For zero-order correlations for the rare birth outcomes see Table 19A.

Effects of MCDP on Offspring Substance Misuse using Propensity for MCDP

The prevalence of alcohol sipping in children without MCDP vs. with MCDP are shown in Table 6. Table 7 presents results from several logistic regression models examining risk for alcohol sipping. The simple logistic regression model (Model 1a) that included MCDP and covariates suggested that MCDP was associated with alcohol sipping in children 1.36 (1.36 (.15), [1.01,1.85]). However, controlling for confounding factors (Model 1b) indicated that this effect was inflated and in fact, MCDP was not associated with alcohol sipping. Further examination of these association using internalizing and externalizing, suggested that greater CBCL externalizing *t*-scores were significantly associated with increased alcohol sipping (1.01 (.003) [1.00, 1.01]), which is consistent with previous findings (De Genna et al., 2021). Consistent with the literature (Bada et al., 2011), there was limited association between CBCL internalizing *t*-scores and alcohol sipping in children (1.00 (.003) [0.99, 1.01]). See Table 8 and 9 for results. For logistic regression model results excluding child-level covariates see Tables 22A, 23A, and 24A.

Direct and Indirect MCDP and Propensity for MCDP effects on Externalizing Behaviors and Childhood Alcohol Sipping

Figure 2 describes the path model used to examine the effect of MCDP and pMCDP on alcohol sipping via externalizing traits. Among the model tested, there was no significant direct (d' or e' path) effect on alcohol sipping in childhood. See Table 10 for a summary of mediation model parameters and see Table 11 for a summary of the direct and indirect effects. Given that indirect effects can exist in the absence of total or direct effects (Rucker et al., 2011), we proceeded to interpret the indirect paths from the model. Both MCDP and pMCDP were associated with externalizing behaviors in children (a and b path) and externalizing behaviors was associated with alcohol sipping in childhood (c path). Tests of the indirect effect using bootstrapped confidence intervals indicated significant mediation of MCDP and pMCDP on alcohol sipping; however, in each case, effects were quite small. While there was no main effect of internalizing traits on alcohol sipping in children, Figure 5A describes the path model used to examine the effect of MCDP and pMCDP on alcohol sipping via internalizing traits and Tables 27A and 28A lend further support for the lack of indirect effect on alcohol sipping via internalizing traits.

Discussion

Summary

Association of Maternal Confounders and MCDP

The first aim of this study examined the maternal risk factors associated with MCDP. Consistent with studies of alcohol and tobacco liability, risk for using cannabis during pregnancy is associated with a number of maternal/familial characteristics that are also associated with fetal development and childhood behaviors and appear to confound the association between MCDP on these outcomes.

Consistent with both the smoking and alcohol literature, evaluating the effect of MCDP requires appropriate accounting of a person's/child's familial liabilities. Previous findings have shown that prenatal exposure, maternal cannabis use prior to pregnancy, and paternal cannabis use were all associated with increased externalizing problems (El Marroun et al., 2018). Additionally, a family history of alcohol or substance use was associated with an increased risk of adolescent substance use and abuse (Kilpatrick et al., 2000). This suggests the possible role of maternal and paternal liabilities on childhood behavioral consequences, that we accounted for within the current study. Additionally, recent reports indicate familial history of substance use predicting age of alcohol onset (Cox et al., 2021). Interestingly, this relationship appeared to be mediated by externalizing traits in adolescents (ages 11 to 16; Cox et al., 2021). Relatedly, within the current study, externalizing traits in childhood appears to mediate the relationship between both MCDP and propensity for MCDP on alcohol sipping in childhood. Overall, children with prenatal cannabis exposure may share similar familial proclivities as supported by maternal/familial behaviors accounting for childhood behavioral consequences such as alcohol sipping.

Link Between MCDP and Birth Outcomes

This study adds to the growing body of literature examining the teratogenic qualities of MCDP. Experiencing nausea, slightly increased prenatal care visits, and paternal immediate family drug use were significantly associated with not breathing at birth (see Table 20A). It can be hypothesized that mothers experiencing greater nausea may be engaging in more frequent cannabis use during pregnancy or may be a result of cannabinoid hyperemesis syndrome, which may be associated with the observed birth outcomes (Badowski & Smith, 2020; Roberson et al., 2014; Westfall et al., 2006). Additionally, increased prenatal care visits may suggest underlying

pregnancy complications that could have also contributed to not breathing at birth. Although, these conclusions are purely speculative and require additional data. Notably, zero-order and simple regression associations indicated that birth outcome associations were upwardly biased with MCDP due to confounding with maternal/familial confounders. These maternal/familial confounders may shed important insight into other risk characteristics that impact fetal development beyond the teratogenic consequences associated with cannabis.

The endocannabinoid system lays the foundation for many important systems through its involvement in synaptic formation, neurogenesis (Pablo et al., 2012) and synaptic plasticity (Lu & Mackie, 2016). The current study results suggest that *in utero* cannabis exposure may interfere with central nervous system development and may disrupt important endocannabinoid pathways (Tree et al., 2014). For instance, a previous study conducted in newborn mice prenatally exposed to WIN55,212-2 (a CB1R agonist) reported modifications in respiration and altered responses to hypoxia, which suggests developmental consequences in important respiration related brain regions, like the brainstem (Tree et al., 2014). Further, prenatal cannabis exposure may impact other central neurotransmitter systems including the catecholamine neurotransmitters, which include dopamine, norepinephrine, and epinephrine, which could lead to important changes in biological systems involved in respiration (Fernández-Ruiz et al., 2004). Additionally, a previous study reported on the association between prenatal cannabis exposure and increased placental weight with increased placental weight occurring as a result of chronic hypoxia (Carter et al., 2016). Although further research should investigate the cannabinoid receptor densities in peripheral tissues within the body and the impact *in utero* cannabis has on the development and function of these biological systems. A large body of research has examined the CB1 and CB2

receptor densities and function in the brain while largely ignoring the CB1 and CB2 receptors in the peripheral nervous system and peripheral tissues.

Although the current findings do not support an association between MCDP and increased occurrence of birth outcomes included within the current study, it does suggest the role of maternal/familial characteristics that may impact these fetal outcomes. While we cannot disregard the previous findings suggesting a direct association between MCDP and negative birth outcomes, such as lower birth weight, smaller head circumference, and increase risk of preterm birth, we must be mindful that past studies were limited due to a lack of biological measures of cannabis use, and many relied on non-representative samples, which limits the generalizability of those findings. Additionally, few studies included proper controls. For instance, it was rare for studies to control for the use of other substances or other risky behaviors in which pregnant women may engage. Further, few studies accounted for potential confounders either specific to cannabis use or maternal level confounders. These limitations in research design contribute to the challenges in interpreting the relationship between prenatal cannabis exposure and these negative birth outcomes. The proposed challenges are not unique to prenatal cannabis studies; they also characterize much of the prenatal alcohol (Mattson et al., 2019) and tobacco (Crume, 2019) literature. Nonetheless, the current finings add to the growing body of literature that examines the teratogenic consequences of *in utero* cannabis exposure.

