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Impact of Prenatal Exposure Characterization on Early Risk Detection: Methodologic Insights for the HEALthy Brain and Child Development (HBCD) Study

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Abstract
Background: A major challenge in prenatal drug exposure research concerns the balance of measurement quality with sample sizes necessary to address confounders. To inform the selection of optimal exposure measures for the HEALthy Brain and Child Development (HBCD) Study, we employed integrated analysis to determine how different methods used to characterize prenatal tobacco exposure influence the detection of exposure-related risk, as reflected in normal variations in birth weight.

Methods: Participants were N=2323 mother-infant dyads derived from 7 independent developmental cohorts harmonized on measures of exposure, outcome (birthweight), and covariates. We compared estimates of PTE-related effects on birthweight derived from linear regression models when PTE was categorized dichotomously based on any fetal exposure (30% exposed; 69% not exposed); versus categorically, based on common patterns of maternal smoking during pregnancy (never smoked 69%; quit smoking 16%; smoked intermittently 2%; smoked persistently 13%). We secondarily explored sex differences in PTE-birthweight associations across these categorization methods.

Results: When PTE was categorized dichotomously, exposure was associated with a -125-gram difference in birthweight (95% C.I. -173.7 – -76.6, p<.001). When PTE was characterized categorically based on maternal smoking patterns, however, exposure was associated with either no difference in birthweight if mothers quit smoking by the end of the first trimester (B=-30.6, 95% C.I. -88.7 – 27.4, p=.30); or a -221.8 gram difference in birthweight if mothers did not [95% C.I. (-161.7 – -282.0); p < .001]. Qualitative sex differences were also detected though PTE x sex interactions did not reach statistical significance. Maternal smoking cessation during pregnancy was associated with a 239.3 gram increase in birthweight for male infants, and a 114.0 gram increase in birthweight for females infants (p=.07).

Conclusions: Categorization of PTE based on patterns of maternal smoking rather than the presence or absence of exposure alone revealed striking nuances in estimates of exposure-related risk. The described method
that captures both between-individual and within-individual variability in prenatal drug exposure is optimal and recommended for future developmental investigations such as the HBCD Study.

**Keywords:** pregnancy, tobacco, infant, birthweight, sex differences, protective factors

1. **INTRODUCTION**

While prenatal tobacco exposure (PTE) is a leading risk factor for a variety of adverse neurodevelopmental and cardiometabolic outcomes across the lifespan (Cornelius & Day, 2009; Ernst, Moolchan, & Robinson, 2001; Horta et al., 2011; Wakschlag, Pickett, Cook Jr, Benowitz, & Leventhal, 2002) underlying mechanisms remain unclear. A major challenge concerns the number and complexity of factors that confound exposure-outcome associations (Knopik, 2009). Large epidemiologic survey studies are well-powered to address numerous confounders, including familial confounders (D'Onofrio, Van Hulle, Goodnight, Rathouz, & Lahey, 2012; Kuja-Halkola, D'Onofrio, Iliadou, Langstrom, & Lichtenstein, 2010; Skoglund, Chen, D'Onofrio, Lichtenstein, & Larsson, 2014) but can lack the sensitivity in risk detection afforded by optimal exposure measures contained in smaller cohort studies (Estabrook et al., 2016b; Massey et al., 2020).

Importantly, smoking during pregnancy is known to vary substantially—both between-individuals and within-individuals (Massey et al., 2011; Pickett, Rathouz, et al., 2009; Pickett, Wakschlag, Dai, & Leventhal, 2003). Within-person fluctuation in smoking and other drug use by pregnant women (Massey et al., 2011; Massey et al., 2012) necessitates thoughtful consideration of how exposure is best quantified in mechanistic studies aimed at identifying the most salient prevention targets. Substantial empirical
evidence supports the importance of characterizing patterns of exposure (i.e., intensity and timing) in developmental research (Eiden et al., 2013; Pickett, Rathouz, et al., 2009; Pickett et al., 2003; Shisler et al., 2017), but the administration of such measures is costly and cumbersome relative to documenting simply the presence or absence of exposure. Thus, delineating the added value, if any, of intensive exposure measurement is of great importance for guiding pragmatic decisions in large scale neurodevelopmental consortia (Morris et al., 2020). We addressed this core issue as part of the planning phase of the HEAlthy Brain and Child Development (HBCD) study to inform exposure measurement design for this large prenatal consortium being envisioned (Volkow, Gordon, & Freund, 2020). Specifically, we created a large, harmonized cohort of multiple observational studies with varied quality of exposure measurement. Our goal was to test how methodologic variation in the characterization of PTE affects estimates of PTE-related risk, and the detection of sex differences in this risk.

