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Co-use of tobacco and marijuana during pregnancy: Pathways to externalizing behavior problems in early childhood

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Abstract

Use and co-use of tobacco and marijuana during pregnancy are associated with the development of social, cognitive, and behavioral problems for infants and children. However, less is known about the potential developmental impact of the use of tobacco and marijuana in tandem. The present study examined an etiological model for the development of externalizing behavior problems (EBP) in early childhood in a high risk sample (N = 247) of mother-infant dyads with prospective data from pregnancy to 36 months of child age. Co-use during pregnancy and continued maternal tobacco and marijuana use from infancy through early childhood were investigated. Although direct pathways from exposure during pregnancy to EBP were not significant, there was a significant indirect pathway from prenatal tobacco use to EBP via lower breastfeeding duration to lower maternal warmth/sensitivity to EBP, and a pathway from higher maternal affective dysregulation to higher EBP. These results highlight the importance of considering cascading effects of substance use during pregnancy on parental processes within the context of developmental risk and protection.

Keywords

Prenatal tobacco exposure; prenatal marijuana/cannabis exposure; problem behavior; breastfeeding

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1. Introduction

Smoking tobacco products during pregnancy is a significant public health concern. Between 8.4 and 15.4 percent of women in the United States smoke tobacco products during their pregnancies, with particularly high rates for at-risk women who are younger, unmarried, and less educated (13–14%; Curtin & Matthews, 2016; SAMSHA, 2014). Further, cigarettes are the most commonly used substance during pregnancy (CDC, 2014; NSDUH, 2005), despite efforts directed at disseminating information regarding the negative impact of persistent smoking. Cigarettes are particularly harmful, as in addition to nicotine, cigarette smoke contains over 7,000 chemical compounds (CDC, 2014). Exposure during both the prenatal and postnatal period increases the risk for negative developmental and health outcomes for children (ACOG, 2010, 2017).

1.1. Co-use of Tobacco and Marijuana during Pregnancy

Understanding the influences of co-use of tobacco and marijuana during pregnancy has important public health implications as marijuana has increasing societal and legal acceptance (Wilkinson, Yarnell, Radhakrishnan, Ball, & D'Souza, 2016) and use of marijuana is increasing in the general population and among pregnant women (NIDA, 2016; SAMSHA, 2014). Further, rates of smoking cigarettes during pregnancy remained stable despite declines in use by women who are not pregnant (SAMSHA, 2017). Reported frequency of marijuana use during pregnancy varies widely [e.g., 1.8% (Ebrahim & Gfroerer, 2003); 2.9% (El Marroun et al., 2008); 10% (Linn et al., 1983); 29.3% (Mark, Desai, & Terplan, 2016)]. Discrepancy in rates is likely due to methodological assessment of use, the timing of assessment as many women cut down on use later in the pregnancy, and the time frame in which the data were collected given the recent major shifts in marijuana perception and use (e.g., Wilkinson et al., 2016). Tandem marijuana and tobacco use during pregnancy is particularly high and suggests the need to consider tandem use separately from tobacco or marijuana use only. For example, rates of using both marijuana and tobacco are as high as 45% of those reporting marijuana use (Chabarria et al., 2016) and 84.5% of those reporting tobacco use during pregnancy (El Marroun et al., 2011). Women also are increasingly reporting marijuana as a problem substance for them during pregnancy (McCabe & Arndt, 2012) and rates of marijuana use for adult women are on the rise for women of reproductive age (Brown et al., 2017; SAMSHA, 2017). Further, the potency of the main psychoactive component of marijuana (i.e., delta-9-tetrahydrocannabinol or THC) increased since the 1990s (e.g., Mehmedic et al., 2010). Tobacco use during pregnancy is the most common, followed by co-use with marijuana, and marijuana use only occurring the least frequently (Coleman-Cowger, Schauer, & Peters, 2017). Given the stability of tobacco use and the rising frequency of marijuana use during pregnancy, investigating co-use is paramount.

Prenatal exposure to tobacco poses risk for later developmental sequelae in both early and later developmental periods, particularly externalizing behavior problems (EBP), including inattention, oppositional behavior, emotional instability, and physical aggression (e.g., Coles, Kable, & Lynch, 2012; Cornelius & Day, 2000; Wakschlag, Pickett, Cook, Benowitz, & Leventhal, 2002). Importantly, continued tobacco use during pregnancy may co-occur

with marijuana use and this co-use may increase the risk for adversity above the impact of tobacco or marijuana exposure alone (Chabarria et al., 2016; Gray et al., 2010a). Evidence suggests that marijuana exposure is associated with lower birth weight (Gunn et al., 2016), can be harmful to embryonic development as early as 2 weeks after conception, and can affect fetal brain development before a woman even recognizes she is pregnant (Psychoyos & Vinod, 2013). In regards to brain morphology, tobacco exposed children demonstrated cortical thinning, especially in the frontal and superior parietal cortices (El Marroun et al., 2016; Toro et al., 2008), while co-exposed children had thicker frontal cortices (El Marroun et al., 2016) indicating altered neurodevelopmental maturation in regions involved in higher order processing. Determining the specific impact of prenatal marijuana exposure can be challenging due to the frequent co-use of tobacco (Gunn et al., 2016). For example, some past research on the impact of prenatal marijuana exposure on EBP incorporated marijuana use only and co-use together (e.g., El Marroun et al., 2011; see Gunn et al., 2016). Indeed, marijuana exposure during pregnancy is also associated with dysregulation, attentional and executive function deficits, impulsivity, and EBP (for reviews see Fried & Smith, 2001; Huiznik, 2014). However, it is less common for research to particularly examine the impact of co-use on externalizing outcomes (e.g., El Marroun et al., 2011) despite evidence that that co-use may exacerbate risk (Chabarria et al., 2016; Coleman-Cowger et al, 2017; Emery, Gregory, Grace, & Levine, 2016; Gray et al., 2010a). As such, understanding the influence of co-use during pregnancy on the development of EBP is an important area for research.