MCDP and Childhood Alcohol Sipping Behavior

The third aim of this study examined the association between MCDP and childhood alcohol sipping behavior. The results show that maternal cannabis use during pregnancy while may initially appear to be directly associated with a 36% increased risk in childhood alcohol sipping (see Table 7, Model 1a), is actually inflated and acts via an indirect mechanism to

influence alcohol behaviors. Specifically, propensity for MCDP or risk of being exposed to cannabis *in utero* based off of maternal behaviors confounded the previous model (Model 1a) results and instead, we observe only a 20% increased risk of childhood alcohol sipping behavior. The original results were in fact confounded by maternal/familial variables. This further emphasizes the need to account for risk of MCDP, as these child level outcomes may be better explained by the risk explained by maternal behaviors rather than the direct effects of MCDP. Additionally, several other factors may be contributing to the association between MCDP and childhood alcohol sipping behavior including environmental, sociocultural, biological, or genetic factors such as drug availability, peer influence, other behavioral traits, and attitudes towards substance use, among others. Past studies have reported positive perceived peer approval of substance use (Jackson et al., 2014) and favorable attitudes towards drugs of abuse (Obando et al., 2014) to be significant predictors of later consumption. However, these studies are limited, and further research is required to elucidate the mechanisms involved in childhood substance misuse. Furthermore, prenatal cannabis exposure may lead to disruptions in the catecholaminergic system (Fernández-Ruiz et al., 2004). Specifically, cannabinoids have been found to increase dopamine function and synthesis, as a well as inhibit dopamine reuptake in important reward related brain regions (Gardner & Vorel, 1998). It is possible that children prenatally exposed to cannabis have alterations in brain regions associated with reward that increase their susceptibility to experience the rewarding qualities of drugs of abuse. This suggests that prenatal cannabis exposure, similar to other teratogens, may predispose individuals to engage in risk taking behaviors early in life, which have implications for behavior in adulthood. While, these conclusions cannot be drawn from the current study results, the present

study offers a promising starting point and understanding of possible factors that may serve as predictors for subsequent substance use.

Strengths, Limitations, and Future Directions

The present study had several strengths and weaknesses that warrant continued research into the effects of MCDP. The study had a number of strengths including the sample size, which allowed for detailed investigation of the relationship between MCDP and offspring consequences. More so, using a propensity score approach allowed for control of critical environmental, behavioral, and biological factors that have largely been ignored in previous studies. Further, this study demonstrated the importance of accounting for maternal confounders/risk factors in the context of MCDP when interpreting study results. The most significant limitation of the current study was the methodological limitations. Specifically, the ABCD study did not capture information regarding cannabis dose, cannabis strain, timing of exposure (e.g., first, second or third trimester), route of administration, motivation, or other maternal demographics at the time of pregnancy. For example, within the current study we could not include maternal demographics such as income, family structure, maternal/familial psychopathology, or marital status because they were asked at baseline, 8-9 years post pregnancy. It is likely that characteristics such as income and marital status have significantly changed over the ~9-year period, which unfortunately would be representative of the current environment but not the environment at the time of the pregnancy. Future studies should continue to account for maternal/familial confounders to begin to elucidate the complex association between MCDP, propensity for MCDP, and various child level outcomes. Additionally, future research should consider alternative propensity score approaches in order to elucidate further patterns of risk for MCDP, for instance at certain points of the pMCDP liability

distribution (Palmer et al., 2016). Alongside, with biological factors it will also be important to account for genetic factors within the propensity score. While the current sample is large and diverse, it is likely that a significant amount of data is missing as only infants that reached full term were included within the sample. This suggests a potential underestimation between MCDP and these rare birth outcomes. Ideally future studies would also incorporate both maternal and paternal reports of cannabis use during pregnancy. Finally, in considering the recent changes in the cannabis landscape it is important to continue to investigate the gaps that exist within the field (Ikeda et al., 2022).

Conclusions & Implications

Findings from the current study indicate that maternal/familial behaviors related to propensity for using cannabis during pregnancy as opposed to maternal reports of cannabis use may better account for the observed negative postnatal and childhood outcomes. These familial confounders should be used when examining associations between prenatal cannabis use and their related outcomes. Overall, the current study highlights important demographic, environmental, behavioral, and biological factors that are associated with propensity for prenatal cannabis use and behavioral outcomes across development (infancy and childhood). Finally, the occurrence of negative postnatal and childhood outcomes suggests that important biological changes may be occurring and that other environmental and maternal factors (e.g., frequency of cannabis use, drug availability, among others) should be accounted for. Translational research will be essential in disentangling the complex relationship between prenatal cannabis exposure and neurobehavioral consequences.

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Table 1. ABCD Study Sample Characteristics

Maternal Variables	No MCDP (N = 10,836)	MCDP (N = 697)
Age, mean (SD)	29.71 (6.14)	25.32 (6.07)
Race/ethnicity		
White	7990 (74%)	416 (60%)
Black	1602 (15%)	228 (33%)
Mixed	41 (0.4%)	8 (1.1%)
Asian	389 (4%)	5 (0.7%)
Alaska/ Native American	31 (0.3%)	2 (0.3%)
Pacific Islander	11 (0.1%)	1 (0.1%)
Hispanic	632 (6%)	28 (4%)
Other	49 (0.5%)	6 (0.9%)
Child/ Adolescent Variables	No MCDP (N = 10,836)	MCDP (N = 697)
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)	11.96 (0.64)	11.84 (0.66)
Race/ethnicity		
White	8205 (76%)	413 (59%)
Black	1653 (15%)	243 (35%)
Mixed	61 (0.6%)	7 (1.0%)
Asian	226 (2%)	4 (0.6%)
Alaska/ Native American	34 (0.3%)	2 (0.3%)
Pacific Islander	10 (0.09%)	3 (0.4%)
Hispanic	545 (5%)	20 (3%)
Other	55 (0.5%)	4 (0.6%)
Sex		
Female	5163 (48%)	347 (50%)
Male	5673 (52%)	350 (50%)

Notation: proportion and percentages reported are relative to the total sample size for the given category for “No MCDP” or “MCDP.”

Table 2. Prevalence (n [%]) of familial factors for MCDP

Familial Factors	No MCDP (N = 10,836)	MCDP (N = 697)
Biological Mom	9,639 (89%)	552 (79%)
Age, mean (SD)	29.71 (6.14)	25.32 (6.07)
Planned Pregnancy	6,876 (63%)	168 (24%)
Prenatal Vitamin	10,173 (94%)	587 (84%)
Nausea	1,472 (14%)	128 (18%)
Maternal Immediate Family Alcohol Use	1,826 (17%)	264 (38%)
Paternal Immediate Family Alcohol Use	2,191 (20%)	252 (36%)
Maternal Immediate Family Drug Use	3,531 (33%)	348 (50%)
Paternal Immediate Family Drug Use	2,305 (21%)	185 (27%)
Alcohol Use During Pregnancy	2,427 (22%)	418 (60%)
Tobacco Use During Pregnancy	1,125 (10%)	416 (60%)
Education Level, mean (SD)	17 (2.78)[a]	15 (2.49)[a]
Prenatal Care, mean (SD)	16 (7.52)	15 (6.47)
Neighborhood Safety, mean (SD)	3.91 (0.96)[b]	3.50 (1.14)[b]

Characteristics of individuals from mothers with MCDP. Notation: proportion and percentages reported are relative to the total sample size for the given category for "No MCDP" or "MCDP." Missingness was accounted for the in the model through a dummy coded variable.