1.1 Fetal exposure versus maternal smoking behavior frameworks for characterizing PTE

The importance of measurement quality in the specificity of exposure-related developmental risk estimates is well established (Eiden et al., 2013; Eiden et al., 2015; Estabrook et al., 2016b; Gaysina et al., 2013; Knopik, Marceau, Palmer, Smith, & Heath, 2016; Shisler et al., 2017). Less studied, is how the conceptual framework for characterizing exposure could influence risk prediction. In developmental studies focused on child outcomes, PTE is conceptualized as an aspect of a child’s intrauterine environment. This conceptual framework, referred to herein, as the fetal exposure framework, provides information about the presence or absence of exposure, and in some cases, the average dose of exposure, i.e., mean cigarettes/day across pregnancy (Cornelius & Day, 2009). PTE can also be characterized with respect to the mother, or within a maternal smoking behavior framework (never smoked during
pregnancy, quit during pregnancy, smoked intermittently during pregnancy, or smoked persistently during pregnancy) (Pickett et al., 2003; Wakschlag et al., 2003). The maternal smoking behavior framework, like the fetal exposure framework, provides information about the presence or absence of PTE, but also captures known within-individual fluctuation in pregnancy smoking, in particular, efforts by many women to reduce smoking documented across quantitative (McGrath et al., 2012; Pickett, Kasza, Biesecker, Wright, & Wakschlag, 2009; Pickett, Rathouz, et al., 2009; Pickett, Wood, Adamson, DeSouza, & Wakschlag, 2008) and qualitative studies (Flemming, Graham, Heirs, Fox, & Sowden, 2013; Graham, Flemming, Fox, Heirs & Sowden, 2014).

1.2 Importance of fluctuations in smoking across pregnancy

While cigarette smoking is a common individual health risk behavior, we have previously proposed that smoking, and changes in smoking, may be more accurately conceptualized as maternal behaviors once a pregnancy is recognized (Flemming et al., 2013; Graham et al., 2014; Massey & Compton, 2012; Massey, Decety, Wisner, & Wakschlag, 2017; Massey et al., 2016; Massey & Wisner, 2018). An estimated 20 – 40% of female smokers quit soon after learning of their pregnancy (pregnancy quitters) prior to their first prenatal visit (Solomon & Quinn, 2004; Wakschlag et al., 2003). Yet this fact can be easily obscured by a dichotomous categorization of PTE as exposed or not exposed (Duko, Ayano, Pereira, Betts, & Alati, 2020; Wang, Hu, Chen, Xue, & Du, 2019). Moreover, our earlier work that examined differences in child outcomes as a function of common patterns of PTE suggests that the extent to which a chosen framework accounts for smoking cessation in early pregnancy could critically affect estimates of PTE-risk (Hutchinson, Pickett, Green, & Wakschlag, 2010; Wakschlag et al., 2011).
Specifically, our earlier study of over 18,000 mother-child dyads categorized for PTE using a maternal behavior framework (never smoked during pregnancy, quit in early pregnancy, smoked intermittently during pregnancy or persistently throughout pregnancy) found that quitting smoking was associated with protective processes beyond simply the relative absence of risk (i.e., less exposure). Infants of pregnancy quitters had easier temperaments than infants of persistent smokers, but also the infants of never smokers (Pickett et al., 2008). At age 3, daughters of pregnancy quitters exhibited fewer behavioral problems relative to daughters of both persistent smokers and never smokers (Hutchinson et al., 2010). Next, in a different cohort, we examined differences in parenting behavior as a hypothesized mechanism for protective effects associated with smoking cessation during pregnancy. As expected, we found that biologically verified pregnancy quitters exhibited more responsive interactions with their children when observed in their homes five years later (Massey, Mroczek, Burns, et al., 2018).

Others have also documented unusually favorable outcomes in prenatally exposed children whose mothers had quit smoking in early pregnancy. Robinson et al. (N=2900) reported better behavioral outcomes in the children of mothers who quit smoking in early pregnancy when compared to the children of persistent pregnancy smokers, and again, compared to women who had never smoked (Robinson et al., 2010). These intriguing findings about children whose mothers quit smoking in early pregnancy support the conceptualization of PTE within a maternal behavior framework. Specifically, persistent pregnancy smoking could be viewed within a broader context of maternal problem behaviors (Kodl & Wakschlag, 2004; McGrath et al., 2012; Wakschlag et al., 2003), while maternal smoking cessation during pregnancy could be viewed as a caregiving behavior (Massey et al., 2015; Massey & Compton, 2012; Massey et al., 2012). In fact, the maternal smoking behavior framework could index between-individual differences in parenting
behavior, especially maternal responsiveness shown to buffer PTE-related effects on problem behavior (Massey, Mroczek, Burns, et al., 2018; Wakschlag & Hans, 2002). Thus, categorization of PTE within a broader maternal behavior framework is particularly relevant for understanding underlying exposure-outcome mechanisms.