Research on the developmental outcomes of co-use of tobacco and marijuana during pregnancy is limited (e.g., Porath & Fried, 2005; Richardson, Day, & Goldschmidt, 1995). However, given the high prevalence of this co-use pattern, elucidating the impact that co-use can have on child development is critical. Despite consistent findings regarding the associations between prenatal exposure to tobacco and marijuana leading to externalizing behavior, little is known about the mechanisms of these relationships or the unique contributions of co-use. Further, continued maternal use during the postnatal period is associated, particularly in the case of tobacco use, to child and adolescent EBP (for review see Cornelius & Day, 2000; Hermann, King, & Weitzman, 2008). In particular, both direct pathways (i.e., from prenatal exposure to EBP) and indirect pathways that may influence development, such as continued postnatal use and parenting, need to be considered together (e.g., D'Onofrio et al., 2008; Knopik, Maccani, Francazio, & McGeary, 2012; Massey et al., 2016), especially in light of evidence from behavior genetic studies indicating that maternal smoking effects on EBP may be explained by family level variables (D'Onofrio et al., 2008). However, this conclusion may be premature given evidence from research designs integrating sophisticated measurement of prenatal substance exposure with genetically informative design indicating unique effects of tobacco use during pregnancy on EBP beyond family level effects (Estabrook et al., 2016). These recent discussions suggest that sophisticated measurement of complex behaviors is important and that models examining EBP need to have strong measurement of both substance use and family processes. However, the role of co-use has not been addressed in these discussions. Therefore, the purpose of the present study is to investigate the cascading impact of co-use of tobacco and marijuana during pregnancy on subsequent maternal parenting (i.e., breastfeeding and warmth and sensitivity) and behavior (i.e., affective dysregulation and continued marijuana

and tobacco use) in infancy and ultimately the development of child externalizing behavior in early childhood. In addition, given that sex difference results on the impact of prenatal tobacco and marijuana exposure on later problem behavior are not consistent and may depend on the specific behavioral outcome and sample assessed, as well as the study design and methods (e.g., Coles et al., 2012; El Marroun et al., 2011; Hutchinson, et al., 2009; Massey et al., 2016), the current study sought to explore potential sex differences in the prediction of EBP.

1.2. Maternal Characteristics

Maternal dysregulated and antisocial behavior may be associated with higher child EBP through shared genetic risk that was well articulated in previous studies (e.g., Knopik, Heath, Bucholz, Madden, & Waldron, 2009; Leve et al., 2010; Schmitz, Cherny, Fulker, & Mrazek, 1994). However, they also provide the context for parental decisions and processes that have a direct effect on child behaviors. Indeed, higher maternal dysregulation may make engaging in positive parenting practices more challenging, beyond any associations with substance use. Mothers who use tobacco and marijuana during their pregnancies often experience higher levels of demographic risk (e.g., younger age; Chabarria et al., 2016), delinquent behavior (El Marroun et al., 2008), and anger and affective dysregulation (Chabarria et al., 2016; Eiden et al., 2011; Ludman et al., 2000). In addition to the potential direct effect of exposure, maternal smoking during pregnancy is associated with negative parenting practices (Wakschlag et al., 2002), such as conflictual parent-child relationships (Brook, Brook, & Whiteman, 2000) and harsh discipline (Tandon et al., 2013). Mothers who smoke were less nurturing (Fergusson, Woodward, & Horwood, 1998), had higher levels of insensitivity, and lower levels of warmth (Massey & Compton, 2013; Massey et al., 2015; Schuetze, Eiden, & Dombkowski, 2006). Less is known about the parenting practices of mothers who use marijuana during their pregnancies. In turn, harsh parenting practices and negative parent-child interactions are associated with EBP outcomes for children, such as dysregulation (Eiden, Schuetze, & Coles, 2011) and aggression (e.g., Dodge, Coie, & Lynam, 2006; Loeber & Hay, 1997). High affective attunement and warmth/sensitivity in the first years of life may be a particularly protective developmental factor through adulthood and predict lower levels of social difficulties, including dysregulation and EBP (Raby, Roisman, Fraley, & Simpson, 2015). Early experiences in infancy with warmth and sensitivity, including physical contact, were significantly implicated in positive developmental outcomes, such as through neural development and genetic expression that could directly impact an infant's regulatory, stress reactivity, and attentional processes (Moore et al., 2017; Tremblay & Cote, 2009). For children already at risk due to prenatal exposure, poor parenting practices and negative parent-child interactions may create a context that increases the risk for EBP; whereas positive experiences with warmth and sensitivity could help to buffer the direct impact of prenatal exposure.

1.3. Breastfeeding in the Context of Maternal Substance Use.

Breastfeeding is a particularly important early experience that serves a protective role for infant development (Horta, Bahl, Martines, & Victora, 2007) and maternal health (Chung et al., 2007; U.S. Department of Health and Human Services, 2011). The Center for Disease Control and Prevention (2009) recommends breastfeeding even when a mother continues to

smoke; however, women who smoke report breastfeeding for shorter durations and being less likely to intend to breastfeed and to initiate breastfeeding than non-smoking women (Liu, Rosenberg, & Sandoval, 2006; for review see Amir, 2001; Amir & Donath, 2002; Horta, Kramer, & Platt, 2001). In fact, a dose-response relation between number of cigarettes smoked and duration of breastfeeding was demonstrated (see Amir & Donath, 2002). Importantly, caution regarding continued smoking and breastfeeding is expressed and the recommendation is for women to cease their use of tobacco and marijuana (American Academy of Pediatrics, 2001). There is limited research on breastfeeding and marijuana use; however, there is evidence that both nicotine (e.g., Liebrechts-Akkerman et al., 2011; Mennella, Yourshaw, & Morgan, 2007) and THC can be passed through breastmilk and that this could negatively impact infant neural and motor development (e.g., Astley & Little, 1990; for review see NIDA; 2016). However, breastfeeding may be protective for mothers and delay returning to preconception smoking rates postpartum (Shisler et al., 2016) and the positive benefits to infants may outweigh the potential risk of exposure through breastmilk (Woodward, Douglas, Graham, & Miles, 1990). A goal of the present study is to understand the relationship between maternal tobacco and marijuana co-use and breastfeeding duration, given the potential influence that breastfeeding can have on both positive outcomes, such as maternal sensitivity (Papp, 2014) and infant health (Horta et al., 2007), and the negative impact that transmission of nicotine and THC could have on child development.

There is evidence for the protective role of breastfeeding for neurodevelopmental outcomes (AAP, 2012), such that shorter duration of breastfeeding is associated with greater levels of behavioral problems (Oddy et al., 2010; Park et al., 2014). Breastfeeding is thought to have an important impact on promoting healthy neural development (Deoni et al., 2013), especially due to the nutritional components of breastmilk that promote neuronal growth and myelination (Guesnet & Alessandri, 2011; Uauy & De Andraca, 1995). Promoting positive structural development in turn supports positive cognitive and behavioral development (e.g., Deoni et al., 2013). However, research on the impact of breastfeeding on longer term behavioral outcomes is mixed (Kramer et al., 2008). It is unclear whether breastfeeding is directly associated with decreased risk for behavioral problems or whether the impact is indirect. More specifically, there is a consistent association between breastfeeding and higher quality parentchild relationships (e.g., Fergusson & Woodward, 1999). Breastfeeding duration is associated with increased maternal sensitivity through the first decade of a child's life (Papp, 2014; Weaver, Schofield, & Papp, 2017) and with higher perceptions of care by children (Fergusson & Woodward, 1999). Therefore, the present study examined the impact of breastfeeding directly on behavioral outcomes and indirectly through parenting behavior.