[a] Educational level values are equal to: 17= Associates degree: Academic Program and 15= Some college

[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 MCDP

Familial Factors	OR (SE)	95% CI [Lower, Upper]	p
Biological Mom	0.67 (0.11)	[0.54,0.82]	0.0002**
Maternal Age	0.93 (0.01)	[0.91, 0.95]	<0.0001***
Planned Pregnancy	0.48 (0.12)	[0.37, 0.61]	<0.0001***
Prenatal Vitamin	0.88 (0.15)	[0.65, 1.19]	0.41
Nausea	1.24 (0.13)	[0.96, 1.61]	0.11
Prenatal Care	0.99 (0.01)	[0.97, 1.00]	0.11
Education Level	0.96 (0.02)	[0.92, 1.00]	0.03*
Maternal Immediate Family Alcohol Use	1.41 (0.12)	[1.12, 1.78]	0.004**
Paternal Immediate Family Alcohol use	1.40 (0.14)	[1.07, 1.83]	0.01**
Maternal Immediate Family Drug Use	1.29 (0.10)	[1.07, 1.55]	0.01**
Paternal Immediate Family Drug Use	0.98 (0.10)	[0.81, 1.19]	0.84
Alcohol Use During Pregnancy	4.20 (0.08)	[3.58, 4.94]	<0.0001***
Tobacco Use During Pregnancy	5.57 (0.08)	[4.76, 6.51]	<0.0001***
Neighborhood Safety	0.81 (0.07)	[0.72, 0.93]	0.002**
Race	1.01 (0.05)	[0.91, 1.12]	0.86

*p<.05, ** p<.01, *** p<.0001

Table 4. Prevalence (n [%]) of birth outcomes for MCDP

Birth Outcomes	No MCDP (N = 10,836)	MCDP (N = 697)
Premature	2046 (19%)	110 (16%)
Blue at Birth	335 (3%)	26 (4%)
Slow Heart Rate	291 (3%)	25 (4%)
Did not Breathe	495 (5%)	41 (6%)
Convulsions	16 (0.1%)	2 (0.3%)
Jaundice	1758 (16%)	107 (15%)
Required Oxygen	1038 (26%)	69 (10%)
Blood Transfusion	52 (0.5%)	3 (0.4%)
Rh Incompatibility	273 (3%)	11 (2%)

Notation: proportion and percentages reported are relative to the total sample size for the given category for “No MCDP” or “MCDP.”

Table 5. Birth outcomes associated with MCDP and Maternal Propensity Score

Dependent Variable	Model	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Premature	Model 1a	MCDP	0.80 (0.15)	[0.59, 1.09]	0.15
	Model 1b	MCDP	0.81 (0.10)	[0.65, 1.01]	0.06
		Propensity Score	0.89 (0.29)	[0.48, 1.64]	0.69
Blue at Birth	Model 2a	MCDP	1.51 (0.35)	[0.74, 3.10]	0.25
	Model 2b	MCDP	1.06 (0.28)	[0.59, 1.90]	0.84
		Propensity Score	4.07 (0.60)	[1.18, 14.10]	0.03*
Slow Heart Rate	Model 3a	MCDP	1.32 (0.25)	[0.79, 2.23]	0.28
	Model 3b	MCDP	1.04 (0.30)	[0.56, 1.93]	0.91
		Propensity Score	2.77 (0.44)	[1.10, 6.93]	0.03*
Did not Breathe	Model 4a	MCDP	1.46 (0.32)	[0.76, 2.81]	0.24
	Model 4b	MCDP	1.06 (0.30)	[0.57, 1.97]	0.85
		Propensity Score	3.69 (0.44)	[1.48, 9.20]	0.007**
Convulsions	Model 5a	MCDP	2.45 (0.81)	[0.45, 13.27]	0.28
	Model 5b	MCDP	2.17 (0.48)	[0.80, 5.87]	0.12
		Propensity Score	2.83 (3.11)	[0.004, >999.99]	0.74
Jaundice	Model 6a	MCDP	1.05 (0.13)	[0.80, 1.38]	0.70
	Model 6b	MCDP	0.94 (0.13)	[0.72, 1.22]	0.63
		Propensity Score	1.51 (0.34)	[0.74, 3.09]	0.24
Required Oxygen	Model 7a	MCDP	1.11 (0.23)	[0.74, 0.96]	0.66
	Model 7b	MCDP	1.00 (0.20)	[0.66, 1.51]	0.99
		Propensity Score	1.59 (0.36)	[0.75, 3.38]	0.22
Blood Transfusion	Model 8a	MCDP	0.62 (0.56)	[0.19, 1.96]	0.39
	Model 8b	MCDP	1.20 (0.64)	[0.32, 4.50]	0.78
		Propensity Score	0.01 (2.65)	[<0.001, 3.27]	0.12
Rh Incompatibility	Model 9a	MCDP	0.66 (0.24)	[0.40, 1.09]	0.10
	Model 9b	MCDP	0.54 (0.28)	[0.30, 0.97]	0.04*
		Propensity Score	2.35 (0.53)	[0.79, 7.01]	0.12

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

Table 6: Prevalence (n [%]) of alcohol sipping for MCDP

Outcome	No MCDP (N = 10,836)	MCDP (N = 697)
Alcohol Sipping	2416 (22%)	176 (25%)

Notation: proportion and percentages reported are relative to the total sample size for the given category for “No MCDP” or “MCDP.”

Table 7. Alcohol sipping associated with MCDP and Maternal Propensity Score

Dependent Variable	Model	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Alcohol Sipping	Model 1a	MCDP	1.36 (0.15)	[1.01, 1.85]	0.04*
	Model 1b	MCDP	1.20 (0.12)	[0.93, 1.55]	0.15
		Propensity Score	1.72 (0.27)	[0.98, 3.02]	0.06

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

Table 8. Alcohol Sipping associated with MCDP, Maternal Propensity Scores, and Externalizing *T*-scores

Dependent Variable	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Alcohol Sipping	MCDP	1.18 (0.12)	[0.92, 1.52]	0.18
	Propensity Score	1.55 (0.28)	[0.87, 2.75]	0.13
	CBCL Externalizing	1.01 (0.003)	[1.00, 1.01]	0.02*

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

Table 9. Alcohol Sipping associated with MCDP, Maternal Propensity Scores, and Internalizing *T*-scores

Dependent Variable	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Alcohol Sipping	MCDP	1.20 (0.12)	[0.93, 1.55]	0.15
	Propensity Score	1.71 (0.28)	[0.96, 3.05]	0.07
	CBCL Internalizing	1.00 (0.003)	[0.99, 1.01]	0.88

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

Table 10. Summary of model parameters

Regression Paths	Est. (SE)	p	95% CI [Lower, Upper]
MCDP -> Externalizing Traits (a)	2.00 (0.59)	0.001**	[1.03, 2.96]
Propensity Score -> Externalizing Traits (b)	15.21 (1.17)	0.00***	[13.41, 17.27]
Externalizing Traits -> Alcohol Sipping (c)	0.004 (0.002)	0.02*	[0.001, 0.007]
MCDP -> Alcohol Sipping (d')	0.10 (0.07)	0.17	[-0.01, 0.22]
Propensity Score -> Alcohol Sipping (e')	0.26 (0.17)	0.12	[-0.04, 0.51]