1.3 *Sex differences in environmental susceptibility*

Growing evidence supports sex differences in early life environmental susceptibility, with males being more vulnerable to intrauterine adversity, but underlying mechanisms are largely unknown (DiPietro & Voegtline, 2017). For example, relative to girls, boys appear to be more vulnerable to PTE-related impairments in stress reactivity during infancy (Eiden et al., 2015) and PTE-related impairment in self-regulation at age 5 (Wiebe, Fang, Johnson, James, & Espy, 2014) but also benefit more from the buffering effect of maternal responsiveness on PTE-related problem behavior (Wakschlag & Hans, 2002). Elucidation of mechanisms linking prenatal exposure with adverse neurodevelopmental outcomes requires thoughtful study designs that capture known between- and within-individual variability in maternal smoking during pregnancy and are adequately powered to examine potential moderators of PTE-related risk, including, but not limited to infant sex.

1.4 *Aims and hypotheses*

To balance data quality with power, in this study, we employed a pooled, harmonized analytic dataset comprised of seven independent longitudinal developmental cohorts. We examined how one particular aspect of study design—characterization of PTE—influences the detection of PTE-related risk, as represented by decrements in infant birthweight. We secondarily explored how characterization of PTE influences the detection of sex differences in PTE-related susceptibility. Specific aims were to:
(1) Compare the estimated effect of PTE on birthweight when exposure is characterized based on a *fetal exposure framework* (exposed vs. not exposed) versus a *maternal smoking behavior framework* (never smoked, quit in during first trimester, continued smoking either intermittently or persistently);

(2) Explore the extent to which sex differences in the PTE-birthweight association are detected using these two frameworks.

We hypothesized that:

(1) Exposed infants would have a lower mean birthweight compared to unexposed infants;

(2) Birthweight of the infants of smokers who quit by the end of the first trimester (quitters) would not be different from the birthweight of infants of women who did not smoke during pregnancy (Veisani, Jenabi, Delpisheh, & Khazaei, 2019; Xaverius, O'Reilly, Li, Flick, & Arnold, 2019);

(3) Exclusion of the infants of quitters from the analysis would strengthen the PTE-related effects on birthweight;

(4) Sex differences in PTE-related susceptibility would be more apparent when PTE is characterized using the maternal smoking behavior framework.

### 2. MATERIALS AND METHODS

#### 2.1 Participants

The analytic sample was comprised of a pooled, harmonized cohort of seven neurodevelopmental studies derived from the Brains Begin Before Birth (B4) consortium of Northwestern University and Washington University in St. Louis as part of the HBCD planning phase (Morris et al., 2020). The seven cohorts include three studies specifically designed to examine PTE effects (e.g.,
oversampling for maternal smoking, intensive prospective measurement): the Family Health and Development Study (FHDP), the East Boston Family Study (EBFS), and the Midwest Infant Developmental Study (MIDS); and four studies focused on early life neurodevelopment but also included assessment of PTE: the Multidimensional Assessment of Preschoolers Study (MAPS), the When to Worry Study (W2W), the Early Life Adversity, Biological Embedding, and Risk for Developmental Precursors of Mental Disorders Study (eLABLE), and the Preschool Depression Study (PDS). Details of individual studies have been described in prior publications (Hanrahan et al., 2012; Pickett, Rathouz, et al., 2009; Tager, Ngo, & Hanrahan, 1995; Wakschlag, Leventhal, Pine, Pickett, & Carter, 2006; Wiebe et al., 2014) and additionally outlined in Supplementary Table 1. All study procedures described were approved by respective local Institutional Review Boards prior to conduct. Mothers provided informed consent for their own participation and their child’s participation in all cohorts.

2.2 Data Harmonization

Data harmonization is a systematic process in which data from multiple studies are combined to create a single analytical cohort. Strengths of this approach include increased sample size to examine less prevalent exposure and/or outcome variables and increased external validity via the diversification of sample demographics (Fortier et al., 2017). Harmonization requires the combination of study-specific variables into a single variable that can be uniformly described and analyzed across the harmonized cohort. A limitation of data harmonization is that variables must be combined to match the classification scheme for the study that has the crudest measurement. Thus, details that collected in some but not all studies are lost. To address this, sensitivity analyses can be run on sub-analysis cohorts containing only these cohorts.
Derivation of the analytic sample is illustrated in Figure 1. The pooled analytic sample of N=2,323 was derived from mother-child dyads from the seven cohorts with complete exposure, outcome, and covariate data. The pooled total sample size was 3,171 participants. There were 524 participants excluded for missing data on PTE, 126 excluded for missing data on birthweight, and 198 excluded for missing data on covariates. Participants who were excluded were more likely to be non-Hispanic white race/ethnicity (53.7% excluded versus 47.9% included), but there were no systematic differences in infant sex (50.4% male in excluded versus 53.8% males in included) or maternal age (mean=27.7 (5.8) excluded versus mean=27.3 (5.0) included).

2.3 Harmonized measures of PTE

Of the seven cohorts harmonized, 4 studies measured PTE prospectively while 3 studies assessed PTE retrospectively. Details on methods used in each study (including assessments of frequency and duration of use) can be found in Supplementary Table 1. Dichotomous, continuous, and categorical prenatal tobacco exposure variables created and harmonized across the seven studies to represent the fetal exposure and maternal smoking behavior conceptual frameworks compared are shown in Table 1.