1.4. Present Study

We examined a conceptual model for development of EBP among prenatally tobaccoexposed, co-exposed (i.e., tobacco- and marijuana-exposed), and demographically similar nonexposed children (see Figure 1). We examined the direct effects of prenatal exposure on EBP at 24 and 36 months of age. We also investigated potential indirect or mediational pathways from prenatal exposure to later behavioral outcomes through maternal warmth, affective dysregulation, and breastfeeding. Early risk through prenatal exposure to marijuana and/or tobacco may have a subsequent impact on later developmental periods,

such as on the likelihood of breastfeeding, that then have a cascading influence on maternal behavior (e.g., maternal warmth) and ultimately behavioral outcomes for children. Early experiences may be especially important due to this cascading influence that could compound risk for later developmental sequelae such as behavioral problems (e.g., Eiden et al., 2016). The influences of continued and chronic maternal substance use in the postnatal period were also examined. The current study also explored potential sex differences in the prediction of EBP.

2. Method

2.1. Participants

The study included 258 mother/infant dyads, with 181 infants prenatally exposed to tobacco (99 boys and 82 girls), and 77 not exposed (35 boys and 42 girls). Pregnant women were recruited at their first prenatal appointment in a local area hospital and screened for eligibility. Women were eligible to participate if they were: less than 20 weeks gestation, at least 18 years old, not using illicit drugs (other than cannabis), not heavy alcohol users (defined as 4 or more drinks in one sitting or drinking an average of more than 1 drink/day), having a singleton birth, and were English speakers. Participating smokers were matched on maternal age and highest educational attainment with the closest eligible nonsmoking woman at the conclusion of each recruitment month. The smoking group was oversampled such that one non-smoker was recruited for every two smokers, allowing for a full range of light to heavy smokers to be represented, as well as for the possibility of higher attrition in the smoking group over time. Of the 258 enrolled participants, 11 had to be dropped from analyses. One mother-infant dyad was dropped because infant meconium was positive for methamphetamine, one because of maternal binge drinking during pregnancy, two because they had hydrocephaly, two because of a later diagnosis of autism, and one additional participant was excluded due to low maternal cognitive functioning. Finally, four participants were excluded because they were not prenatal tobacco smokers, but were smoking moderate amounts of marijuana during pregnancy. This resulted in a final sample size of 247 mother-infant dyads with 81 tobacco exposed, 97 tobacco and marijuana exposed, and 69 not exposed.

Maternal age ranged from 18 to 39 at the time of their first appointment ($M = 24.09$, $SD = 5.00$). The women in the sample were 51% African-American, 31% Caucasian, 19% Hispanic, and 8% other or mixed race, with several identifying as more than one race. Forty-five percent of the expectant mothers were married or living with a partner, 33% were in a relationship but not living with a partner, 21% were single, and 1% were divorced. Finally, 29.5% of the women had less than a high school education, 29.5% completed high school, 28% completed some college, 9% had a vocational/technical or associates degree, and 4% had a bachelor's degree.

2.2. Procedures and Instruments

The study protocol was approved by the Children and Youth Institutional Review Board at the State University of New York. Informed written consent was obtained from all interested and eligible participants at their first laboratory visit, during the first trimester of pregnancy.

Laboratory assessments were conducted once during each trimester, at 2, 9, and 16 months infant age (corrected for prematurity), and at 24 months child age. At 36 months child age, mothers completed an interview over the phone and a packet of questionnaires were mailed, completed by the mothers, and returned. Participants were informed that data confidentiality was protected by a Federal Certificate of Confidentiality issued by the National Institute on Drug Abuse. Participants received payments for completed prenatal assessments, and a combination of payments and toys for their children at all postnatal assessments.

2.2.1. Prenatal Substance Use.—Maternal use of tobacco, cannabis, and alcohol during the prenatal period was measured by maternal self-report and biologically verified using maternal saliva and infant meconium. At each prenatal interview the Timeline Follow-Back Interview (TLFB; Sobell & Sobell, 1992) was used to gather daily tobacco, cannabis, and alcohol use for the previous three months. The method was established as a reliable and valid method of obtaining daily data on substance use patterns, showed good test-retest reliability, and was highly correlated with other intensive self-report measures (Brown et al., 1998). In the present study, the TLFB yielded data on the average number of cigarettes and joints smoked per day across the entire pregnancy, as well as the average number of alcoholic drinks per day across pregnancy. There was no missing data on any of the prenatal substance use variables.

These self-reports were biologically verified with maternal oral fluid specimens, taken once each trimester. Oral fluid samples were assayed for cotinine using liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the majority of cases (with the exception of the first 32 women recruited into the study who had their first trimester oral fluid samples assayed by ELISA at a 10 ng/ml cutoff). Maternal oral fluid cotinine ranged from 0 to 569 ng/ml. Infant meconium (i.e., the first neonatal feces) was collected after birth twice daily until the appearance of milk stools. Meconium was transferred to storage containers and frozen at -80°C until transport to the National Institute on Drug Abuse for analysis, where they were assayed with a validated LC-MS/MS method (Gray et al., 2010b) with limits of quantification (LOQ) of 2.5 ng/g nicotine, 1 ng/g cotinine, and 5 ng/g trans-3' hydroxycotinine (OHCOT). Mothers were assigned to the prenatal tobacco exposure group if they acknowledged smoking during pregnancy, if oral fluid samples were positive for cotinine at or above 10 ng/ml, or if infant meconium was positive for cotinine, nicotine, or OHCOT.