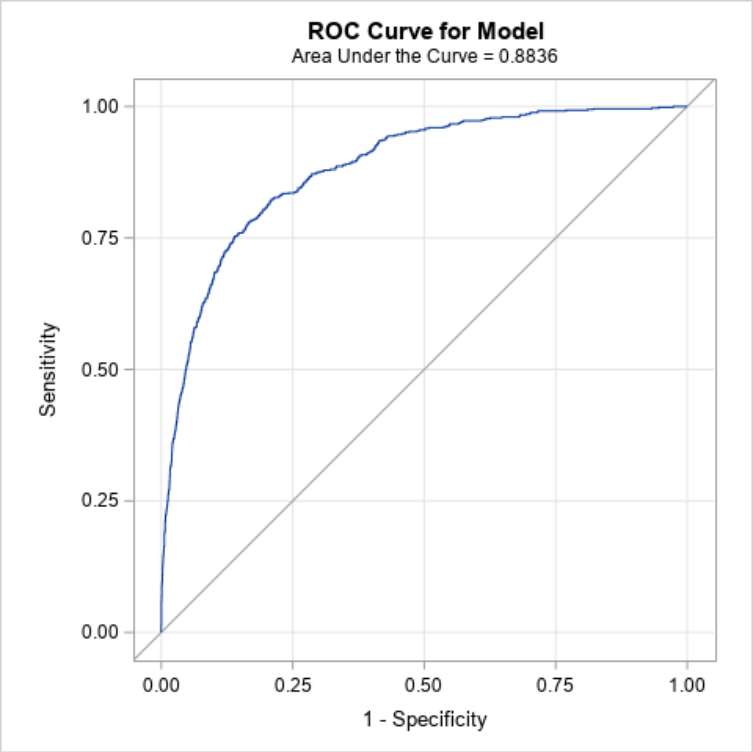
*p<.05, ** p<.01, *** p<.0001. See Figure 2 for a conceptual model of paths a, b, c, d', and e'. Covariates are included to adjust the effects of age, sex, income, and race. Covariate effects not shown.

Table 11. Summary mediation path estimates (probit regression estimates) and corresponding 95% bootstrapped CI

Effects from MCDP to Alcohol Sipping	
Total indirect effect via externalizing (ac)	0.009 [0.001, 0.018]
Total direct effect (d')	0.10 [-0.03, 0.24]
Effects from Propensity Score to Alcohol Sipping	
Total indirect effect via externalizing (bc)	0.07 [0.01, 0.12]
Total direct effect (e')	0.26 [-0.11, 0.55]

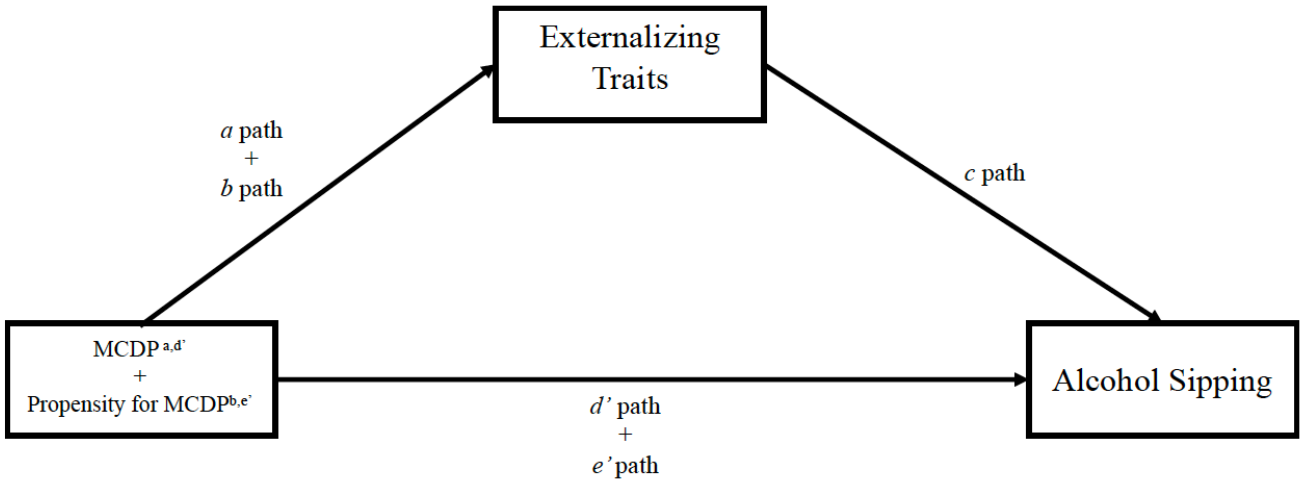
Results presented adjust for the effects of age, sex, race, and income. Covariate effects not shown.

Figure 1. ROC Curve of Model Predicting MCDP



Logistic regression using 15 maternal risk factors to predict MCDP robustly captured mothers who ‘did smoke’ versus ‘did not smoke’ (area under the ROC curve = 0.88) non-biological mothers, younger mothers, lower education level, unplanned pregnancy, maternal and paternal immediate family alcohol use, maternal immediate drug use, prenatal alcohol and tobacco use, and lower neighborhood safety predicted greater odds of MCDP.

Figure 2. Path model of mediation



The externalizing traits are baseline *t*-scores and covariates included for this model were: sex, age, race, and income. Covariate effects not shown.

Appendix

Table 12A. Prevalence (n [%]) of familial factors for MCDP by non-biological mother and biological mother

Familial Factors	Non-Bio Mom		Bio Mom	
	No MCDP (N = 1,197)	MCDP (N = 145)	No MCDP (N = 9,639)	MCDP (N = 552)
Maternal Age, mean (SD)	30.49 (6.44)	25.15 (6.97)	29.62 (6.10)	25.36 (5.85)
Planned Pregnancy	810 (68%)	19 (13%)	6,066 (63%)	149 (27%)
Prenatal Vitamin	1,037 (87%)	68 (47%)	9,136 (95%)	519 (94%)
Nausea	109 (9%)	20 (14%)	1,363 (14%)	108 (20%)
Maternal Immediate Family Alcohol Use	159 (13%)	62 (43%)	1,667 (17%)	202 (37%)
Paternal Immediate Family Alcohol Use	208 (17%)	48 (33%)	1,983 (21%)	204 (37%)
Maternal Immediate Family Drug Use	296 (25%)	62 (43%)	3,235 (34%)	286 (52%)
Paternal Immediate Family Drug Use	272 (23%)	33 (23%)	2,033 (21%)	152 (28%)
Alcohol Use During Pregnancy	287 (24%)	98 (68%)	2140 (22%)	320 (58%)
Tobacco Use During Pregnancy	106 (9%)	102 (70%)	1019 (11%)	314 (57%)
Education Level, mean (SD)	17 (2.76)[a]	16 (2.54)[a]	17 (2.78)[a]	15 (2.47)[a]
Prenatal Care, mean (SD)	14 (4.68)	11 (5.65)	16 (7.75)	15 (6.45)
Neighborhood Safety, mean (SD)	3.14 (0.94)[b]	2.90 (1.06)[b]	2.91 (1.01)[b]	2.43 (1.19)[b]

Notation: proportion and percentages reported are relative to the total sample size for the given category for "No MCDP" or "MCDP."