Smoking patterns were determined using trimester-specific information: quitters were defined as individuals who smoked only during the first trimester, consistent with literature on spontaneous quitters who quit soon after recognizing the pregnancy (Solomon & Quinn, 2004); persistent smokers were defined as individuals who smoked in all three trimesters; and intermittent smokers were defined as those with all other smoking patterns during the pregnancy. In sub analyses, specific patterns of smoking during pregnancy were compared against one another in the following combinations: quitters versus non-quitters (those who smoked persistently or intermittently); quitters versus women who never smoked; persistent smokers versus non-persistent smokers (those who had quit or
smoked intermittently). Between-study differences in how these variables were derived, then harmonized, by study, are outlined in Supplementary Table 2.

2.4 Birthweight

The primary outcome of interest was a continuous measure of birthweight in grams. All studies collected information on birthweight. In the two studies that reported birthweight in pounds and ounces (MAPS, W2W), and we used a conversion factor of 28.3495 grams per ounce to harmonize these data.

2.5 Covariates

The following covariates were selected due to their known association with either PTE (maternal age, educational attainment (Higgins et al., 2009; Zheng et al., 2016)) or birthweight (race and ethnicity, infant sex, length of gestation (Dougherty & Jones, 1982)) and availability in the harmonized dataset. Household income and maternal height were considered as covariates but ultimately excluded due to extensive missing data in one or more of the cohorts. Age in years during the pregnancy was reported by mothers directly in 6 of the seven cohorts; in MDS P, it was calculated using data on mothers’ date of birth and the date of the interview. Maternal educational attainment was collected in different ways across studies, for example, as the highest degree obtained in some cases, or in years of education completed in others. To harmonize, we categorized educational attainment as follows: less than high school diploma (less than 12 years); high school diploma and/or some college (at least 12 but less than 16 years); bachelor’s degree (16 years); and graduate degree (greater than 16 years). Maternal race and ethnicity were collected using non-overlapping categories across different studies, limiting harmonization. Since minority race and ethnicity can be markers of confounding socioeconomic
status, we created a dichotomous variable reflecting participants’ identification with any racial or ethnic minority group, versus as non-Hispanic white. Infant sex was collected dichotomously as male or female in all studies. Lastly, we included length of gestation, harmonized as number of weeks.

2.6 Statistical Analysis

After checking the distribution of all variables for normality, we used linear regression to estimate PTE-birthweight associations separately, using the fetal exposure and maternal smoking behavior characterization frameworks, adjusting for maternal age, education, race/ethnicity, length of gestation, infant sex, and original study cohort. To examine whether there were any sex-specific differences in PTE-associations, we performed a sensitivity analysis in which we created and tested a multiplicative interaction term for sex and PTE and reported the linear regression models stratified by sex. We also conducted sensitivity analyses in which quitters were excluded from the fetal exposure framework, again using linear regression. Statistical significance was set a priori at \( \alpha=0.05 \). All analyses were conducted using the SAS statistical software package, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. RESULTS

3.1 Descriptive analyses (Table 1)

Demographic characteristics of the pooled sample (\( N=2,323 \)) and subsamples characterized by exposure are shown in Table 1. Under both fetal and maternal characterization frameworks, PTE was associated with younger maternal age (26.1 ± 5.3 years vs. 28.4 ± 5.8 years, \( p < .001 \)), a lower likelihood of having completed high school (12.0% vs. 8.2%, \( p<.001 \)); and identification as a non-
Hispanic white (73.7% vs. 44.9%, \( p < .001 \)). Differences in birthweight between exposed and unexposed pregnancies were not observed in these descriptive analyses (3328 ± 567 vs. 3313 ± 559, \( p = 0.54 \)).

3.2 Differential effects of PTE on birthweight by framework, adjusted for confounders (Table 2)

Estimated marginal mean birthweights categorized using fetal exposure status (top) and maternal smoking pattern frameworks (bottom) from linear regression models controlling for maternal age, education, race and ethnicity, length of gestation, infant sex, and cohort are shown in Table 2. When categorized dichotomously by fetal exposure status, any PTE was associated with a 125.2-g decrement in infant birthweight (95% C.I. -173.7 to -76.6). When categorized based on maternal smoking patterns, however, PTE showed more nuanced effects. Exposed infants did not differ in birth weight from unexposed infants if their mothers smoked only in the first trimester. Thus, the failure to quit smoking in the first trimester, rather than PTE pers se, was associated with decreased birth weight. Infants born to intermittent [95% C.I. (-421.9 to -154.9)] and persistent pregnancy smokers [95% C.I. (-269.9 to -142.1)], were lighter than infants of quitters by 288.4 and 206.0 grams, respectively.