Maternal self-reported marijuana use was also biologically validated via maternal oral fluid and infant meconium. Maternal oral fluid samples were analyzed by the US Drug Testing Laboratory (Des Plaines, IL) for THC, the primary psychoactive component of cannabis, by immunoassay screening (4.0 $\mu\text{g/L}$ cutoff) and GC-MS confirmation (4.0 $\mu\text{g/L}$ cutoff). Meconium samples were assayed with a validated 2-dimensional GC-MS analytical method for THC, 11-hydroxy-THC, 8,11-dihydroxy-THC, 11-nor-9-carboxy-THC (THCCOOH) and cannabinol (Gray et al., 2010a). LOQ for cannabinoid meconium assays were 10ng/g for all analytes, except 11-hydroxy-THC at 15 ng/g. Participants were assigned to the prenatal tobacco and marijuana exposure group if, in addition to meeting the criteria for the prenatal tobacco exposure group, they self-reported cannabis use during pregnancy, their infant's meconium tested positive for cannabis, or if their oral fluid was positive for cannabis in any

of the 3 trimesters, They were assigned to the non-exposed group if there was a negative results on all the no substance exposure group ($n = 69$) smoked 0 ($SD = 0.0$) cigarettes and 0 ($SD = 0.0$) joints per day across their pregnancy. The tobacco exposure group ($N = 81$) smoked on average 4.28 ($SD = 4.61$) cigarettes and 0 ($SD = 0.0$) marijuana joints per day during pregnancy. Finally, women in the tobacco and marijuana co-use group ($n = 97$) smoked on average 5.56 ($SD = 4.63$) cigarettes per day during pregnancy and on average 0.57 ($SD = 0.86$) joints per day during pregnancy. In subsequent analyses, the trichotomous variable of 0 = control, 1 = tobacco only, and 2 = tobacco and marijuana co-use was dummy coded following Aiken and West (1991, p. 117) into two dummy coded variables for the a priori group contrasts of interest: tobacco only vs. not (1 compared to 0 and 2) and co-use vs. not (2 compared to 0 and 1).

2.2.2. Postnatal Substance Use.—Toddler postnatal tobacco exposure was assessed during the 2-, 9-, 16-, and 24-month appointments by maternal self-reports on the TLFB (Sobell & Sobell, 1992) a reliable and valid procedure for obtaining longitudinal data on substance-use patterns (Brown et al., 1998). There was minimal missing data at each assessment (0–8% missing) and those missing data were not significantly different on any major study variables in comparison to those with complete data. The TLFB yielded data on the average number of cigarettes smoked per day during each assessment period, and the four time points were averaged to create a composite for postnatal tobacco exposure to provide an overall assessment of child exposure over time. Correlations across time points ranged from $r_s = .65$ to $.83$.

Postnatal marijuana exposure was also measured via maternal self-report on the TLFB at the 2-, 9-, 16-, and 24-month appointments. The TLFB yielded data on the average number of joints smoked per day during each assessment period, and the four time points were again averaged to create a composite for postnatal marijuana exposure. Correlations across time points ranged from $r_s = .31$ to $.77$.

2.2.3. Cumulative Demographic Risk.—The cumulative demographic risk score was comprised of 4 factors: maternal race, maternal education, maternal occupation, and maternal partner status. The maternal race risk variable was coded as positive (1) if mothers indicated that they belonged to any minority race. In this sample, 69% met this criteria. For maternal education, the risk variable was coded as positive (1) if the participant had not received a high school diploma or equivalent, and 29.5% met this criteria. For the maternal occupation risk variable, maternal occupation was coded using the Hollingshead scale ($M = 2.06$, $SD = 1.6$, $Range = 1–8$; Hollingshead, 1975). This score was divided by the maximum value of 9 in order to create a proportion and recoded such that higher numbers indicated greater risk (lower occupational status). For partner status, the risk variable was coded as positive (1) if the participant was not married or living with a partner, and 55% of the sample met this risk criteria. The final cumulative demographic risk index was created by averaging the 4 items described above, with a possible maximum score of 1 ($M = .49$, $SD = .25$, $Range = .04 – .89$). Given past research on partner use (e.g., El Marroun et al., 2008; 2011; Homish, Eiden, Leonard, & Kozlowski, 2012), potential differences between maternal partner status and partner use were explored based on maternal report of partner status and

partner use of tobacco and marijuana. An ANOVA was conducted to examine differences between 3 groups: 1) mothers without stable partners, 2) mothers with a stable partner who was not a reported user of tobacco or marijuana, and 3) mothers with a stable partner who was a reported tobacco or marijuana user. There were no significant group differences (all p 's > .05) on either externalizing behavior at 24 or 36 months. Given the lack of significant differences and that past research has not suggested that paternal use impacts externalizing outcomes (e.g., Marroun et al., 2011), partner status was included as a component of the cumulative demographic risk variable instead of as a separate predictor.

2.2.4. Maternal Affective Dysregulation in Infancy.—Maternal affective dysregulation in infancy was measured using maternal self-reports of the Dysexecutive Functioning Questionnaire (DEX; Wilson, Alderman, Burgess, Emslie, & Evans, 1996; Wilson, Evans, Emslie, Alderman, & Burgess, 1998) during the 9 month assessment. The DEX consists of 20 items that measure everyday signs of dysregulation. Items are scored on a 5-point Likert scale ranging from 0 (never) to 4 (very often). Internal consistency of the scale in the current sample was excellent, Cronbach's $\alpha = .90$.

2.2.5. Maternal Sensitivity in Infancy.—Maternal sensitivity during infancy was assessed during a free play interaction in the laboratory at 9 months of infant age. Mothers were asked to spend some time with their infant as they normally would at home in a room that was furnished as a living room with a play mat and toys on the floor. Mother-infant interactions were videotaped and coded using a collection of global five point rating scales developed by Clark et al. (Clark, 1999; Clark, Musick, Scott, & Klehr, 1980). These scales were applicable for coding mother-child interactions for children ranging in age from 2 months to 5 years (Clark, 1999). A composite scale for maternal sensitivity was derived from 14 of these items (e.g., expressed positive affect, warm, kind tone of voice, contingent responsiveness to infant behavior, and connectedness). This scale had high internal consistency with Cronbach's $\alpha = 0.95$. Two coders blind to group status rated maternal behavior. After training, inter-rater reliability was conducted on a random selection of 11% of the interactions ($n = 28$). The intra-class correlation coefficient for the association between the two coders was .90 for maternal sensitivity at 9 months.

2.2.6. Breastfeeding.—Breastfeeding status was assessed via maternal self-report at the 2-, 9-, and 16-month assessments, and was coded as the total number of days the mother breastfed the infant (*Range* 0–480).

