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Additive drug-specific and sex-specific risks associated with co-use of marijuana and tobacco during pregnancy: Evidence from 3 recent developmental cohorts (2003–2015)

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Abstract

Background: Methodologic challenges related to the concomitant use (co-use) of substances and changes in policy and potency of marijuana contribute to ongoing uncertainty about risks to fetal neurodevelopment associated with prenatal marijuana use. In this study, we examined two biomarkers of fetal neurodevelopmental risk—birth weight and length of gestation—associated with prenatal marijuana use, independent of tobacco (TOB), alcohol (ALC), other drug use (OTH), and socioeconomic risk (SES), in a pooled sample ($N = 1191$) derived from 3 recent developmental cohorts (2003–2015) with state-of-the-art substance use measures. We examined differential associations by infant sex, and multiplicative effects associated with co-use of MJ and TOB.

Methods: Participants were mother-infant dyads with complete data on all study variables derived from Growing Up Healthy ($n = 251$), Behavior and Mood in Babies and Mothers (Cohorts 1 and *2;* $n = 315$), and the Early Growth and Development Study ($N = 625$). We estimated direct effects on birth weight and length of gestation associated with MJ, TOB, and co-use (MJ x TOB), using linear regression analysis in the full sample, and in male ($n = 654$) and female ($n = 537$) infants, separately.

Results: Mean birth weight and length of gestation were 3277 g ($SD = 543$) and 37.8 weeks (SD = 2.0), respectively. Rates of prenatal use were as follows: *any* use, $n = 748$ (62.8%); MJ use, $n =$ 273 (22.9%); TOB use, $n = 608$ (51.0%); co-use of MJ and TOB, $n = 230$ (19.3%); ALC use, $n =$ 464 (39.0%); and OTH use $n = 115$ (9.7%.) For all infants, unique effects on birth weight were observed for any MJ use [$B(SE) = -$ 84.367(38.271), 95% C.I. −159.453 to −9.281, $p = .028$], any TOB use *[*$B(SE) = -0.99.416(34.418)$, 95% C.I. −166.942 to − 31.889, $p = .004$], and each cigarette/day in mean TOB use [$B(SE) = -12.233(3.427)$, 95% C.I. −18.995 to −5.510, $p < .001$]. Additional effects of co-use on birth weight, beyond these drug-specific effects, were not supported. In analyses stratified by sex, while TOB use was associated with lower birth weight in both sexes, MJ use during pregnancy was associated with lower birth weight of *male* infants *[*$B(SE) = -153.1$ (54.20); 95% C.I. −259.5 to −46.7, $p = .005$], but not female infants [$B(SE) =$ 8.3(53.1), 95% C.I. −96.024 to 112.551, $p = .876$]. TOB, MJ, and their co-use were not associated with length of gestation.

Conclusions: In this sample, intrauterine co-exposure to MJ and TOB was associated with an estimated 18% reduction in birth weight not attributable to earlier delivery, exposure to ALC or OT΄H drugs, nor to maternal SES. We found evidence for greater susceptibility of male fetuses to any prenatal MJ exposure. Examination of dose-dependence in relationships found in this study, using continuous measures of exposure, is an important next step. Finally, we underscore the need to consider (a) the potential moderating influence of fetal sex on exposure-related neurodevelopmental risks; and (b) the importance of quantifying expressions of risk through subtle alterations, rather than dichotomous outcomes.

1. Introduction

Marijuana is the most commonly-reported illicit drug used by pregnant women in the United States (Berg et al., 2015; SAMHSA, 2013). Based on epidemiologic surveys, between 5% and 28% of the approximately 4 million infants born annually in the United States are born prenatally-exposed to marijuana (Ko et al., 2018). As intrauterine exposure to marijuana is not apparent at birth via a recognizable morphologic or physiologic syndrome, as is the case with alcohol (Clarren and Smith, 1978), and late term opioid exposure (Jansson and Velez, 2012), respectively, the nature and magnitude of impact on fetal development is an area of intense inquiry (Volkow et al., 2017).

Marijuana could adversely influence fetal development via several biological mechanisms (Grant et al., 2017; Richardson et al., 2016). A full third of THC consumed during pregnancy reaches the fetal circulation through the placenta (Hurd et al., 2005; Little and VanBeveren, 1996) and is met by cannabinoid receptors present in placental and fetal tissue, including the fetal brain, from early stages of embryonic development (Galve-Roperh et al., 2009; Park et al., 2003). Preclinical studies document alterations in normal patterns of fetal brain development (Jutras-Aswad et al., 2009), intrauterine growth, and early social and cognitive function of offspring prenatally exposed to marijuana, with early evidence for increased vulnerability in males (Bara et al., 2018; Benevenuto et al., 2017). Results from clinical studies are inconclusive, with confounding by concomitant use (or co-use) with tobacco and drugs as a major methodologic limitation of research to date (Huizink, 2014).

Separate from methodologic challenges, are recent changes in public perception, state policy, and apparent potency of marijuana in the United States (ElSohly et al., 2016; Warner et al., 2014). Critically, these changes occurred since the largest and most comprehensive teratologic investigations developed for this purpose were conducted (Day and Richardson, 1991; Jaddoe et al., 2012). While ramifications of these changes are yet to be fully appreciated, concern about greater prevalence and magnitude of prenatal exposures is warranted. Marijuana is perceived by many pregnant women as ‘natural,’ and relatively safe, and even preferable to prescription and over-the-counter remedies for nausea and hyperemesis (Oh et al., 2017). In the context of the resulting urgency to provide contemporary estimates of risk associated marijuana use during pregnancy, we conducted a secondary analysis using existing data from several recent well-described birth cohorts to overcome several critical methodologic barriers to knowledge.