[a] Educational level values are equal to: 17= Associates degree: Academic Program, 16= Associate degree: Occupational, and 15= Some college

[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 13A. Familial risk factors/confounders associated with MCDP by non-biological mother and biological mother

Familial Factors	Non-Bio Mom			Bio Mom		
	OR (SE)	95% CI [Lower, Upper]	p	OR (SE)	95% CI [Lower, Upper]	p
Maternal Age	0.93 (0.02)	[0.89, 0.96]	0.0001**	0.93 (0.01)	[0.91, 0.95]	<0.0001***
Planned Pregnancy	0.26 (0.31)	[0.14, 0.49]	<0.0001***	0.52 (0.13)	[0.40, 0.66]	<0.0001***
Prenatal Vitamin	0.50 (0.35)	[0.25, 0.99]	0.05	1.13 (0.24)	[0.71, 1.82]	0.61
Nausea	1.85 (0.44)	[0.78, 4.40]	0.16	1.17 (0.13)	[0.90, 1.50]	0.24
Prenatal Care	0.97 (0.05)	[0.89, 1.07]	0.56	0.99 (0.008)	[0.97, 1.00]	0.13
Education Level	0.91 (0.05)	[0.82, 1.02]	0.10	0.96 (0.03)	[0.91, 1.01]	0.12
Maternal Immediate Family Alcohol Use	1.19 (0.44)	[0.51, 2.80]	0.69	1.44 (0.14)	[1.11, 1.88]	0.007**
Paternal Immediate Family Alcohol use	1.01 (0.28)	[0.59, 1.74]	0.96	1.42 (0.14)	[1.08, 1.88]	0.01*
Maternal Immediate Family Drug Use	0.73 (0.40)	[0.34, 1.59]	0.43	1.36 (0.10)	[1.12, 1.64]	0.002**
Paternal Immediate Family Drug Use	1.50 (0.31)	[0.82, 2.74]	0.19	0.94 (0.12)	[0.74, 1.18]	0.58
Alcohol Use During Pregnancy	4.79 (0.40)	[2.19, 10.48]	<0.0001***	4.05 (0.10)	[3.33, 4.92]	<0.0001***
Tobacco Use During Pregnancy	19.01 (0.32)	[10.17, 35.53]	<0.0001***	4.83 (0.09)	[4.08, 5.71]	<0.0001***
Neighborhood Safety	1.08 (0.11)	[0.86, 1.34]	0.52	0.78 (0.07)	[0.67, 0.90]	0.0009**
Race	0.85 (0.18)	[0.60, 1.21]	0.37	1.02 (0.05)	[0.93, 1.12]	0.64

*p<.05, ** p<.01, ***p<.0001

Table 14A. Parameter Estimates of familial risk factors/confounders associated with MCDP by non-biological mother and biological mother

Familial Factors	Non-Bio Mom				Bio Mom			
	Estimate	SE	95% CI [Lower, Upper]	p	Estimate	SE	95% CI [Lower, Upper]	p
Maternal Age	-0.08	0.02	[0.89, 0.96]	0.0001**	-0.07	0.01	[0.91, 0.95]	<0.0001***
Planned Pregnancy	-1.33	0.31	[0.14, 0.49]	<0.0001***	-0.66	0.13	[0.40, 0.66]	<0.0001***
Prenatal Vitamin	-0.70	0.35	[0.25, 0.99]	0.05	0.12	0.24	[0.71, 1.82]	0.61
Nausea	0.62	0.44	[0.78, 4.40]	0.16	0.15	0.13	[0.90, 1.50]	0.24
Prenatal Care	-0.03	0.05	[0.89, 1.07]	0.56	-0.01	0.008	[0.97, 1.00]	0.13
Education Level	-0.09	0.05	[0.82, 1.02]	0.10	-0.04	0.03	[0.91, 1.01]	0.12
Maternal Immediate Family Alcohol Use	0.17	0.44	[0.51, 2.80]	0.69	0.37	0.14	[1.11, 1.88]	0.007**
Paternal Immediate Family Alcohol use	0.01	0.28	[0.59, 1.74]	0.96	0.35	0.14	[1.08, 1.88]	0.01*
Maternal Immediate Family Drug Use	-0.32	0.4	[0.34, 1.59]	0.43	0.3	0.1	[1.12, 1.64]	0.002**
Paternal Immediate Family Drug Use	0.41	0.31	[0.82, 2.74]	0.19	-0.07	0.12	[0.74, 1.18]	0.58
Alcohol Use During Pregnancy	1.57	0.4	[2.19, 10.48]	<0.0001***	1.4	0.1	[3.33, 4.92]	<0.0001***
Tobacco Use During Pregnancy	2.95	0.32	[10.17, 35.53]	<0.0001***	1.57	0.09	[4.08, 5.71]	<0.0001***
Neighborhood Safety	0.07	0.11	[0.86, 1.34]	0.52	-0.25	0.07	[0.67, 0.90]	0.0009**
Race	-0.16	0.18	[0.60, 1.21]	0.37	0.02	0.05	[0.93, 1.12]	0.64

*p<.05, **p<.01, ***p<.0001

Table 15A. Prevalence (n [%]) of birth outcomes for MCDP by non-biological mother and biological mother

Birth Outcomes	Non-Bio Mom		Bio Mom	
	No MCDP (N = 1,197)	MCDP (N = 145)	No MCDP (N = 9,639)	MCDP (N = 552)
Premature	195 (16%)	19 (13%)	1851 (19%)	91 (16%)
Blue at Birth	30 (3%)	5 (3%)	305 (3%)	21 (4%)
Slow Heart Rate	24 (2%)	3 (2%)	267 (3%)	22 (4%)
Did not Breathe	45 (4%)	9 (6%)	450 (5%)	32 (6%)
Convulsions	1 (.08%)	1 (.7%)	15 (.2%)	1 (.2%)
Jaundice	145 (12%)	14 (10%)	1613 (17%)	93 (17%)
Required Oxygen	83 (7%)	14 (10%)	955 (10%)	55 (10%)
Blood Transfusion	1 (.08%)	1 (.7%)	51 (.5%)	2 (.4%)
Rh Incompatibility	9 (.8%)	1 (.7%)	264 (3%)	10 (2%)

Notation: proportion and percentages reported are relative to the total sample size for the given category for “No MCDP” or “MCDP.”

Table 16A. Birth outcomes associated with MCDP and Maternal Propensity Scores- biological mothers with covariates

Dependent Variable	Model	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Premature	Model 1a	MCDP	0.84 (0.15)	[0.62, 1.14]	0.25
	Model 1b	MCDP	0.84 (0.10)	[0.68, 1.03]	0.09
		Propensity Score	0.93 (0.35)	[0.45, 1.91]	0.83
Blue at Birth	Model 2a	MCDP	1.24 (0.36)	0.59, 2.61]	0.55
	Model 2b	MCDP	0.88 (0.28)	[0.49, 1.58]	0.65
		Propensity Score	5.10 (0.65)	[1.32, 19.66]	0.02*
Slow Heart Rate	Model 3a	MCDP	1.29 (0.23)	[0.81, 2.07]	0.27
	Model 3b	MCDP	0.96 (0.26)	[0.56, 1.64]	0.87
		Propensity Score	4.19 (0.54)	[1.38, 12.79]	0.01*
Did not Breathe	Model 4a	MCDP	1.27 (0.25)	[0.75, 2.14]	0.36
	Model 4b	MCDP	0.93 (0.24)	[0.56, 1.54]	0.76
		Propensity Score	4.44 (0.47)	[1.67, 11.80]	0.005**
Convulsions	Model 5a	MCDP	0.85 (0.97)	[0.11, 6.37]	0.87
	Model 5b	MCDP	4.36 (1.04)	[0.50, 37.65]	0.17
		Propensity Score	<0.001 (11.35)	[<0.001, <0.001]	0.01**
Jaundice	Model 6a	MCDP	1.11 (0.13)	[0.85, 1.47]	0.42
	Model 6b	MCDP	0.99 (0.13)	[0.76, 1.29]	0.96
		Propensity Score	1.63 (0.40)	[0.71, 3.72]	0.23
Required Oxygen	Model 7a	MCDP	1.02 (0.19)	[0.69, 1.51]	0.93
	Model 7b	MCDP	0.91 (0.18)	[0.63, 1.32]	0.61
		Propensity Score	1.79 (0.39)	[0.80, 4.01]	0.15
Blood Transfusion	Model 8a	MCDP	0.47 (0.68)	[0.12, 1.92]	0.28
	Model 8b	MCDP	0.91 (0.80)	[0.17, 4.81]	0.91
		Propensity Score	0.005 (3.39)	[<0.001, 6.29]	0.14
Rh Incompatibility	Model 9a	MCDP	0.64 (0.29)	[0.35, 1.16]	0.13
	Model 9b	MCDP	0.50 (0.31)	[0.26, 0.96]	0.04*
		Propensity Score	3.33 (0.54)	[1.09, 10.17]	0.04*