2.2.7. Maternal Aggressive Disposition in Pregnancy.—Maternal aggressive disposition in pregnancy was assessed during the third trimester using the Buss Perry Questionnaire (BPQ; Buss & Perry, 1992). The BPQ consists of 29 items measuring four dimensions related to aggression: physical aggression, verbal aggression, anger, and hostility. Due to human error, the mothers were administered 28 items as the last item was inadvertently omitted in the prenatal appointment. Mothers self-reported on their aggression dispositions using a Likert scale ranging from 1 (extremely uncharacteristic of me) to 5 (extremely characteristic of me). Scoring of positively worded items was reversed resulting

in higher scores indicating more aggressive dispositions. Internal consistency of the scale was excellent, Cronbach's $\alpha = 0.92$.

2.2.8. Toddler and Early Childhood Externalizing Behavior Problems (EBP).—

EBP were assessed at 24 ($M = 23.80$ months, $SD = 0.89$) and 36 ($M = 35.47$ months, $SD = 2.3$) months of child age with maternal reports on the Brief Infant Toddler Social Emotional Assessment (BITSEA; Briggs-Gowan & Carter, 2006). The BITSEA is a 42 item measure that assesses social-emotional and behavioral problems and/or delays as well as social-emotional competence on a 3-point Likert scale ranging from 0 = Not True/Rarely to 2 = Very True/Often. The 6 item externalizing behavior subscale (e.g., "Hits, shoves, kicks, or bites children" and "Is restless and can't sit still") was included at both 24 (Cronbach's $\alpha = .67$) and 36 months (Cronbach's $\alpha = .71$).

2.3. Analytic Strategy

According to the guidelines provided by Kline (2016), data were subject to several phases of data cleaning prior to any analysis. First, distributions of the study variables were examined. All variables demonstrated univariate normality, such that each variable was < 3 for skew and < 8 for kurtosis, except postnatal marijuana exposure. Due to the non-normality of this variable in the model, analyses robust to non-normality were used (MLR). Examination of the direct relation between prenatal exposure and child externalizing behavior at 24 and 36 months was conducted through ANOVA and path analyses. Potential sex differences in externalizing behavior were also investigated. Path analysis also tested the hypothesized model with maternal affective dysregulation, breastfeeding duration, maternal affective regulation, and maternal warmth and sensitivity in infancy, as well as continued use of tobacco and marijuana from child age of 2 months to 36 months, as intervening variables between prenatal exposure and child externalizing behavior at 24 and 36 months. All paths within the model were tested simultaneously. Path analyses were conducted using Mplus, Version 8 software (Muthen & Muthen, 1998–2015). Full-information maximum likelihood estimation procedures (Arbuckle, 1996) were used with standard errors and chi-square statistic that are robust to non-normality and can be estimated with missing data (MLR). The MLR estimation in Mplus corrects for non-normality of errors and heteroscedasticity (Yuan & Bentler, 2000). Indirect effects were tested using the bias-corrected bootstrap method. This method was found to provide a more accurate balance between Type 1 and Type 2 errors compared with other methods testing indirect effects (MacKinnon, Lockwood, & Williams, 2004). Five thousand bootstrap samples and the 95% bias-corrected confidence intervals (CIs) tested the significance of indirect effects.

3. Results

3.1. Descriptive Statistics

Descriptive statistics and correlations among indirect and outcome variables included in model testing are presented in Table 1. Reported EBP at 24 and 36 months was significantly positively associated with maternal affective dysregulation at 9 months of child age. Externalizing at 24 months was also significantly positively associated with the continued postnatal marijuana use composite from 2 to 24 months of child age. Child externalizing

behavior at 36 months was significantly negatively associated with breastfeeding duration, and externalizing behavior at 24 months was significantly negatively associated with maternal warmth and sensitivity at 9 months of child age and significantly positively associated with maternal aggressive disposition during pregnancy.

3.2. Direct Effect of Exposure on Externalizing Behavior and Sex Differences

There were no direct associations between tobacco exposure with or without marijuana co-exposure and child externalizing behavior at either 24 or 36 months (β s from $-.03$ to $.10$, *n.s.*), and exploration with ANOVA of group differences on prenatal exposure also yielded no significant differences ($F(2, 160) = 0.26$, *n.s.* at 24 months; $F(2, 160) = 0.52$, *n.s.* at 36 months).

Sex differences were also examined. In the overall sample, there was a marginal sex difference on externalizing behavior at 36 months ($t(177) = -1.91$, $p = .06$), such that males had slightly higher levels of externalizing behavior (Males $M = 2.52$, $SD = 2.38$; Females $M = 1.93$, $SD = 1.64$). There were no significant differences at 24 months ($t(201) = -1.25$, *n.s.*). An interaction between child sex and exposure group was also examined and there were no significant main or interaction effects (F 's ranging from $0.17 - 2.27$, *n.s.*) predicting EBP at 24 months (Non-Exposure Group: Males $M = 3.33$, $SD = 2.18$; Females $M = 1.90$, $SD = 1.69$; Tobacco Exposure Group: Males $M = 2.56$, $SD = 1.98$; Females $M = 2.61$, $SD = 1.61$; Co-Exposure Group: Males $M = 2.80$, $SD = 1.89$; Females $M = 2.79$, $SD = 2.43$). At 36 months, there was a trend for a main effect of sex ($F(1, 157) = 3.06$, $p = .08$) and the main effect of exposure group was not significant ($F(2, 157) = 0.69$, *n.s.*). There was a significant interaction of exposure group X sex ($F(2, 157) = 3.72$, $p = .026$), such that males in the non-exposure group had significantly higher reported externalizing at 36 months than females (Non-Exposure Group: Males $M = 3.33$, $SD = 3.10$; Females $M = 1.57$, $SD = 1.40$; Tobacco Exposure Group: Males $M = 1.81$, $SD = 1.75$; Females $M = 2.17$, $SD = 1.98$; Co-Exposure Group: Males $M = 2.28$, $SD = 2.05$; Females $M = 2.00$, $SD = 1.69$). Although the findings were not consistent across analyses, child sex was included as a covariate in the overall model given past research finding sex differences with similar constructs (e.g., Coles et al., 2012).