1.1 Co-use of marijuana with tobacco, alcohol and other drugs

Among the most challenging methodologic dilemmas in etiologic research on substance use disorders is the common practice of co-use. In the examination of any particular substance of abuse, failure to detect co-use by women who are categorized as *users* could inflate estimates of risk, while failure to detect substances used by women categorized as *non-users* could dilute between-group differences (Conner et al., 2016). Indeed, conflicting findings to date regarding the risk for preterm delivery of low birth weight infants following marijuana during pregnancy derived from the Ottawa Prenatal Prospective Study (Fried et al., 1998), the Maternal Health Practices and Child Development Study (MHPCD) (Day and Richardson, 1991), and the Generation R study (El Marroun et al., 2009) has been attributed to confounding by tobacco and other drugs (Huizink, 2014). Two comprehensive reviews and meta-analyses of these and other studies were similarly limited in their ability to adjust for co-use (Conner et al., 2016; English et al., 1997; Huizink, 2014).

The most recent and well-controlled meta-analysis to our knowledge which included 31 studies of prenatal marijuana exposure published through August of 2015 also concluded a lack of risk for preterm delivery and low birth weight infants associated with prenatal marijuana use once tobacco and maternal socioeconomic factors were controlled (Conner et al., 2016). However, most cohorts included in this metaanalysis were recruited prior to aforementioned policy and potency changes. Moreover, only four of reviewed studies assessed drugs other than tobacco, rendering between-sample harmonization of alcohol or other drug use during pregnancy impossible. Finally, only 5.9% of infants in the meta-analytic sample were prenatally exposed to marijuana; Conner et al. (2016) cautioned that analyses was severely underpowered to detect a statistically-significant effect, were it present. To provide risk estimates that capture recent changes in policy, perception, and potency of marijuana in the U.S., and are adequately powered to detect effects on birth outcome, we examined prenatal cohorts recruited domestically between 2003 and 2015 that were directly or indirectly oversampled for tobacco and other drug exposures.

1.2. Measurement quality

We addressed two additional limitations of research to date that have received less attention, the first of which concerns measurement quality. Measurement can have a robust influence on estimates−of prevalence, extent, and putative effects of−prenatal tobacco exposure (Estabrook et al., 2016; Gunn et al., 2016; Shisler et al., 2017) yet is highly variable. Measurement quality is typically highest in mechanism-focused cohort studies that are usually underpowered to stratify outcomes by substances, and very limited in survey-based reports of use in large epidemiologic cohorts. This dilemma could contribute to mixed findings and inaccurate estimates of effects. To illustrate, in an earlier study of over 1200 women, Zuckerman and colleagues found that prenatal marijuana use was independently associated with fetal growth restriction, but only when urine screens for THC were used, and *not* when exposure was measured by self-reports alone (Zuckerman et al., 1989).

Indeed, even with widespread legalization and increased social acceptance of marijuana (Berg et al., 2015), when studying pregnant women, non-disclosure of marijuana use (Chang et al., 2017), and also tobacco use (Pickett et al., 2005; Shisler et al., 2017), still constitute potential sources of error. Data used in the current study contained finegrained interview-based multi-substance prenatal exposure measures collected in the context of multiple post-2000 mechanistic studies. These cohorts contained a substantially higher prevalence of exposure (s), (two were specifically oversampled for tobacco exposure) which enhanced our power to quantify substance-specific effects.

1.3 Variations in birth weight and length of gestation versus risk for clinically-defined benchmarks

Separate from measures of independent variables, i.e., co-exposures and other confounders, there has been less attention directed towards the selection of birth outcome measures.

Studies to date have overwhelmingly examined dichotomous primary outcomes, namely, low birth weight, defined as < 2500 g, rather than continuously. This provides a clinically-informative risk ratio, but is a coarse measure of neurodevelopmental risk, when compared to the estimation of alteration in birth weight. While reductions in birth weight of normal weight infants may not be clinically significant at the time of birth, there is growing recognition of how the intrauterine environment powerfully shapes trajectories of health and disease across the lifespan (Barker, 1995). Birth weight is a highly-sensitive and well-established biomarker of intrauterine adversity and a strong predictor of neurodevelopmental and cardio-metabolic outcomes in later life (Johnson et al., 2017), including cognitive function 75 years later (Muller et al., 2014). Furthermore, natural variations in birth weight, *within the normal range,* have been shown to independently predict cortical surface area, total brain volume, and caudate volume, in healthy 6-year-old children, more strongly, in fact, than variations in low or high birth weight ranges (Walhovd et al., 2012). Thus, with a broader focus on estimating of neurodevelopmental risk, rather than simply confirming or refuting short-term morbidity and mortality, in this study we conceptualized birth outcomes as markers of long term risk, and examined them as continuous measures (birth weight, length of gestation).

1.4. Consideration of sex differences

Finally, while mechanisms are not well-understood, sex differences in the developmental impact of maternal smoking during pregnancy (Cross et al., 2017), and many other environmental insults across neonatal medicine (Rosen and Bateman, 2010), are widely observed, yet have not been a central focus of teratologic investigations concerning marijuana. To consider the possibility for sex differences in marijuana's risk, we analyzed the full sample as a whole, consistent with nearly all studies to date, and then, male and female infants separately.

For clarity, we will use the terms, *substance use* and *drug use,* inter changeably, to refer to the use of *any* of the following: tobacco, alcohol, marijuana, other illicit drugs, and non-medical use of prescribed controlled substances. References made to substances used 'during pregnancy' will refer to the period from the estimated date of conception through delivery, consistent with intrauterine exposure.

2. Materials and methods

2.1. Participants and procedures

All study procedures described were approved by respective local Institutional Review Boards (IRB) prior to conduct. A flow chart showing the derivation of the pooled analytic sample of $N = 1191$ is shown in Fig. 1. Details of individual cohorts are described below.