3.3 Differential impact of framework on PTE-related effects on birthweight

Unstandardized coefficients from linear regression models used to estimate PTE-related effects across different characterization frameworks are shown in Table 3. Any PTE was associated with a 125.2 g decrement in infant birthweight (SE=24.8, \( p < .001 \), \( R^2 = 0.31 \)), with each cigarette/day of mean exposure across gestation associated with a 14.1-gram decrement in birthweight (SE =-2.4, \( p < .001 \)). Characterization of PTE via the maternal smoking behavior framework (Table 3, bottom) indicated that, among women who smoked at any time during pregnancy, quitting was
associated with a 167.8-gram increase in birth weight (SE=37.4, \( p < .001, R^2 = .29 \)). Relative to non-persistent smoking, persistent smoking was associated with a 135.8-gram decrement in birth weight (SE=37.5, \( p < .001, R^2 = .28 \)).

3.4 Sex differences in PTE-related effects on birthweight (Table 3)

There were no statistically significant differences by sex in associations between birthweight and any PTE (\( p = 0.17 \)), mean daily cigarettes smoked (\( p = 0.53 \)), quitting smoking (versus not quitting) (\( p = 0.07 \)), and persistent smoking (versus non-persistent smoking) (\( p = 0.11 \)). However, when samples were stratified by infant sex, there were qualitative differences; associations between any PTE and birthweight, quitting smoking and birthweight, and persistent smoking and birthweight were stronger among males.

3.5 Estimates of PTE-related effects with quitters included vs. excluded from analyses

In Table 4, PTE-related effects on birthweight, expressed in terms of the difference in estimated marginal mean birthweight from unexposed infants, are shown. When infants of mothers who quit smoking were excluded, PTE was associated with a -221.8 g difference in birthweight \([95\% \text{ C.I. (161.7 to 282.0)}]\). The PTE-related difference in birthweight when quitters were included was 125.2 g (SE=24.8, \( p < .001, R^2 = .31 \)).

4. DISCUSSION

Recent advances in neurodevelopmental science enable the characterization of the developmental origins of risk and resilience pathways with increasing specificity and earlier in the developmental sequence (Camerota & Willoughby; Wakschlag et al., 2018; Wakschlag et al., 2019; Wakschlag et al., 2020). The complexity of potential mechanisms linking PTE with the adverse child outcomes (Knopik, 2009) requires data-rich samples with more extensive PTE assessments than single item questions typically
available in large epidemiologic survey samples (Estabrook et al., 2016a; Shisler et al., 2017). Integration of seven developmental cohorts allowed us to increase our sample size to detect more modest exposure-outcome associations while retaining nuances afforded by more extensive PTE assessments. Further, combining samples enabled the inclusion of greater geographic, socioeconomic, and racial/ethnic diversity than is typically possible from a single cohort, thereby increasing the generalizability of our findings. Our results illustrate how optimal modeling of prenatal exposure to detect neurodevelopmental effects requires a data science approach that moves beyond the conventional risk orientation (i.e., maternal smoking during pregnancy) to a more nuanced characterization that considers protective processes, especially, quitting smoking in early pregnancy applicable to a substantial proportion of tobacco-exposed pregnancies (Morris et al., 2020; Solomon & Quinn, 2004).

Our results are strikingly consistent with prior characterizations of between-individual variability in PTE and birth weight (Cornelius & Day, 2009; Vardavas et al., 2010). The similarity between the 14.1-gram decrement in birth weight associated with each mean cigarette per day smoked during pregnancy estimated from the current study and the 12.2-gram decrement estimated from an integrated analysis of three different prenatal exposure cohorts (Massey, Mroczek, Reiss, et al., 2018) supports the generalizability of current findings. Prior studies on the extent to which birthweight mediates PTE-related risk for psychopathology also underscore the importance of PTE characterization. Birthweight was found to mediate PTE-related effects on psychiatric symptoms (N=6,039) when PTE was defined dichotomously as a mean of 10 or more cigarettes/day across pregnancy (Talati, Wickramaratne, Wesselhoeft, & Weissman, 2017), but not when PTE was defined as 6 cigarettes/day (N=6,039)(Brannigan, Healy, Cannon, Leacy, & Clarke, 2020).
Yet, this study extends knowledge by comparing estimates of PTE effects on birthweight as a function of divergent conceptual frameworks—fetal exposure vs. maternal smoking behavior.

4.1 Importance of between- and within-individual variability in PTE

As hypothesized, the latter maternal smoking behavior framework, which captures both between- and within-individual fluctuation in pregnancy smoking, revealed nuances in PTE-birthweight effects not detectable via the conventional fetal exposure characterization framework. This is significant because while infants of mothers who quit smoking in early pregnancy are prenatally exposed, and typically categorized as such, they did not differ in birthweight from unexposed infants (Table 2). Indeed, estimates of PTE-related effects on birthweight were attenuated when quitters were included. Thus, prior findings of studies examining PTE-related outcomes may be influenced by how “smoking during pregnancy” was defined, both by investigators and by participating mothers alike. Specifically, if smoking during pregnancy was defined/interpreted as smoking after the pregnancy was recognized, then infants of quitters would be categorized as unexposed. If smoking during pregnancy is defined/interpreted as smoking between the estimated date of conception and delivery, then the infants of quitters would be defined as exposed. Our findings indicate that categorization of infants of quitters as exposed leads to an underestimation of PTE effects on birth weight.