3.3. Model Testing

Path analysis was used to test the mediational model (see Figure 1). The conceptual model tested included dummy-coded variables for group status (tobacco only vs. not and co-use vs. not), maternal aggressive disposition during pregnancy, breastfeeding duration, maternal warmth/sensitivity during mother–infant interactions at 9 months of infant age, maternal affective dysregulation at 9 months of infant age, average cigarette and marijuana use per day from child age of 2 to 24 months, and child externalizing behavior at 24 months and 36 months (see Figure 1). The model included direct paths from the group status use variables to externalizing at 24 and 36 months, as well as from breastfeeding duration and maternal aggressive disposition to externalizing behavior at 24 and 36 months; paths from predictors to breastfeeding duration, maternal warmth/sensitivity, maternal affective dysregulation, and maternal cigarette and marijuana use postnatally; paths from breastfeeding duration to maternal warmth/sensitivity, maternal affective dysregulation, and maternal cigarette and

marijuana use postnatally; paths from maternal warmth/sensitivity, maternal affective dysregulation, and maternal cigarette and marijuana use postnatally to externalizing at 24 and 36 months. The model included covariances between endogenous (dummy coded prenatal use, maternal aggressive disposition, demographic risk, and child sex) and between the residuals of exogenous predictors (maternal warmth and sensitivity, maternal affective dysregulation, and average cigarette and marijuana postnatal use). Finally, demographic risk and child sex were included in the model, with paths to maternal warmth/sensitivity, maternal affective dysregulation, and maternal cigarette and marijuana use postnatally and EBP at 24 and 36 months. Goodness of fit indices indicated that this hypothesized model fit the data well, $\chi^2(14) = 17.67, p = .22, CFI = .99, RMSEA = .03, 95\% CI [.00, .07]$. Important to note, the proportional maternal demographic risk variable and child sex were used as covariates in the model. The inclusion or exclusion of these variables did not significantly impact model fit. Results indicated that many of the prenatal variables were associated with each other and that the combination of prenatal tobacco and marijuana exposure was associated with continued postnatal tobacco and marijuana use and maternal affective regulation. Prenatal tobacco exposure was significantly associated negatively with breastfeeding duration, positively with maternal continued postnatal tobacco use, and tended to be associated with affective dysregulation. There were no direct associations between prenatal exposure and maternal warmth or child externalizing behavior. There were also no direct associations between maternal aggressive disposition and child EBP. Maternal aggressive disposition was significantly associated with maternal affective dysregulation and postnatal tobacco use. Breastfeeding duration was predictive of maternal warmth and sensitivity at 9 months of child age and tended to be predictive of maternal regulation at 9 months of child age. Maternal warmth and sensitivity, maternal affective dysregulation, and continued maternal postnatal marijuana use were then each directly associated with child externalizing behavior at 24 months. Breastfeeding duration was also significantly directly associated with child EBP at 36 months. Demographic risk was negatively associated with maternal warmth and sensitivity, maternal affective dysregulation, and the continued cigarette use composite, and tended to be associated with reduced breastfeeding duration. Child sex tended to be associated with maternal affective dysregulation for females and was significantly associated with externalizing at 24 months for males. Together, prenatal exposure, demographic risk, breastfeeding, maternal affective dysregulation, maternal warmth sensitivity, and continued postnatal maternal marijuana and tobacco use accounted for 18% of the variance for child externalizing behavior at 24 months and 33% at 36 months.

Indirect effects and the pattern of path coefficients provided support for potential indirect pathways from prenatal exposure and EBP via breastfeeding, maternal warmth and sensitivity, maternal affective dysregulation, and continued postnatal marijuana use. The indirect association between combined marijuana and tobacco exposure and externalizing behavior at 24 months via maternal affective dysregulation was significant, $\beta = -.28, 95\% CI [-.58, -.10]$ as was this pathway when the association with externalizing behavior at 36 months was included, $\beta = -.14, 95\% CI [-.33, -.05]$. The indirect association between tobacco exposure and externalizing behavior at 36 months via breastfeeding duration, maternal warmth, and externalizing behavior at 24 months, $\beta = .03, 95\% CI [.004, .09]$, was significant, $\beta = .02, 95\% CI [.002, .06]$. Further, the indirect pathway from prenatal tobacco

exposure to externalizing behavior at 36 months via breastfeeding was also significant, $\beta = .12$, 95% CI [.02, .29].

Finally, models were explored including breastfeeding initiation (dummy coded as no breastfeeding vs. breastfeeding initiated) in the place of breastfeeding duration and in tandem with breastfeeding duration. The only changes to the model with the inclusion of breastfeeding duration were that prenatal tobacco and marijuana exposure was significantly associated with less breastfeeding initiation ($\beta = -.14$, $p = .03$) and the associations between breastfeeding and demographic risk was no longer significant. Although the magnitude of associations changed slightly, the overall findings were consistent when both duration and initiation were included in the model (i.e., associations between breastfeeding and reduced externalizing at 36 months were significant for both duration and initiation). For ease of communication and to reflect the dose-response association between smoking and breastfeeding (see Amir & Donath, 2002), the duration variable was maintained for analyses.

4. Discussion

The present study examined a conceptual model of the direct and indirect early developmental pathways from prenatal exposure to tobacco and marijuana to EBP in early childhood in a high risk sample. There were no significant direct links from prenatal exposure to either tobacco alone or tandem tobacco and marijuana use to externalizing behavior at 24 or 36 months of child age. Although this is inconsistent with past research (Ashford et al., 2008; Coles et al., 2012; Cornelius & Day, 2000; Day et al., 2000; El Marroun et al., 2011; Hutchinson, Pickett, Green, & Wakschlag, 2009; Wakschlag et al., 2002) and previous work found a direct link during the same developmental time period as assessed in the present study (e.g., Dolan et al., 2016; Hutchinson et al., 2009), the influence of co-exposure was not considered in many previous studies in concert with examining exposure to tobacco and this may account for differences in effects. Further, it is possible that there is a sleeper effect from prenatal tobacco and marijuana exposure on the development of externalizing behavior. The toddler and preschool period are considered early for the development of EBP (e.g., Campbell, Shaw, & Gilliom, 2000), with increasing levels of stability in externalizing behavior as children enter middle childhood (i.e., elementary school ages; Keenan, Shaw, Delliquadri, Giovannelli, & Walsh, 1998). For example, the teratogenic effect of prenatal exposure may impact the neural substrates that form the basis of regulated behavior later in development (e.g., during middle childhood when new academic and peer developmental tasks emerge, such as attention and behavioral control), but the effect may not emerge until those behaviors are developmentally salient (Maurer, Mondloch, & Lewis, 2007). Therefore, the direct effect may emerge when specific developmental tasks or stressors emerge, such as in the context of academic or peer settings in middle childhood. Future research should thus extend the present work to look at later developmental periods beyond early childhood to understand the interplay of early and later developmental influences (e.g., peers) in the manifestation of externalizing behavior. Externalizing behavior is also not a unidimensional construct, and future research should investigate potential differential pathways to different dimensions of externalizing (e.g., inattention, aggression, impulsivity/hyperactivity, antisocial behavior; Hinshaw, 2002) as

past research found direct effects when considering specific dimensions (El Marroun et al., 2011; Estabrook et al., 2016). Past research also was mixed on the potential indirect pathways from prenatal adversity that may impact the development of externalizing behavior outcomes (D'Onofrio et al., 2008; Knopik et al., 2012; Massey et al., 2016). The current research highlights the importance of examining the differential cascading impact of co-use of marijuana and tobacco during pregnancy. Including indirect pathways via parent behavior, such as warmth and sensitivity, during the early years of development.