2.1.1. The Growing Up Healthy study (GUH)—We included $n = 251$ mothers with complete data (i.e. all variables described in regression analyses) from the full sample of 258, from GUH, a longitudinal study of prenatal tobacco exposure and child selfregulation. From 2006 to 2009, English-speaking women ≥18 years old with singleton pregnancies at ≤ 20 weeks of gestation were recruited from an urban hospital-based obstetric clinic in the

Northeastern United States. Exclusion criteria were: any reported or biomarker (maternal saliva, infant meconium) evidence of illicit drug use *other* than marijuana during pregnancy, reported consumption of 4 or more alcoholic drinks/drinking occasion after the estimated date conception, or > 1 drink/day following the recognition of the pregnancy. At one-month intervals following enrollment, pregnant smokers were matched on age and education with the closest eligible non-smoking woman from the clinic. Smokers were oversampled to maximize range of smoking frequency, and in anticipation of greater attrition relative to non-smokers. Additional details can be found at (Eiden et al., 2018).

2.1.2. The Mood and Behavior in Mothers and Babies studies (BAM BAM and BAM BAM-2)—Participants in the pooled analytic sample were also derived from two larger studies with complementary methods−the Behavior and Mood in Babies and Mothers (BAM BAM) Study (2006–2010), and the BAM BAM-2 Study (2012–2015), referred to collectively, herein, as BAM BAM. The aim of both studies was to understand the effects of maternal perinatal smoking on fetal and infant outcomes (Stroud et al., 2014; Stroud et al., 2016). For both studies, pregnant women were recruited from obstetric clinics, health centers, and community postings in the Northeastern United States, oversampling for (tobacco) cigarette smokers. Women were excluded from participation if they were <18 or > 40 years of age, had current or prior involvement with child protective services, were pregnant with more than one fetus, or had serious psychiatric conditions (e.g., bipolar or psychotic disorders) or any serious medical condition during pregnancy (e.g., preeclampsia). Both studies utilized prospective interview- and biochemically-based assessments of substance use in the second and/or third trimesters of pregnancy, and at delivery. Additional details may be found in published reports from these data, for example (Massey et al., 2015; Stroud et al., in press).

2.1.3. The Early Growth and Development study (EGDS)—Finally, the pooled sample included 625 biological mothers (from a total of 914) from the EGDS, an ongoing, longitudinal, multi-site study that utilizes the parent-offspring within-family design to examine prenatal and postnatal environmental influences on child health outcomes, separate from genetic influences. Biological mothers were recruited from 2003 to 2010 from 45 adoption agencies in 15 states, across Mid-Atlantic, Southwestern, Midwestern, and Pacific Northwestern regions of the U.S., and represented the spectrum of public, private, religious, and secular agencies, including those favoring both open and closed adoptions. All EGDS biological mothers placed their children with unrelated adoptive parents at or shortly after delivery (M = 6.2 days, SD = 12.5, range = 0–91). Infants born with major congenital conditions, or who were delivered before 28 weeks of gestation (extreme prematurity) were excluded from participation. Additional information about the sample can be found at (Leve et al., 2013; Marceau et al., 2016; Massey et al., 2016).

2.2. Measures

2.2.1. Interview-based maternal reports of substance use during pregnancy —In all cohorts, maternal reports of drug use during pregnancy were assessed using well-validated calendar-based interview methods−the Life History Calendar (LHC) in EGDS (Caspi et al., 1996), and Timeline Follow Back Interviews in GUH and BAM BAM (Sobell and Sobell, 1996). Interviews were conducted prospectively in GUH and BAM BAM, and at 3–6 months postpartum (after finalization of adoption procedures) in EGDS. To minimize social desirability biases in reporting of stigmatizing information, the EGDS utilized computer-assisted personal interviewing (Gnambs and Kaspar, 2015).

2.2.2. Biomarkers of drug use during pregnancy—Biomarker verification of reported use was employed in GUH and BAM BAM, representng nearly half of the full analytic sample (47.5%, $n = 566$ out of 1191). In GUH, biomarkers of use were quantified from maternal saliva, collected during each trimester of pregnancy, and from meconium at delivery. Infant meconium samples were collected across several days, in one collection bottle, then assayed with a validated LC-MSMS method (Gray et al., 2010a) at 2.5ng/g nicotine, 1 ng/g nicotine, and 5 ng/g OHCOT for tobacco; and with a validated 2-di-mensional GC-MS analytical method for THC, 11-hydroxy-THC; 8,11-dihydroxy-THC; 11-nor-9-carboxy-THC (THC-COOH) and cannabinol (Gray et al., 2010b) for marijuana. Metabolites of cannabis, ethanol, amphetamines, opiates, and cocaine were tested with immunoassay screening (4.0 ng/L cutoff), followed by gas chromatography-mass spectrometry (GC-MS) confirmation (4.0 ng/L cutoff) (Gray et al., 2010). In BAM BAM, mothers provided saliva samples for cotinine assays using ELISA kits at 30 and 35 weeks, and at delivery (Salimetrics, 2006). Following delivery, infant meconium samples were collected for up to three days, then assayed for metabolites of marijuana, cocaine, and other illicit drugs (Gray et al., 2010; Moore et al., 1998).

2.2.3 Infant sex, birth weight, and gestational age at delivery—Data on birth outcomes were derived from medical records for all studies.

2.3 Data analysis

Measures of tobacco use in cigarettes/day across all cohorts enabled harmonization to create a continuous measure of prenatal tobacco exposure. For alcohol, marijuana, and other drugs, GUH and BAM BAM quantified use in units/day, while EGDS assessed severity of use patterns as evidenced by diagnostic criteria for substance use disorders endorsed. Thus, for alcohol and marijuana, we created categorical variables indicating the presence or absence of use at any time during pregnancy. Close to a dozen illicit drugs other than marijuana were assessed across cohorts, including non-medical use of prescription narcotics in EGDS. However, since the frequency of each drug was low, they were collapsed into a fourth dichotomous substance use variable, referred to, herein, as *other* drugs. As continuous independent variables are methodologically favorable to dichotomous variables in regression models (Royston et al., 2006), mean tobacco exposure in cigarettes/day was selected for use in models. However, we also examined tobacco as a dichotomous variable (any use) to facilitate the comparison of its effect with dichotomous marijuana and other drug variables.