Indeed, Suzuki et al., found that quitting smoking in early pregnancy negated the impact of PTE on risk for low birthweight, small for gestational age, and overweight at age 3, all defined dichotomously (Suzuki et al., 2014). Other studies have found quitting smoking after recognition of the pregnancy to be associated with normal or increased fetal growth not accounted for by body mass index, when compared to never smoking (Abel, 1980; Macarthur & Knox, 1988).
Summarily, a potential source of error not previously considered concerns the failure to account for the protective effect of quitting smoking on PTE-related growth. This is startling given the preponderance of existing studies that have characterized PTE dichotomously (Shisler et al., 2017) which threatens to obscure the categorization of quitters (Marufu, Ahankari, Coleman, & Lewis, 2015).

4.2 Patterns of maternal smoking vs. PTE for risk prediction

In light of the robust association between normal variation in birthweight and a range of offspring neurodevelopmental and other health outcomes, results indicate that common patterns of pregnancy smoking, rather than pregnancy smoking per se, constitute more sensitive markers of developmental risk. Specifically, in contrast to the estimated -125 g difference in birthweight associated with any PTE, characterized dichotomously, intermittent smoking, persistent smoking, and the failure to quit smoking in the first trimester were associated with -288-gram, -206-g, and -168-gram differences in birthweight, respectively (Table 3).

Enhanced risk prediction observed using the maternal smoking behavior framework for characterizing PTE is not surprising. Women who quit smoking after they learn they are pregnant differ from women who do not in ways that could influence other health behaviors during pregnancy (Massey et al., 2015; Massey & Compton, 2012; Massey et al., 2011; Massey et al., 2012) and ways they relate to their children after delivery (Massey, Mroczek, Burns, et al., 2018; Massey et al., 2016). Moreover, smokers’ perceptions of, and concerns for the well-being of others, and the fetus, appear to buffer smoking related processes once the pregnancy is recognized (Massey et al., In review). Comparison of these characterization frameworks for predicting internalizing and externalizing symptoms previously linked to PTE is strongly recommended to fully elucidate the implications of PTE characterization.
4.3 Sex differences in quitting-related impact

Our prior studies of PTE effects on birthweight (Massey, Mroczek, Reiss, et al., 2018) and self-regulation at 6 months (Wiebe et al., 2014) did not show sex differences in PTE-related risk. These prior studies, however, characterized PTE using the more commonly used fetal exposure framework, as mean cigarettes/day smoked during pregnancy. Our current integrated sample was uniquely powered to stratify analyses by specific patterns of maternal smoking. Using this approach, we found that male infants may be more sensitive to both the detrimental effect of persistent smoking on birth weight and also the protective effect of quitting smoking on birth weight (Table 4). However, as the PTE x sex interaction terms only showed trend level significance, application of our modeling approach to data from the larger HBCD consortium is strongly recommended to clarify the role of sex in PTE-related vulnerability.

4.4 Limitations

Results should be interpreted in the context of a number of limitations. First, quitting smoking during pregnancy was defined as having smoked during the first trimester but not during the second or third trimesters. However, we cannot rule out the possibility that timing of PTE (which trimester), rather than maternal smoking pattern, could have accounted for the lack of PTE effect on birthweight in infants of pregnancy quitters. Next, lack of PTE biomarker data in many of the included studies restricted our modeling to data by maternal report. The extent to which this affected accuracy of estimates is unknown. For example, our prior work in EBFS which contains rich biomarker and maternal report measures did not support an added value of biomarkers for quantifying exposure effects (Pickett, Rathouz, et al., 2009). Yet, in a different within-family design sample, integration of biomarkers with maternal report
using our previously described “best estimate” algorithm (Pickett, Rathouz, et al., 2009; Wakschlag et al., 2011) did add incremental utility to risk prediction (Estabrook et al., 2016b). Clearly, these diverse modeling strategies should be explored for use in consortia like HBCD since both types of exposure indicators are likely to be available.

Third, our modeling focused solely on PTE. The extent to which our findings apply across the range of substances commonly used during pregnancy should be examined since use of more than one substance is common (Massey, Mroczek, Reiss, et al., 2018). Fourth, infant weight at birth is a single, albeit robust, marker of fetal growth and of PTE-related effects on brain development. Adjustment of birthweight by maternal height, second-hand smoke exposure, and consideration of other birth outcomes such as Apgar scores, head circumference, and birth complications would have been optimal for providing a broader view of PTE-related effects. Finally, the well-established complexity of processes that confound the PTE-birthweight link necessitates a range of methodologic approaches to identify the most salient targets for prevention (Knopik, 2009). Our prior work across numerous developmental exposure cohorts indicates that smoking during pregnancy, and smoking cessation during pregnancy, are linked to specific maternal phenotypes that also influence parenting (Massey et al., 2015; Massey & Compton, 2012; Massey et al., 2011; Massey, Mroczek, Burns, et al., 2018; Massey et al., 2017; Massey et al., 2016). Thus, in addition to the modeling approaches used in this study, there is a great need for genetically informed designs that separate patterns of exposure from maternal processes with which they are associated (Harold, Leve, & Sellers, 2017). For example, the parent offspring adoption design separates exposure from maternal characteristics associated with exposure since children are raised by biologically-unrelated parents (Leve et al., 2019).