The role of child sex was also examined given past research demonstrating that males exposed prenatally to tobacco are especially at risk for the development of EBP (Coles et al., 2012; Hutchinson, et al., 2009) and that girls exposed to marijuana prenatally are especially at risk for aggression and inattention (El Marroun et al., 2011). In the present study, there was some evidence, albeit mixed, for the greater susceptibility of males to the development of EBP. More specifically, there tended to be group differences in externalizing behavior at 36 months, such that males tended to have higher levels of externalizing problems. Further, an exposure group by sex interaction was significant, such that males had higher levels of EBP at 36 months, particularly for children that were not exposed to tobacco or marijuana use prenatally. Interestingly, girls in the exposure groups exhibited levels of EBP similar to exposed boys. Given the mixed findings in the present study and in previous research regarding potential sex differences in prenatal exposure and the later development of externalizing behavior, it is important to continue to consider and explore the potential moderating influence of sex in development of psychopathology. In particular, there may be sex differences in the development of the different dimensions (e.g., aggression) of EBP.

4.1. Indirect Pathways from Prenatal Exposure to Externalizing Behavior Problems

Although there was not a significant direct effect from either tobacco exposure or tobacco and marijuana co-exposure, there were several conceptually and empirically relevant indirect pathways to child externalizing behavior. First, there were interesting differences between pathways to risk beginning with tobacco exposure and co-exposure. Only prenatal tobacco and marijuana co-exposure demonstrated a significant indirect pathway via maternal affective dysregulation at 9 months of child age to child externalizing at 24 months. Importantly, the effects to maternal affective dysregulation were in different directions for prenatal tobacco exposure and co-exposure, such that prenatal tobacco exposure tended ($p = .051$) to be associated with reduced regulation whereas co-exposure was associated with fewer regulation deficits. The direction of the effect for co-exposure was not in the hypothesized direction and is contrary to past work, particularly on the short and long term impact of marijuana use on cognitive functioning (e.g., Crean, Crane, & Mason, 2011). The negative cognitive impact of marijuana use may be particularly the case with frequent use of marijuana (Bolla, Brown, Eldreth, Tate, & Cadet, 2002). Marijuana may be used by mothers in particular to self-medicate in the context of higher risk and use could impact maternal reporting of child behavioral problems. Therefore, future research should examine the dose-response of both tobacco and marijuana use, maternal behavior, and child EBP with multiple assessment methodologies (e.g., direct observations of maternal regulation) over the course of the pregnancy to reexamine this effect. However, continued tobacco use during pregnancy has been found to be associated with maternal affective and cognitive dysregulation and

reactivity (e.g., Eiden et al., 2011; Ludman et al., 2000) and tended to be predictive of maternal affective dysregulation in the present study. Deficiency in affective regulation was then directly associated with EBP. Interestingly, there was a unique role Parents may be modeling unpredictable, impulsive, or disorganized behavior and this may also be reflected in less consistent parenting practices, which are frequently implicated in the development of child EBP (e.g., Wahler & Dumas, 1986).

From prenatal tobacco exposure to child externalizing behavioral problems, there were several significant indirect pathways. Consistent with our hypotheses, there was an indirect pathway from prenatal tobacco exposure to externalizing behavior at 24 and 36 months via breastfeeding duration and maternal warmth and sensitivity at 9 months of child age. Consistent with a large body of past work (for review see Amir, 2001; Amir & Donath, 2002; Horta et al., 2001), persistent tobacco use during pregnancy was associated with reduced breastfeeding duration. Reduced breastfeeding duration was then associated directly to higher levels of child externalizing at 36 months and indirectly with greater EBP at 24 months via reduced maternal warmth and sensitivity. These findings highlight the protective roles of both maternal warmth and sensitivity and greater breastfeeding duration for positive behavioral outcomes for children. Past research emphasized the risk for disruptive behavior in the context of harsh and unresponsive parenting behavior (e.g., Dodge et al., 2006) and conversely, demonstrated the importance of early experiences with responsive care in promoting positive child development (e.g., Raby et al., 2015), as well as the promotive role of breastfeeding in enhancing maternal sensitivity (Papp, 2014). Results from the indirect pathways to EBP in early childhood in particular highlight the enduring protective effects of maternal warmth and sensitivity and longer duration of breastfeeding (e.g., AAP, 2012; Raby et al., 2015), as well as the increased risk for behavioral problems with maternal regulation deficits.

4.2. Limitations and Future Research

The present study has potential limitations. To begin, the influence of prenatal exposure to marijuana only could not be investigated given the low number of women who met that criteria in the present sample. Future research should, therefore, examine the role of marijuana and tobacco both separately and in tandem, and examine potential dose-response effects of occasional to frequent marijuana exposure during the prenatal period. The sample was also primarily mothers who were lower income, lower education, younger, and were more likely to be single or without a live-in partner and thus may not be generalizable to the larger population. However, the sample was representative of women who smoke tobacco and marijuana during their pregnancies (Curtin & Mathews, 2016; Ebrahim, Floyd, Merritt, Decoufle, & Holtzman, 2000; El Marroun et al., 2008; 2011).

Additionally, the use of maternal reports of substance use in the postnatal period may be problematic as it is unclear whether these substances were used in the presence of the child, making it difficult to determine the relationship between mother's reported substance use and child's actual postnatal exposure. This is further complicated by the fact that other potential sources of environmental exposure may exist. Future studies may address this issue by using biological validation methods to directly assess child exposure. Observational and

paternal or partner report should also be obtained when applicable in future research (e.g., El Marroun et al., 2011) to reduce potential shared method variance and to examine differential impact of maternal versus paternal use. However, maternal perceptions are important, as they are based on multiple contexts and may determine how mothers treat their children. In addition, given that only heavy alcohol use during pregnancy (i.e., defined as 4 or more drinks in one sitting or drinking an average of more than 1 drink/day) was used as an exclusionary criterion, low to moderate alcohol exposure in utero was possible. However, the reported alcohol use by the sample during pregnancy was low ($M = .07$, $SD = .17$ drinks per day). Further, given the dynamic and bidirectional interactions of the parent-child relationship, future research should also incorporate additional infant characteristics and behavior into understanding the link between prenatal exposure and later behavioral difficulties. Finally, given the potential epigenetic and neural development impact of physical contact and breastfeeding in early development (e.g., Moore et al., 2017), research on the interaction between the biological underpinnings of externalizing behavior with early experiences and later influential developmental factors would be informative (e.g., Eiden et al., 2016; Massey et al., 2016). Finally, with regards to assessment, the internal consistency of the assessment of externalizing behavior at 24 months was marginal ($\alpha = .67$). Further, several maternal behavior assessments, such as postnatal use, as well as child externalizing behavior were based on maternal report and as such, the associations may partially reflect shared method bias due to the same reporter. Therefore, future studies with observational or teacher reports (when developmentally salient in older ages) of child externalizing behavior would be helpful.