To estimate additional effects on outcomes associated with co-use of tobacco and marijuana (beyond effects of tobacco and marijuana individually), we created the interaction term, mean TOB exposure x MJ, by multiplying standardized mean cigarettes/day by any marijuana use. Among many maternal demographic factors considered for inclusion as covariates (Kramer, 1987), we selected those correlated with either birth weight or length of gestation, in any individual cohort, or in the pooled sample ($p < .05$). These covariates −maternal age at delivery, minority race (non-White) or ethnicity (Hispanic), less than high school educational attainment, and male sex, were entered in all models (with the exception of male sex, removed for analyses stratified by sex).

After ruling out multi-collinearity among variables (defined a priori, as $r > 0.6$) using bivariate correlation analysis (Table 2), we estimated specific substance-outcome associations (effects) using linear regression analysis, with birth weight, then length of gestation, as the dependent variable. As independent variables, we entered the 4 exposure variables (mean TOB exposure, any MJ use, any ALC use, and any OTHER drug use) together with all covariates. Next, the interaction term for co-use of MJ and TOB was added to examine any *additional* effect (Table 3). These same models were then fitted, separately, to male ($N = 654$) and female ($N = 537$) infants (Table 4).

3. Results

3.1. Descriptive characteristics (N = 1191)

Characteristics of mothers and infants in pooled and individual cohorts, and between-cohort differences, are shown in Table 1. For the pooled sample, mothers were typically high school-educated women in their mid-20's ($M = 24.4$ years, $SD = 5.7$) who delivered at a mean gestational age of 37.8 weeks ($SD = 2.0$). About two thirds of mothers (62.8%, $n = 748$) used at least one substance during pregnancy. Approximately half used tobacco (n = 608, 51.0%); over a third used alcohol (n = 464, 39.0%); almost 1 in 4 used marijuana ($n = 273$, 22.9%); and about 1 in 10 used a drug *other* than tobacco, alcohol or marijuana (n = 115, 9.7%). About 1 in 5 women used tobacco and marijuana concomitantly ($n = 230$, 19.3%). Newborns were 54.9% male, weighing an average of 3277 g ($SD = 543$), equivalent to 7.2 lbs. Seven percent of infants ($n = 85$) were low birth weight (< 2500 g).

Between-cohort differences in demographic and substance use variables are shown in Table 1. Briefly, GUH participants were least likely to have completed high school, most racially and ethnically diverse, and most likely to use any substance during pregnancy. Mean tobacco use (cig/d) among mothers who smoked at any time during gestation was lowest in GUH, however ($M = 5.4$ cig/d, $SD = 4.6$), and highest in EGDS ($M = 6.9$ cig/d, $SD = 5.2$; F(all cohorts) = 5.284; df 2, 579; $p = .005$). GUH mothers were heavier marijuana users, relative to BAM BAM mothers, reporting the equivalent of just over 1 joint consumed every 2 days ($M = 0.57$ joints/d, $SD = 0.85$), compared to 1 joint every 8 days in BAM BAM ($M = 0.13$ joints/d, $SD = 0.73$, F(GUH, BAM BAM) = 15.154, d/1, 164; $p < .001$). Mean birth weights among the 3 cohorts were not different ($F = 2.762$, df 1, *1189*, p = NS), while mean lengths of gestation were ($F = 440.170$, $p < .01$). EGDS mothers delivered earliest, at a mean of 36.6 weeks ($SD = 1.4$), followed by GUH mothers ($M = 38.9$ weeks, $SD = 1.8$).

3.2. Correlations among maternal and infant characteristics

Bivariate correlations among variables are shown in Table 2. All substances used during pregnancy were moderately inter-correlated with one another, and inversely associated with birth weight, with the exception of alcohol use (no correlation). For length of gestation, maternal alcohol use ($r = 0.251$, $p < .01$) was associated with a longer gestation. We interpreted the statistically significant but near zero association between marijuana and length of gestation ($r = 0.058$, $p < .05$) as not significant.

Use of tobacco and other drugs during pregnancy were unrelated.

3.3. Exposures and birth weight, analysis of full sample (Table 3, top)

Estimates of birth weight effects associated with specific prenatal exposures from linear regression analysis of the full sample all infants are shown in Table 3, top. Any use of tobacco during pregnancy was associated with lower birth weight by approximately 100 g [*B (SE)* = −0.99.416(34.418), 95% C.I. −166.942 to −31.889, $p = .004$] (model not shown), with each cigarette/day in mean TOB exposure accounting for an estimated 12.23-gram reduction in birth weight (*SE* = 3.43, 95% C.I. −18.96 to −5.51, $p < .001$). Any use of marijuana was also associated with a reduction in birth weight, by 84.367 g (*SE* = 38.27, 95% C.I. −159.45 to −9.28, $p = .028$). Maternal minority status was linked to lower birth weight [*B (SE)* = −196.94 (32.08), 95% C.I. −259.87 to −134.01, $p < .001$], while male sex and prenatal alcohol use were associated with increased birth weight [*B (SE)* = 125.53 (30.67), 95% C.I. 65.36 tol85.69, $p < .001$] and [*B (SE)* = 66.33 (32.42), 95% C.I. 2.73 to 129.93, $p = .041$], respectively. Co-use of tobacco and marijuana during pregnancy was not associated with additional effects on birth weight beyond individual drug effects noted above [*B* (*SE*) = −55.15 (36.67), 95% C.I. −127.10 to 16.80, $p = .133$] (model not shown).