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

Table 17A. Birth outcomes associated with MCDP and Maternal Propensity Scores- biological mothers without covariates

Dependent Variable	Model	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Premature	Model 1a	MCDP	0.83 (0.15)	[0.61, 1.14]	0.24
	Model 1b	MCDP	0.84 (0.11)	[0.67, 1.05]	0.12
		Propensity Score	0.91 (0.35)	[0.44, 1.87]	0.79
Blue at Birth	Model 2a	MCDP	1.23 (0.36)	[0.59, 2.56]	0.57
	Model 2b	MCDP	0.84 (0.26)	[0.49, 1.45]	0.52
		Propensity Score	5.74 (0.68)	[1.39, 23.69]	0.02*
Slow Heart Rate	Model 3a	MCDP	1.29 (0.23)	[0.81, 2.06]	0.27
	Model 3b	MCDP	0.97 (0.26)	[0.57, 1.65]	0.89
		Propensity Score	4.09 (0.52)	[1.40, 11.97]	0.01**
Did not Breathe	Model 4a	MCDP	1.25 (0.26)	[0.73, 2.13]	0.40
	Model 4b	MCDP	0.92 (0.25)	[0.55, 1.54]	0.73
		Propensity Score	4.33 (0.47)	[1.64, 11.41]	0.005**
Convulsions	Model 5a	MCDP	0.84 (0.97)	[0.11, 6.37]	0.86
	Model 5b	MCDP	4.27 (1.04)	[0.49, 36.95]	0.18
		Propensity Score	<.0.001 (11.93)	[<0.001, 0.002]	0.02*
Jaundice	Model 6a	MCDP	1.10 (0.13)	[0.84, 1.44]	0.49
	Model 6b	MCDP	0.98 (0.12)	[0.76, 1.26]	0.88
		Propensity Score	1.60 (0.39)	[0.72, 3.59]	0.24
Required Oxygen	Model 7a	MCDP	0.99 (0.19)	[0.67, 1.47]	0.95
	Model 7b	MCDP	0.89 (0.18)	[0.62, 1.28]	0.51
		Propensity Score	1.75 (0.38)	[0.79, 3.88]	0.16
Blood Transfusion	Model 8a	MCDP	0.46 (0.67)	[0.11, 1.86]	0.26
	Model 8b	MCDP	0.89 (0.80)	[0.17, 4.71]	0.89
		Propensity Score	0.005 (3.48)	[<0.001, 6.84]	0.14
	Model 9b	MCDP	0.49 (0.33)	[0.25, 0.96]	0.04*
		Propensity Score	3.28 (0.54)	[1.07, 10.04]	0.04*

*p<.05, **p<.01, ***p<.0001

Table 18A. Birth outcomes associated with MCDP and Maternal Propensity Score without covariates

Dependent Variable	Model	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Premature	Model 1a	MCDP	0.80 (0.15)	[0.59, 1.09]	0.14
	Model 1b	MCDP	0.82 (0.11)	[0.66, 1.02]	0.08
		Propensity Score	0.86 (0.29)	[0.47, 1.58]	0.62
Blue at Birth	Model 2a	MCDP	1.49 (0.34)	[0.73, 3.02]	0.26
	Model 2b	MCDP	1.01 (0.26)	[0.60, 1.72]	0.96
		Propensity Score	4.45 (0.60)	[1.27, 15.66]	0.02*
Slow Heart Rate	Model 3a	MCDP	1.31 (0.25)	[0.78, 2.21]	0.30
	Model 3b	MCDP	1.03 (0.30)	[0.56, 1.91]	0.93
		Propensity Score	2.73 (0.43)	[1.11, 6.72]	0.03*
Did not Breathe	Model 4a	MCDP	1.44 (0.32)	[0.75, 2.79]	0.26
	Model 4b	MCDP	1.05 (0.30)	[0.56, 1.97]	0.87
		Propensity Score	3.61 (0.43)	[1.46, 8.93]	0.008**
Convulsions	Model 5a	MCDP	2.45 (0.82)	[0.44, 13.59]	0.29
	Model 5b	MCDP	2.19 (0.48)	[0.81, 5.94]	0.12
		Propensity Score	2.78 (3.08)	[0.005, >999.99]	0.74
Jaundice	Model 6a	MCDP	1.04 (0.13)	[0.79, 1.37]	0.77
	Model 6b	MCDP	0.93 (0.12)	[0.73, 1.20]	0.58
		Propensity Score	1.50 (0.33)	[0.75, 3.00]	0.24
Required Oxygen	Model 7a	MCDP	1.09 (0.23)	[0.68, 1.75]	0.72
	Model 7b	MCDP	0.99 (0.20)	[0.65, 1.49]	0.94
		Propensity Score	1.55 (0.36)	[0.74, 3.27]	0.23
Blood Transfusion	Model 8a	MCDP	0.60 (0.55)	[0.19, 1.89]	0.36
	Model 8b	MCDP	1.18 (0.63)	[0.32, 4.36]	0.79
		Propensity Score	0.01 (2.71)	[<0.001, 3.45]	0.12
Rh Incompatibility	Model 9a	MCDP	0.66 (0.25)	[0.39, 1.11]	0.11
	Model 9b	MCDP	0.54 (0.29)	[0.30, 0.99]	0.05*
		Propensity Score	2.28 (0.52)	[0.77, 6.76]	0.13

*p<.05, **p<.01, ***p<.0001

Table 19A. Zero order correlations for birth outcomes

	1	2	3	4	5	6	7	8	9
1. Premature	1								
2. Blue at Birth	0.06**	1							
3. Slow Heart Rate	.06**	.28**	1						
4. Did not Breathe	.08**	.43**	.25**	1					
5. Convulsions	0.01	.07**	.06**	.05**	1				
6. Jaundice	.21**	.06**	.05**	.09**	.03**	1			
7. Required Oxygen	.37**	.25**	.20**	.34**	.04**	.21**	1		
8. Blood Transfusion	.09**	.10**	.07**	.09**	.16**	.08**	.16**	1	
9. Rh Incompatibility	0.003	.05**	.03**	.03**	.07**	.05**	.03**	.08**	1

$p<.05$, $^{**}p<.01$, $^{***}p<.0001$

Table 20A. Exploratory post-hoc analysis of birth outcomes that remained significant after correcting for multiple comparisons