4.5 Conclusions
Due to the complexity of large national consortia such as the HBCD, methodologic decisions too often drift towards convention (i.e., the way things have always been done) rather than being grounded in solid empirical evidence. Within this context, we embarked on this modeling endeavor with the goal of identifying optimal approaches in the detection of exposure effects. Our results support the characterization of patterns of maternal smoking (and other drug use) during pregnancy, when possible, rather than conventional dichotomous indicators of exposure, as a best practices recommendation for the planned HBCD study. Application of our modeling approach to the detection of exposure effects for other drugs is recommended.

Furthermore, our prior work supports the presence of an early protective pathway associated with maternal smoking cessation during pregnancy, observable in infants (Pickett et al., 2008), toddlers (Hutchinson et al., 2010), and preschoolers (Massey, Mroczek, Burns, et al., 2018). The current study indicates this early protective pathway is observable even earlier at the time of delivery. Beyond the added value of characterizing patterns of maternal smoking and substance use during pregnancy for mechanistic studies, lack of a significant effect of maternal smoking during pregnancy on birthweight when smoking is suspended by the end of the first trimester underscores the importance of early prenatal intervention on smoking. Application of the described maternal smoking behavior framework of exposure characterization to studies that examine child outcomes later in the developmental sequence are recommended as the next step.

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**Conflicts of Interest**

Authors have no conflicts of interest to disclose.

**Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**References**


Camerota, M., & Willoughby, M. T. Applying Interdisciplinary Frameworks to Study Prenatal Influences on Child Development. *Child Development Perspectives.*


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Figure 1. Derivation of the analytic sample (N=2323) from seven original cohorts
Table 1. Descriptive characteristics by prenatal tobacco exposure (PTE) characterized by fetal exposure and maternal smoking behavior frameworks

<table>
<thead>
<tr>
<th></th>
<th>Fetal exposure framework</th>
<th>Maternal smoking behavior framework</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No exposure (ref.) n=1616</td>
<td>Any exposure (ref.) n=707</td>
<td>Did not smoke at any time during pregnancy (ref.) n=1598</td>
<td>Quit smoking n=370</td>
<td>Smoked Intermittently n=51</td>
<td>Smoked Persistently n=304</td>
<td>Total N=2323</td>
<td></td>
</tr>
<tr>
<td>% within framework</td>
<td>69.6%</td>
<td>30.4%</td>
<td>68.8%</td>
<td>69.9%</td>
<td>2.2%</td>
<td>13.1%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>28.4 (5.8)</td>
<td>26.1 (5.3)*</td>
<td>28.4 (5.8)</td>
<td>53.3 (5.5)*</td>
<td>26.7 (5.3)*</td>
<td>26.2 (5.5)</td>
<td>27.7 (5.8)</td>
<td></td>
</tr>
<tr>
<td>&lt;High school education</td>
<td>133 (8.2)</td>
<td>85 (12.0)*</td>
<td>122 (8.1)</td>
<td>40 (10.8)*</td>
<td>6 (11.8)*</td>
<td>39 (12.8)*</td>
<td>218 (9.4)</td>
<td></td>
</tr>
<tr>
<td>High school/some college</td>
<td>923 (57.1)</td>
<td>572 (80.9)</td>
<td>301 (81.4)</td>
<td>38 (74.5)</td>
<td>250 (82.2)</td>
<td>251 (82.2)</td>
<td>1495 (64.4)</td>
<td></td>
</tr>
<tr>
<td>Bachelor’s Degree</td>
<td>311 (19.3)</td>
<td>40 (5.7)</td>
<td>312 (19.5)</td>
<td>20 (5.4)</td>
<td>5 (9.8)</td>
<td>14 (4.6)</td>
<td>351 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Graduate Degree</td>
<td>249 (15.4)</td>
<td>10 (1.4)</td>
<td>247 (15.5)</td>
<td>9 (2.4)</td>
<td>2 (3.9)</td>
<td>1 (0.3)</td>
<td>259 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>726 (44.9)</td>
<td>521 (73.2)*</td>
<td>721 (45.1)</td>
<td>260 (70.3)*</td>
<td>25 (49.0)</td>
<td>241 (79.3)*</td>
<td>1247 (53.7)</td>
<td></td>
</tr>
<tr>
<td>Male infant</td>
<td>815 (50.4)</td>
<td>355 (50.2)</td>
<td>808 (50.6)</td>
<td>178 (48.1)</td>
<td>25 (49.0)</td>
<td>159 (52.3)</td>
<td>1170 (50.4)</td>
<td></td>
</tr>
<tr>
<td>Length, gestation (weeks)</td>
<td>38.5 (2.3)</td>
<td>38.5 (2.1)</td>
<td>38.5 (2.3)</td>
<td>38.4 (2.2)</td>
<td>38.3 (2.3)</td>
<td>38.5 (2.1)</td>
<td>38.5 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Birthweight (grams)</td>
<td>3328 (567)</td>
<td>3313 (559)</td>
<td>3332 (566)</td>
<td>3388 (574)</td>
<td>3014 (598)*</td>
<td>3255 (516)</td>
<td>3323 (564)</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates a statistically significant difference (p < 0.05) relative to reference category—either “not-exposed” in the fetal exposure framework or “pregnancy non-smokers” in the maternal smoking behavior framework (exposed or non-smokers, respectively).