4.3. Implications and Conclusions

The present study has many strengths, including using multiple assessments of maternal substance use during pregnancy and considering the role of prenatal co-exposure to marijuana and tobacco, and continued postnatal use on child behavioral outcomes in a high risk sample. Given past research on the increased risk of co-exposure (e.g., Chabarria et al., 2016; Gray et al., 2010a), understanding and preventing substance use during pregnancy is critical. This is particularly the case for combined tobacco and marijuana use given the growing frequency and increased social acceptability of marijuana use. Intervention and prevention efforts targeted at increasing breastfeeding initiation and duration and fostering parental warmth and regulation may be particularly important given that they may be protective for both parents and children.

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Highlights

- - A cascade model from prenatal exposure to externalizing behavior is proposed.
- - Direct and indirect paths from tobacco and marijuana co-exposure are examined
- - Indirect paths via maternal behavior and parenting are investigated.
- - Indirect paths via breastfeeding, maternal warmth, and regulation supported.

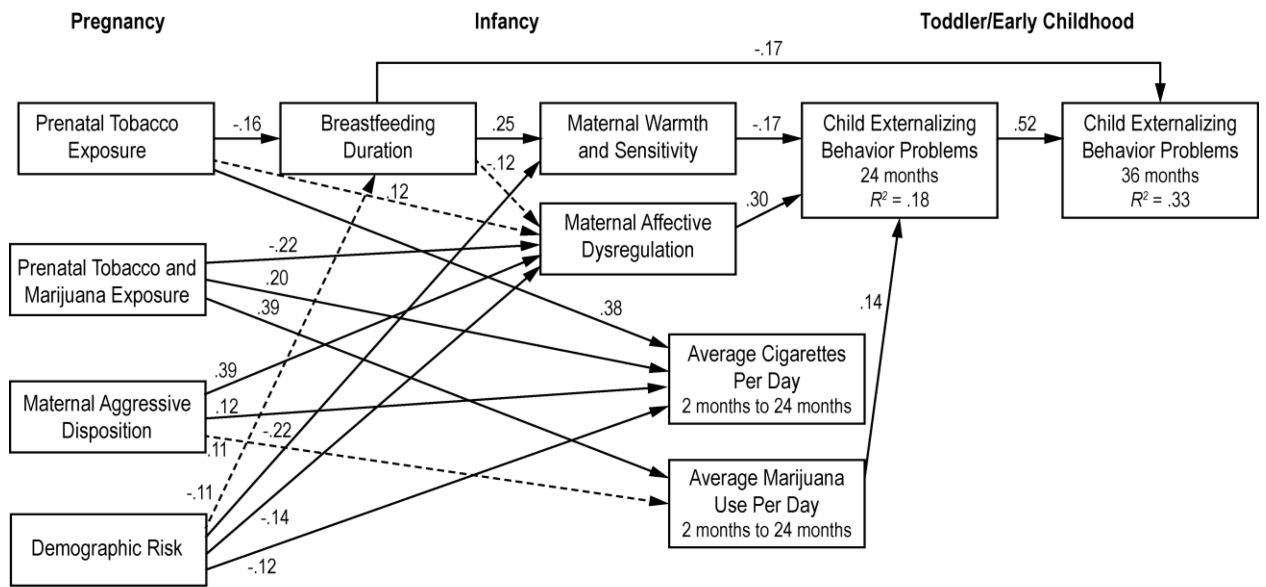


Figure 1. Path Analysis Model for Prenatal Tobacco and Marijuana Exposure and Early Childhood Externalizing Behavior
 Note: Non-significant paths and residuals are not depicted in the model for ease of presentation. The numbers are standardized path coefficients. Solid lines indicate paths that are p < .05 and dotted lines indicate paths that are p < .10. Child sex was also included in the model and was only significantly associated with externalizing at 24 months for males but was not depicted for ease of presentation. Maternal alcohol use during pregnancy was not significantly associated with child externalizing at 24 or 36 months (*r*'s < .06).

Table 1.

Descriptive Statistics and correlations among mediator and outcome variables

	1	2.	3	4	5	6	7	8	9
<u>1. Breastfeeding Duration (days)</u>	X								
<u>2. Maternal Agg. Disposition Preg.</u>	-.13 [*]	X							
<u>3. Maternal Warmth/ Sensitivity 9 mos</u>	.29 ^{***}	-.19 [*]	X						
<u>4. Maternal Affective Dysregulation 9 mos</u>	-.16 [*]	.37 ^{***}	-.17 [*]	X					
<u>5. Average Cigarettes Per Day 2 to 24 mos</u>	-.10	.25 ^{***}	.06	.07	X				
<u>6. Average Joints Per Day 2 to 24 mos</u>	-.05	.19 ^{**}	-.15 [*]	.08	.17 ^{**}	X			
<u>7. Externalizing Behavior 24 mos</u>	-.13 ⁺	.21 ^{**}	-.24 ^{**}	.31 ^{***}	.02	.16 [*]	X		
<u>8. Externalizing Behavior 36 mos</u>	-.23 ^{**}	.18 [*]	-.09	.18 [*]	-.03	.10	.51 ^{***}	X	
<u>9. Maternal Demographic Risk</u>	-.10	.11	-.27 ^{***}	-.11	-.11 ⁺	.06	.01	.03	X
<u>Mean</u>	50.75	2.71	4.07	14.17	4.32	0.29	2.84	2.23	0.49
<u>Standard Deviation</u>	104.44	0.71	0.61	11.25	4.95	.82	2.14	2.07	0.25

Note.

⁺
 $p < .10$ ^{*}
 $p < .05$ ^{**}
 $p < .01$ ^{***}
 $p < .001$.

Agg = Aggressive; Preg = Pregnancy; Mos = months