Dependent Variable	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Did not Breathe	Biological Mother	1.03 (0.17)	[0.74, 1.44]	0.85
	Maternal Age	1.00 (0.01)	[0.98, 1.02]	0.93
	Planned Pregnancy	0.87 (0.11)	[0.71, 1.08]	0.21
	Prenatal Vitamin	0.90 (0.20)	[0.60, 1.34]	0.59
	Nausea	1.37 (0.14)	[1.04, 1.80]	0.03*
	Prenatal Care	1.02 (0.004)	[1.01, 1.03]	<0.001***
	Education Level	0.97 (0.03)	[0.91, 1.01]	0.08
	Maternal Immediate Family Alcohol Use	1.00 (0.14)	[0.77, 1.32]	0.98
	Paternal Immediate Family Alcohol Use	1.23 (0.15)	[0.92, 1.66]	0.17
	Maternal Immediate Family Drug Use	1.23 (0.11)	[0.99, 1.54]	0.06
	Paternal Immediate Family Drug Use	1.23 (0.09)	[1.03, 1.47]	0.02*
	Alcohol Use During Pregnancy	0.93 (0.11)	[0.74, 1.16]	0.50
	Tobacco Use During Pregnancy	1.25 (0.23)	[0.80, 1.95]	0.32
	Neighborhood Safety	0.94 (0.05)	[0.85, 1.03]	0.20

*p<.05, **p<.01, ***p<.0001

Table 21A. Exploratory post-hoc analysis of birth outcomes that remained significant after correcting for multiple comparisons by biological mother

Dependent Variable	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Did not Breathe	Maternal Age	1.00 (0.01)	[0.98, 1.02]	0.91
	Planned Pregnancy	0.87 (0.10)	[0.71, 1.06]	0.16
	Prenatal Vitamin	0.98 (0.26)	[0.58, 1.65]	0.94
	Nausea	1.28 (0.14)	[0.96, 1.69]	0.09
	Prenatal Care	1.02 (0.004)	[1.01, 1.03]	<0.0001***
	Education Level	0.96 (0.03)	[0.91, 1.01]	0.11
	Maternal Immediate Family Alcohol Use	1.07 (0.15)	[0.80, 1.44]	0.65
	Paternal Immediate Family Alcohol Use	1.30 (0.15)	[0.98, 1.73]	0.07
	Maternal Immediate Family Drug Use	1.18 (0.12)	[0.94, 1.48]	0.16
	Paternal Immediate Family Drug Use	1.24 (0.11)	[1.01, 1.54]	0.04*
	Alcohol Use During Pregnancy	0.98 (0.12)	[0.78, 1.24]	0.87
	Tobacco Use During Pregnancy	1.13 (0.21)	[0.74, 1.71]	0.57
	Neighborhood Safety	0.94 (0.05)	[0.85, 1.03]	0.17
Convulsion	Maternal Age	1.03 (0.04)	[0.95, 1.11]	0.49
	Planned Pregnancy	0.56 (0.74)	[0.13, 2.40]	0.44
	Prenatal Vitamin	1.11 (1.22)	[0.10, 12.17]	0.93
	Nausea	0.87 (0.89)	[0.15, 4.99]	0.88
	Prenatal Care	1.04 (0.02)	[1.01, 1.07]	0.02*
	Education Level	0.89 (0.06)	[0.79, 1.01]	0.07
	Maternal Immediate Family Alcohol Use	0.26 (1.10)	[0.03, 2.19]	0.21
	Paternal Immediate Family Alcohol Use	1.14 (0.84)	[0.22, 5.94]	0.88
	Maternal Immediate Family Drug Use	0.66 (0.83)	[0.13, 3.36]	0.62
	Paternal Immediate Family Drug Use	0.28 (0.99)	[0.04, 1.98]	0.20
	Alcohol Use During Pregnancy	0.38 (0.80)	[0.08, 1.80]	0.22
	Tobacco Use During Pregnancy	<0.001 (0.42)	[<0.001, <0.001]	<0.0001***
	Neighborhood Safety	0.76 (0.32)	[0.41, 1.42]	0.39

*p<.05, **p<.01, ***p<.0001

Table 22A. Alcohol sipping associated with MCDP and Maternal Propensity Score without covariates

Dependent Variable	Model	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Alcohol Sipping	Model 1a	MCDP	1.28 (0.15)	[0.93, 1.76]	0.12
	Model 1b	MCDP	1.35 (0.13)	[0.90, 1.57]	0.20
		Propensity Score	1.35 (0.28)	[0.76, 2.41]	0.29

Table 23A. Alcohol Sipping associated with MCDP, Maternal Propensity Scores, and Externalizing *T*-scores without covariates

Dependent Variable	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Alcohol Sipping	MCDP	1.18 (0.13)	[0.89, 1.56]	0.23
	Propensity Score	1.27 (0.29)	[0.70, 2.30]	0.41
	CBCL Externalizing	1.00 (0.003)	[1.00, 1.01]	0.16

Table 24. Alcohol Sipping regressed on MCDP, Maternal Propensity Scores, and Internalizing *T*-scores without covariates

Dependent Variable	Independent Variable	OR (SE)	95% CI [Lower, Upper]	p
Alcohol Sipping	MCDP	1.19 (0.13)	[0.90, 1.58]	0.20
	Propensity Score	1.34 (0.29)	[0.75, 2.48]	0.30
	CBCL Internalizing	1.00 (0.003)	[0.99, 1.00]	0.89

Table 25A. Repeated Measures ANOVA post hoc analysis comparing means for externalizing behaviors at baseline, 1-year-follow-up, and 2-year-follow-up

Pairwise Comparison			Mean Difference	SE	95% CI [Lower, Upper]	p
No MCDP	Externalizing Baseline	Externalizing 1-year	0.49	0.1	[0.26,0.72]	<.001
		Externalizing 2-year	0.96	0.1	[0.71,1.20]	<.001
MCDP	Externalizing Baseline	Externalizing 1-year	1.45	0.41	[0.46,2.44]	0.001
		Externalizing 2-year	2.18	0.44	[1.13,3.23]	<.001

Table 26A. Repeated Measures ANOVA post hoc analysis comparing means for internalizing behaviors at baseline, 1-year-follow-up, and 2-year-follow-up

Pairwise Comparison			Mean Difference	SE	95% CI [Lower, Upper]	p
No MCDP	Internalizing Baseline	Internalizing 1-year	-0.07	0.11	[-0.34,0.20]	1.00
		Internalizing 2-year	0.68	0.11	[0.40,0.96]	<.001
MCDP	Internalizing Baseline	Internalizing 1-year	0.94	0.48	[-0.21,2.09]	0.15
		Internalizing 2-year	1.44	0.50	[0.24,2.65]	0.01

Table 27A. Summary of model parameters- internalizing traits

Regression Paths	Est. (SE)	p	95% CI [Lower, Upper]
MCDP -> Internalizing Traits (f)	1.07 (0.31)	0.001**	[0.92, 1.44]
Propensity Score -> Internalizing Traits (g)	10.63 (1.15)	0.00***	[10.27, 11.86]
Internalizing Traits -> Alcohol Sipping (h)	0.00 (0.003)	0.93	[0.002, 0.004]
MCDP -> Alcohol Sipping (i')	0.11 (0.04)	0.009**	[0.05, 0.09]
Propensity Score -> Alcohol Sipping (j')	0.33 (0.18)	0.07	[0.10, 0.34]