Table 2. LEFT: Mean s by PTE, characterized by the fetal exposure (TOP) and maternal smoking behavior (BOTTOM) conceptual frameworks; RIGHT: Differences in birthweight from reference category (i.e., not exposed (fetal exposure framework) or non-smokers (maternal smoking behavior framework).
<table>
<thead>
<tr>
<th>Fetal exposure</th>
<th>Birthweight (g)</th>
<th>Estimated marginal mean (SE)</th>
<th>95% C.I.</th>
<th>Difference from unexposed</th>
<th>95% C.I.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not exposed (ref.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3326 (16.1)</td>
<td>3294-3358</td>
<td>-125.2</td>
<td>-173.7, -76.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maternal smoking behavior</th>
<th>Birthweight (g)</th>
<th>Estimated marginal mean (SE)</th>
<th>95% C.I.</th>
<th>Difference from non-smokers</th>
<th>95% C.I.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers (ref.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quitters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3326 (16.1)</td>
<td>3294-3358</td>
<td>-125.2</td>
<td>-173.7, -76.6</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Covariates: maternal age, educational attainment, minority race/ethnicity, length of gestation, infant sex, and cohort.

Table 3. Estimates of prenatal tobacco exposure (PTE)–related effects on birthweight when using: (a) dichotomous (yes/no) versus continuous (mean cig/d) measure of PTE; and (b) fetal exposure vs. maternal smoking behavior framework for characterizing PTE; and (c) stratified by infant sex.

<table>
<thead>
<tr>
<th>Fetal exposure</th>
<th>All infants (N=2323)</th>
<th>Male infants (N=1170)</th>
<th>Female infants (N=1152)</th>
<th>interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (SE)</td>
<td>p-value</td>
<td>R²</td>
<td>B (SE)</td>
</tr>
<tr>
<td>Any PTE</td>
<td>-125.2 (24.8)</td>
<td>&lt;.001</td>
<td>0.31</td>
<td>-167.1 (36.2)</td>
</tr>
<tr>
<td>Each cig/d, mean exposure</td>
<td>-14.1 (2.4)</td>
<td>&lt;.01</td>
<td>0.28</td>
<td>-14.0 (4.3)</td>
</tr>
<tr>
<td>Maternal smoking behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quitting smoking (vs. not quitting)</td>
<td>167.7 (7.4)</td>
<td>&lt;.001</td>
<td>0.29</td>
<td>239.3 (54.4)</td>
</tr>
<tr>
<td>Persistent smoking (vs. non-persistent smoking)</td>
<td>-135.8 (37.5)</td>
<td>&lt;.001</td>
<td>0.28</td>
<td>-216.4 (54.4)</td>
</tr>
</tbody>
</table>

Covariates: maternal age, education, race/ethnicity, length of gestation, child sex, cohort

Table 4. Comparison of estimated prenatal tobacco exposure (PTE)-related effects with quitters included vs. excluded
Quitters included (N=2323)

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Not exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3201 (24.6)</td>
<td>3326 (16.1)</td>
</tr>
<tr>
<td></td>
<td>3153 - 3249</td>
<td>3294 - 3358</td>
</tr>
<tr>
<td></td>
<td>-125.2</td>
<td>-</td>
</tr>
</tbody>
</table>

Quitters excluded (N=1953)

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Not exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3116 (30.6)</td>
<td>3337 (16.6)</td>
</tr>
<tr>
<td></td>
<td>3056 - 3175</td>
<td>3305 - 3370</td>
</tr>
<tr>
<td></td>
<td>-221.8</td>
<td>-</td>
</tr>
</tbody>
</table>

Covariates: maternal age, education, race/ethnicity, length of gestation, child sex, cohort

Highlights

- Prenatal exposures are conventionally categorized dichotomously (exposed or not).
- Within-person fluctuation in prenatal use is not captured by a dichotomous measure.
- Maternal smoking cessation during pregnancy is a source of error in risk estimates.
- Boys may be more sensitive to protective effects of prenatal smoking cessation.
- Categorization of patterns of exposure is recommended for optimal risk detection.