3.4. Exposures and length of gestation, analysis of full sample (Table 3, bottom)

As shown in the bottom portion of Table 3, tobacco exposure [B (*SE)* = 0.001 (0.012), 95% C.I. −0.24 to 0.25, $p = .965$] and marijuana exposure [*B(SE)* = 0.142 (0.139), 95% C.I. −0.130 to 0.414, $p = .304$] were both unrelated to length of gestation. The interaction of tobacco and marijuana also was not significant [*B(SE)* = −0.082 (0.133), 95% C.I. −0.343 to 0.179 $p = .538$]. Any alcohol use during pregnancy was associated with a longer length of gestation, by nearly a week [*B (SE)* = 0.992 (0.117), 95% C.I. 0.762 to 1.222, $p < .001$], while use of drug(s) other than tobacco, alcohol, and marijuana was associated with a shorter length of gestation by over a week [B(SE) = −1.276 (0.194), 95% C.I. −1.657 to −0.895, $p < .001$].

3.5. Sex-specific analyses of exposures and birth weight (Table 4, top); and length of gestation (Table 4, bottom)

Analyses stratified by infant sex are shown in Table 4. For male infants, each cigarette/day in mean tobacco exposure was associated with a 10.995-gram reduction in birth weight (*SE* = 4.74, 95% C.I. −20.30 to −1.70, $p = .021$); any marijuana exposure was associated with a 153.09-gram reduction (*SE* = 54.20, 95% C.I. −259.52 to −46.66, $p = .005$). Prenatal tobacco exposure was associated with a similar magnitude of reduction in birth weight in female infants [B (*SE)* = −13.45 (4.91), 95% C.I. −23.10 to −3.79, $p = .006$]. However, unlike male infants, no effect of marijuana exposure was observed for females [*B* (*SE*) = 8.26, 95% C.I. −96.02 to 112.55, $p = .876$]. Evidence for effects of co-use (TOB x MJ) above and beyond the effects of each drug alone was not supported, for males [*B* (*SE*) =

−97.404 (54.358), 95% C.I. [−204.143–9.335], $p = .074$] nor for females [*B (SE)* = 3.184 (49.184), 95% C.I. [−93.437–99.805], $p = .948$].

4. Discussion

4.1. Unique contributions of the current study

The pooled sample of 1191 mother-infant dyads described in this study represented a rare balance of statistical power, measurement quality, and high rates of drug exposures. Nearly 1 in 4 (22.9%) mothers in the pooled sample used marijuana while pregnant, compared to 2.7% in the Stillbirth Collaborative Research Network (Metz and Stickrath, 2015); 3.2% in the National Birth Defects Prevention Study (van Gelder et al., 2010), 4.6% in the National Survey on Drug Use and Health (Ko et al., 2018), and 5.9% in the most recent and well-controlled meta-analysis to date (Conner et al., 2016). Mothers were recruited between 2003 and 2015 concurrent with marijuana's evolution in policy, public perception, and potency. Third, consistent with the rapidly-expanding body of clinical evidence supporting normal variation in birth weight as a sensitive marker of the intrauterine environment and neurodevelopmental risk, manifested across the life span (Cook and Fletcher, 2015; Muller et al., 2014; Walhovd et al., 2012), we departed from the convention of estimating risks for clinically-defined benchmarks (i.e., low birth weight and preterm birth). Instead, we provided estimates of birth weight effects associated with marijuana and tobacco, independent from one another, and of their co-use, in light of evidence for additive risks of co-use in non-pregnant individuals (Meier and Hatsukami, 2016). Finally, in the context of evidence for sex differences in offspring susceptibility to prenatal tobacco exposure (Cornelius and Day, 2009) and early preclinical evidence for a sex differences in embryonic and fetal vulnerability to THC exposure (Benevenuto et al., 2017), we examined exposure-outcome relationships for male and female infants separately.

4.2. Percentage versus absolute effects and sex differences in mean birth weights

The inverse association between prenatal tobacco exposure (mean cigarettes/day) and birth weight found in this sample mirrors existing evidence in this regard (Ernst et al., 2001). However, while the absolute reduction in birth weight associated with each cigarette/day in mean prenatal tobacco exposure was similar for male (about 11 g) and female infants (13 g), respectively, this estimate represented a greater proportion of total body weight for female infants, who were lighter, when averaged across the pooled sample (3335.4 ± 566 g in males versus 3206.9 ± 504.3 g in females, $F = 4.345$, $df = 1189$, $p < .001$). While this was not an a priori focus of the current investigation, consideration of adjustment for sex differences in sensitive biomarkers of risk such as birth weight may be important. Our recent 3-year follow up of toddlers from GUH showed a stronger association between prenatal tobacco exposure and internalizing, sleep, and attention problems in girls, relative to boys (Eiden et al., 2018). Confirming that female infants were lighter than male infants in the GUH sample, together with these recent findings in toddlers raises the possibility that a more nuanced approach to exposure-outcome associations is needed. Specifically, estimation of relative reduction in birth weight via the integration of sex differences in birth weight (and other biomarkers), may be a more predictive marker for neurodevelopmental risk than estimation of absolute effects, or risk for low birth weight, as has been conventionally done.

4.3. Sex differences in vulnerability may vary by developmental stage

This is the first study to our knowledge to suggest a sex-specific association between prenatal marijuana exposure and birth weight. This observation is consistent with a large body of research supporting sex-specific vulnerability of males to early environmental adversity more broadly (Rosen and Bateman, 2010), and early preclinical evidence for increased morphologic (Benevenuto et al., 2017) and neurodevelopmental (Silva et al., 2012) susceptibility of males to prenatal cannabis exposure. Increased male vulnerability to epigenetic alterations in differentially methylated regions, especially in the Insulin-like Growth Factor 2 regulatory genes (i.e., IGF2 and H19), is a proposed mechanism for sex-specific vulnerability to prenatal tobacco exposure (Murphy et al., 2012). Sex-specific vulnerability could operate even earlier, at the embryonic stage.