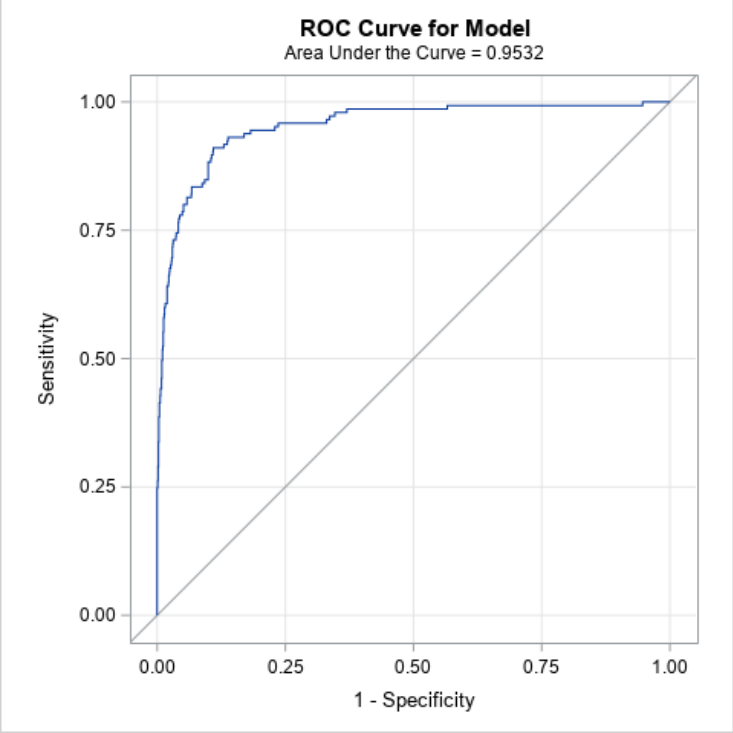
*p<.05, ** p<.01, *** p<.0001. See Figure 2 for a conceptual model of paths a, b, c, d', and e'. Covariates are included to adjust the effects of age, sex, income, and race. Covariate effects not shown.

Table 28A. Summary mediation path estimates (probit regression estimates) and corresponding 95% bootstrapped CI- internalizing traits

Effects from MCDP to Alcohol Sipping	
Indirect effect (fh)	0.0001 [0.002, 0.006]
Direct effect (i')	0.11 [0.05, 0.09]
Effects from Propensity Score to Alcohol Sipping	
Indirect effect (gh)	0.003 [0.02, 0.05]
Direct effect (j')	0.33 [0.10, 0.34]

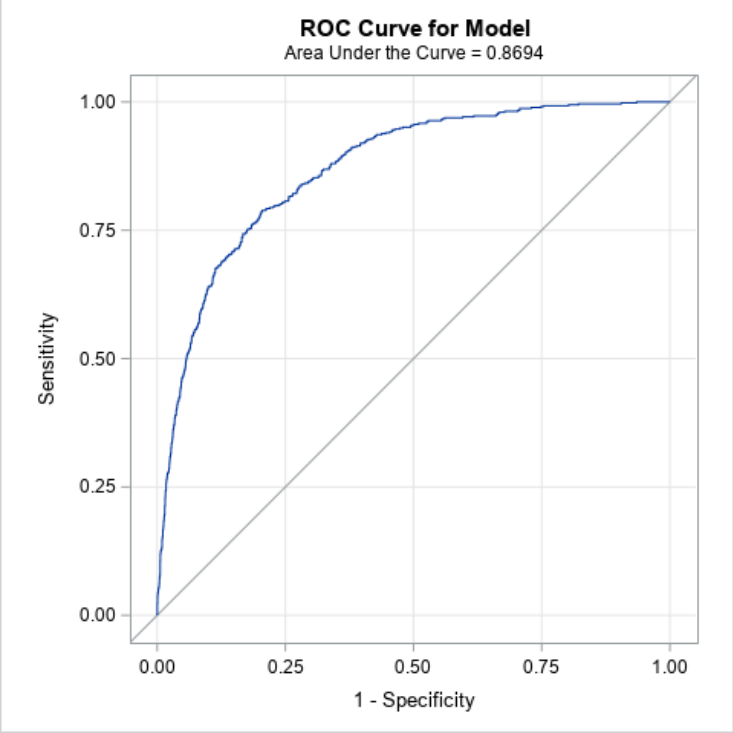
Results presented adjust for the effects of age, sex, race, and income. Covariate effects not shown.

Figure 3A. ROC Curve of Model Predicting MCDP in Non-Biological Mothers



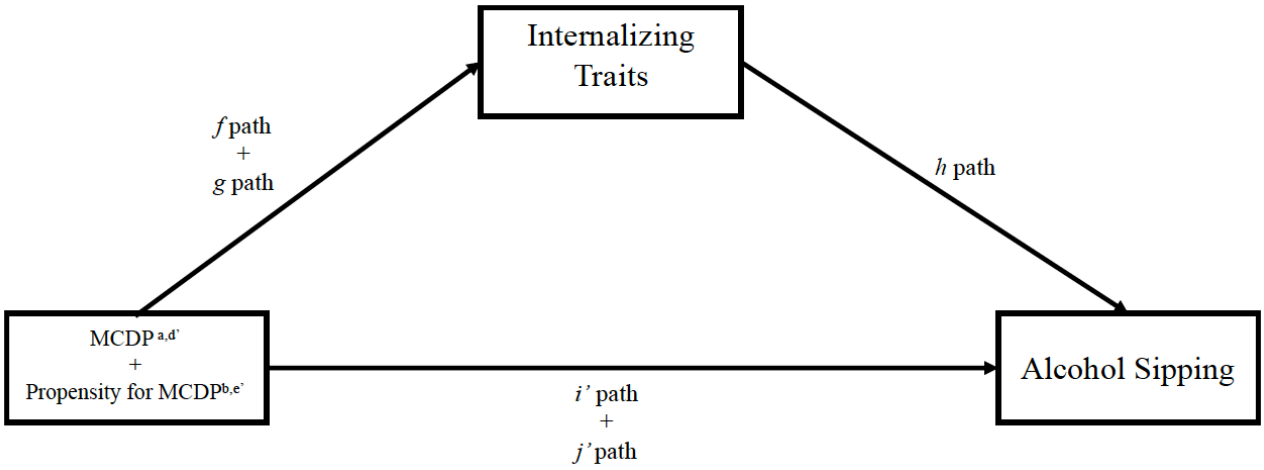
Logistic regression using 15 maternal risk factors to predict MCDP robustly captured non-biological mothers secondary report of mothers who ‘did smoke’ versus ‘did not smoke’ (area under the ROC curve = 0.95) younger mothers, unplanned pregnancy, prenatal alcohol, and prenatal tobacco use predicted greater odds of MCDP. Although some maternal risk factors no longer appeared to significantly predict greater odds of MCDP from the non-biological mother’s secondary report, parameter estimates remained consistent.

Figure 4A. ROC Curve of Model Predicting MCDP in Biological Mothers



Logistic regression using 15 maternal risk factors to predict MCDP robustly captured biological mothers who 'did smoke' versus 'did not smoke' (area under the ROC curve = 0.87) younger mothers, unplanned pregnancy, maternal and paternal immediate family alcohol use, maternal immediate family drug use, prenatal alcohol and tobacco use, and lower neighborhood safety predicted greater odds of MCDP. In examination of both ROC curves, it is evident that both sources of information, non-biological mother and biological mother reports, perform well. The decision was made to incorporate both non-biological mother and biological mothers reports as both reports capture unique information about the children including within the ABCD study.

Figure 5A. Path model of mediation- internalizing traits



The externalizing traits are baseline *t*-scores and covariates included for this model were: sex, age, race, and income