For instance, Benevenuto et al. (2017) noted a greater proportion of male pups in litters born to dams exposed to marijuana, relative to litters born to non-exposed dams, coupled with double the rate of postimplantation pregnancy loss of female embryos (though the latter. difference was not statistically significant) (Benevenuto et al., 2017). Regardless, our results emphasize the importance of examining exposure-outcome effects separately by offspring sex, especially since undetected sex differences could dilute true associations. Analysis of pooled data from other recent cohorts well-characterized for exposures, stratified by sex, is recommended to clarify results to date derived from previous studies that have not stratified by sex.

4.4. Estimating subtle alterations in birth weight associated with exposure to elucidate pathways of neurodevelopmental risk

Relatedly, while the majority of prior studies and meta-analyses have not supported an independent risk for low birth weight associated with prenatal marijuana exposure (Conner et al., 2016), the multitude of plausible risk mechanisms (Richardson et al., 2016), combined with preclinical studies suggesting subtle, yet persistent cognitive and social deficits (Silva et al., 2012), together, support a more nuanced approach to quantifying neurodevelopmental risk that involves the estimation of effects on a continuous measure of birth weight rather than a singular focus on risk for low birth weight.

As is the case with prenatal tobacco exposure (Estabrook et al., 2016; Knopik, 2009), association does not imply causality, in light of measured and unmeasured influences, including, but not limited to couse of other substances, maternal stress and its psychopathological manifestations, and associated environmental risks (Borders et al., 2007; Grote et al., 2010). Our results support the presence of risk to fetal growth associated with MJ exposure, particularly in the presence of TOB exposure, combined with the need for more investigation to confirm specificity to male infants. Since our data do not provide the framework for discerning underlying mechanisms of observed sex differences, further investigation using a combination of preclinical and clinical approaches is recommended to establish a dose-dependent relationship, and to elucidate pathways and targets for preventive interventions.

4.5. Lower birth weight associated with marijuana and tobacco exposures was not explained by a shorter length of gestation

Like birth weight, many factors other than cigarette smoking could adversely influence the length of gestation, i.e., maternal infections and other illnesses, pre-pregnancy weight, prior history of spontaneous abortion or preterm delivery, and prenatal exposure to diethyl-stilbestrol (Kramer, 1987). Neither tobacco, nor marijuana, was significantly associated with length of gestation. We considered that the relatively low mean level of prenatal tobacco exposure of approximately 3 cigarettes/day ($SD = 4.8$) in the full sample, and about 6 cigarettes/day among women who smoked during pregnancy ($SD = 5.3$), combined with the exclusion criteria typical of developmental cohorts could have contributed to range restriction in length of gestation. However, the significant direct effects on length of gestation observed for drugs other than marijuana do not support this explanation. The observed reduction in birth weight associated with prenatal marijuana and tobacco exposure not accounted for by earlier delivery, then, would be consistent with intrauterine growth restriction. This and other findings must be viewed, however, in the context of limitations of this study.

4.6. Limitations

Despite a much higher prevalence of prenatal exposure to marijuana in our sample compared to epidemiologic cohorts (details above), the prevalence of marijuana use alone, at the exclusion of other substances, especially tobacco, was still quite rare ($n = 25$; 2.1%). We wish to underscore the impact of this finding alone, that, together with studies across several decades (Coleman-Cowger et al., 2017; Conner et al., 2016; Ko et al., 2018), imply that *studying, or evaluating for, one drug, in the scientific or clinical setting, as the case may be, necessitates consideration of the other.* Evidence derived from the current study provides an important framework of comparison to be considered with evidence from large epidemiologic studies with much lower rates of exposures, and have not found independent effects (Ko et al., 2018; van Gelder et al., 2010**).**

Next, the range of exposures was relatively small; frequent and/or heavy use of tobacco, marijuana, and other drugs was rare (Table 1) (Eiden et al., 2018; Massey et al., 2015; Massey et al., 2011). Moreover, we did not utilize a continuous measure of marijuana and other drug exposures, account for timing of exposures in gestation, or assess interindividual and intra-individual fluctuations in use, known to exist for cigarette smoking (Eiden et al., 2013; Pickett et al., 2003).

Third, birth weight and its maternal and child correlates are partially heritable. Quasi-experimental approaches such as genetically-in-formed designs and within-individual designs could provide more robust controls for individual-level confounders (Mosing et al., 2016). Indeed, many unmeasured influences other than marijuana that could have influenced birth weight (Knopik et al., 2016). Notably, socioeconomic status was a robust predictor of birth weight, as expected (Kramer, 1987; Kramer et al., 2000). Being either a racial (non-White) or ethnic (Hispanic) minority showed a consistent inverse association with birth weight−across both sexes (Tables 3 and 4)−and was actually associated with a greater effect on birth weight than any specific exposure [*B(SE)* = −196.943 (32.075), 95% C.I. [−259.873 to - 134.014], $p < .001$].

These effects led us to consider the possibility that specific substances used were markers of demographic confounders, especially in the case of alcohol use, which was paradoxically associated with higher birth weight and length of gestation, and inversely associated with having less than a high school education ($r = -0.115$, $p < .01$) (Table 2). One plausible explanation for this unexpected finding is selection bias—alcohol users eligible for GUH were women who used alcohol infrequently and/or limited their drinking to 1 drink/day after recognizing the pregnancy (Fig. 1). Relatedly, the apparent protective effect associated with moderate alcohol use could be an artifact, reflecting risks in women who abstained from alcohol completely, mimicking the widely-replicated J-shaped curve phenomenon of moderate drinking and cardiovascular mortality (Di Castelnuovo et al., 2006).

In contrast to alcohol, prenatal marijuana use was neither correlated with education ($r = 0.28$, p = NS), nor with identification as a racial or ethnic minority ($r = 0.022$, p = NS), or any other demographic variable. This provided a measure of support for the validity of our results supporting an independent risk of marijuana exposure to fetal growth. Establishing dose dependence of exposure-outcome relationships found in this study are needed, however, prior to translating results to clinical recommendations.

4.7. Conclusion

We reiterate the importance of interpreting these results within the sheer breadth of environmental factors besides substance exposures that could influence birth weight—contextual (i.e., local traumatic events, neighborhood crime), spousal/familial (i.e., intimate partner violence, spousal/household smoking), and individual-level factors (i.e., maternal behavior, mood, and overall health) are well-established determinants of birth weight, all of which are strongly implicated in the transmission of health risks inter-generationally. However, maternal substance abuse is malleable, and arguably, must be addressed to ensure optimal child health.

Maternal behavior may be the most profound determinant of children's rearing environment, making a focus on maternal well-being paramount in the prevention of child psychopathology (Grant et al., 2018; Massey et al., 2017; Shankaran et al., 2007). To this end, we recommend future research utilizing the approach described in this study—that blends high quality exposure measurement with adequate prevalence and power to understand *the extent and nature of risk* associated with marijuana use during pregnancy. This knowledge is sorely needed by policymakers, obstetric providers, pregnant women, and sexually-active women of child-bearing age (Mark and Terplan, 2017).

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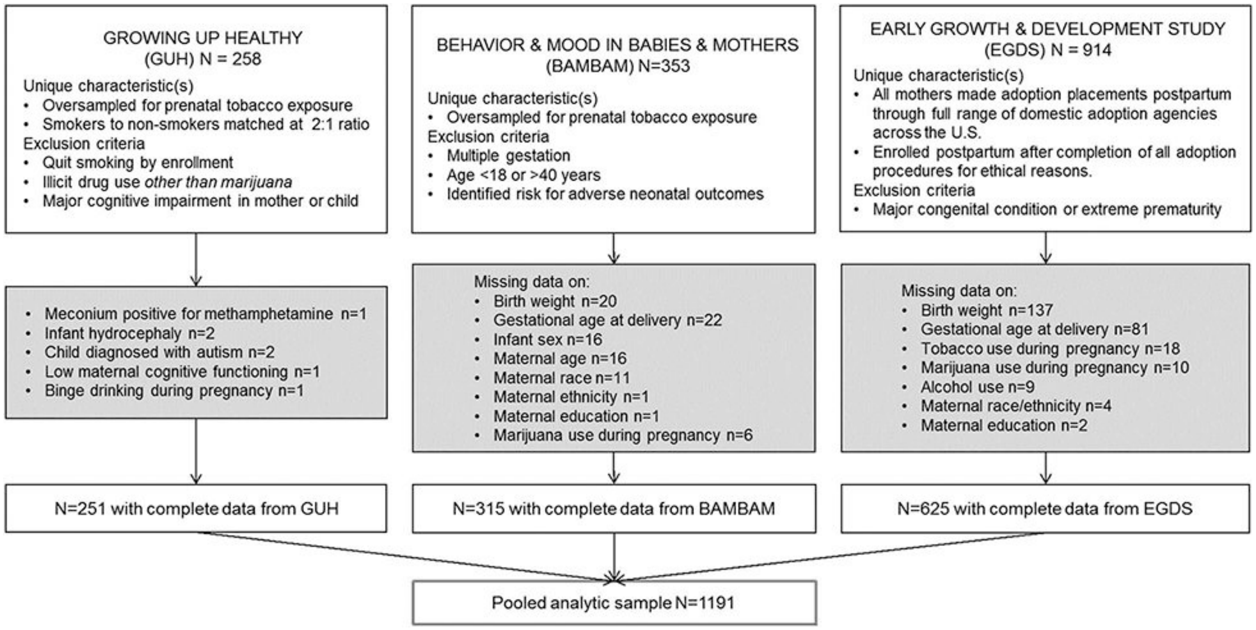

Fig. 1.

Individual cohorts and derivation of the analytic sample ($N = 1191$).

Table 1

Descriptive characteristics of mothers and infants in pooled (*N* = 1191) and individual cohorts.

	Pooled sample N=1191	Growing Up Healthy N=251	Behavior & Mood in Mothers & Babies N=315	Early Growth & Development Study N=625	F or χ^2 statistic
Mothers, pregnancy			Mean ± SD or n (%)		
Age at delivery, (years)	24.4 ± 5.7	24.0 ± 5.0	25.9 ± 5.1	23.8 ± 6.1	14.713***
Less than H.S. education	272 (22.8%)	74 (29.5%)	70 (22.2%)	128 (26.2%)	8.327*
Racial or ethnic minority	480 (40.3%)	177 (70.5%)	139 (44.4%)	164 (26.2%)	148.531***
Any use	748 (62.8%)	215 (85.7%)	170 (54.0%)	363 (58.1%)	72.615***
Any tobacco (TOB) use	608 (51.0%)	178 (70.9%)	160 (50.8%)	270 (43.2%)	55.063***
Mean TOB exposure (cigs/d)	3.01 ± 4.8	3.53 ± 4.5	2.71 ± 4.4	2.94 ± 5.1	2.102
Mean cig/d, TOB users only	6.15 ± 5.32	5.37 ± 4.61	5.66 ± 4.96	6.92 ± 5.82	5.284**
Any MJ use	273 (22.9%)	101 (40.2%)	66 (21.0%)	105 (16.8%)	56.694***
Mean MJ exposure (joints/d)	0.12 ± 0.43	0.24 ± 0.62	0.024 ± 0.12	Not assessed	36.330***
Mean joints/d, MJ users only	0.41 ± 0.73	0.57 ± 0.85	0.13 ± 0.25	Not assessed	15.154***
Co-use of TOB & MJ	230 (19.3%)	97 (38.6%)	56 (17.8%)	77 (12.3%)	80.294***
Any alcohol (ALC) use	464 (39.0%)	153 (61.0%)	162 (51.4%)	149 (23.8%)	131.743***
Any OTHER drug use includes misuse of prescription drugs	115 (9.7%)	5 (2.0%)	6 (1.9%)	104 (16.6%)	73.542***
Infants, at delivery			Mean ± SD or n (%)		
Male	654 (54.9%)	131 (52.2%)	163 (51.7%)	360 (57.6%)	3.850
Birth weight (g)	3,277 ± 543	3,224 ± 582	3,335 ± 505.7	3,266 ± 543	2.762
Low birthweight (<2,500 g)	85 (7.1%)	20 (8.0%)	16 (5.1%)	49 (7.8%)	2.740
Gestational age (weeks)	37.8 ± 2.0	38.9 ± 1.8	39.4 ± 1.5	36.6 ± 1.4	440.170***

Grey rows shown for descriptive purposes only; all other rows show variables used in subsequent analyses.

* $p < .05$

** $p < .01$

*** $p < .001$ for two-tailed tests.

Table 2

Bivariate correlations among), outcomes and variables ($N = 1191$).

	1	2	3	4	5	6	7	8	9
1. Maternal age									
2. <H.S. education	−0.131**								
3. Minority race/eth.	0.025	0.095**							
4. Male infant	0.023	−0.009	−0.030						
5. TOB (cig/d)	0.152**	0.123**	−0.170**	0.043					
6. Any MJ use	−0.027	0.028	0.022	−0.030	0.203**				
7. Any ALC	0.023	−0.115**	0.018	−0.020	0.088**	0.218**			
8. Any OTHER use	0.094**	0.012	−0.130**	0.005	0.216**	0.134**	−0.034		
9. Birth weight	0.033	−0.093**	−0.161**	0.118**	−0.090**	−0.090**	0.038	−0.052	
10. Length of gestation	0.070*	0.018	0.139**	−0.009	−0.011	0.058*	0.251**	−0.195**	0.422**

* $p < .05$

** $p < .01$ for two-tailed tests.

Highlighted, are correlates of mean tobacco use and any marijuana use during pregnancy.

Table 3

Estimated effects on birth weight (top) and length of gestation (bottom) associated with maternal tobacco, marijuana, alcohol, and other drug use during pregnancy from linear regression ($N = 1191$).

Birth weight (grams)	B	SE	β	t	P	95% C.I. for B	
Constant	3232.824	73.256		44.130	.000	3089.097	3376.551
Maternal age	4.383	2.762	.046	1.587	.113	−1.036	9.801
< High school	−60.342	37.626	−.047	−1.604	.109	−134.162	13.479
Minority race or ethnicity	−196.943	32.075	−.178	−6.140	.000	−259.873	−134.014
Male infant	125.525	30.667	.115	4.093	.000	65.358	185.692
Any alcohol use	66.332	32.415	.060	2.046	.041	2.734	129.930
Any other drug use	−83.695	53.614	−.046	−1.561	.119	−188.884	21.494
Mean tobacco use (cigs/d)	−12.233	3.427	−.109	−3.570	.000	−18.955	−5.510
Any marijuana use	−84.367	38.271	−.065	−2.204	.028	−159.453	−9.281

Length of gestation (weeks)	B	SE	β	t	P	95% C.I. for B	
Constant	36.549	.265		137.771	.000	36.028	37.069
Maternal age	.031	.010	.086	3.065	.002	.011	.050
< High school	.231	.136	.048	1.694	.090	−.036	.498
Minority race or ethnicity	.427	.116	.104	3.675	.000	.199	.655
Male infant	−.005	.111	−.001	−.046	.963	−.223	.213
Any alcohol use	.992	.117	.239	8.450	.000	.762	1.222
Any other drug use	−1.276	.194	−.187	−6.570	.000	−1.657	−.895
Mean tobacco use (cigs/d)	.001	.012	.001	.044	.965	−.024	.025
Any marijuana use	.142	.139	.030	1.027	.304	−.130	.414

Table 4

Estimated effects on birth weight (top) and length of gestation (top) associated with maternal use of tobacco, marijuana, alcohol, and other drug(s) during pregnancy, stratified by infant sex, from linear regression.

	MALE (n=654)					FEMALE (n=537)				
Birth weight (grams)			95% C.I. for B					95% C.I. for B		
	B	SE	Lower	Upper	P	B	SE	Lower	Upper	P
Constant	3441.657	99.348	3246.573	3636.741	.000	3117.925	101.110	2919.299	3316.552	.000
Maternal age	.126	3.828	−7.391	7.644	.974	10.147	3.933	2.421	17.872	.010
< High school	−103.449	53.425	−208.357	1.458	.053	−19.821	51.971	−121.917	82.274	.703
Minority race/eth.	−184.974	45.744	−274.800	−95.149	.000	−200.744	44.124	−287.424	−114.064	.000
Any alcohol use	165.613	45.413	76.439	254.787	.000	−57.994	45.533	−147.441	31.454	.203
Any other drug use	−90.039	74.072	−235.491	55.413	.225	−107.041	77.042	−258.386	44.305	.165
Mean TOB use (cigs/d)	−10.995	4.736	−20.295	−1.695	.021	−13.445	4.913	−23.095	−3.794	.006
Any MJ use	−153.087	54.199	−259.515	−46.659	.005	8.263	53.087	−96.024	112.551	.876
Length of gestation (weeks)			95% C.I. for B					95% C.I. for B		
	B	SE	Lower	Upper	P	B	SE	Lower	Upper	P
Constant	36.625	.336	35.965	37.284	.000	36.420	.403	35.628	37.212	.000
Maternal age	.027	.013	.002	.053	.035	.036	.016	.006	.067	.021
< High school	.320	.181	−.035	.674	.077	.099	.207	−.308	.506	.633
Minority race/eth.	.321	.155	.017	.625	.039	.568	.176	.223	.914	.001
Any alcohol use	1.240	.154	.939	1.542	.000	.674	.182	.318	1.031	.000
Any other drug use	−1.393	.251	−1.885	−.901	.000	−1.168	.307	−1.771	−.564	.000
Mean TOB use (cig/d)	−.007	.016	−.039	.024	.647	.009	.020	−.030	.047	.663
Any MJ use	−.025	.183	−.385	.335	.890	.367	.212	−.049	.783	.084