

Impact of prenatal exposure characterization on early risk detection: Methodologic insights for the HEALthy Brain and Child Development (HBCD) study

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ARTICLE INFO

Editor: Kimberly Yolton

Keywords:

Pregnancy
Tobacco
Infant
Birthweight
Sex differences
Protective factors

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 -g difference in birthweight (95% C.I. $-173.7 - -76.6$, $p < .0001$). 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 g difference in birthweight if mothers did not [95% C.I. $(-161.7$ to $-282.0)$; $p < .001$]. Qualitative sex differences were also detected though PTE x sex interactions did not reach statistical significance. Maternal smoking cessation during

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<https://doi.org/10.1016/j.ntt.2021.107035>

Received 5 March 2021; Received in revised form 27 September 2021; Accepted 28 September 2021

Available online 1 October 2021

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pregnancy was associated with a 239.3 g increase in birthweight for male infants, and a 114.0 g 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.

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 and Day, 2009; Ernst et al., 2001; Horta et al., 2011; Wakschlag et al., 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 et al., 2012; Kuja-Halkola et al., 2010; Skoglund et al., 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 et al., 2009b; Pickett et al., 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 et al., 2009b; 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 et al., 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 et al., 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 and 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 et al., 2009a; Pickett et al., 2009b; Pickett et al., 2008) and qualitative studies (Flemming et al., 2013; Graham et al., 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 and Compton, 2012; Massey et al., 2017; Massey et al., 2016; Massey and 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 and 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 et al., 2020; Wang et al., 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 et al., 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 et al., 2018a).

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 and 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 and 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 et al., 2018a;

Wakschlag and 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 and 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 et al., 2014) but also benefit more from the buffering effect of maternal responsiveness on PTE-related problem behavior (Wakschlag and 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 et al., 2019; Xaverius et al., 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., 1992; Pickett et al., 2009b; Tager et al., 1995; Wakschlag et al., 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 Fig. 1. The pooled analytic sample of $N = 2323$ was derived from mother-child dyads from the seven cohorts with complete exposure, outcome, and covariate data. The pooled total sample size was 3171 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 (6.0) 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 and 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.

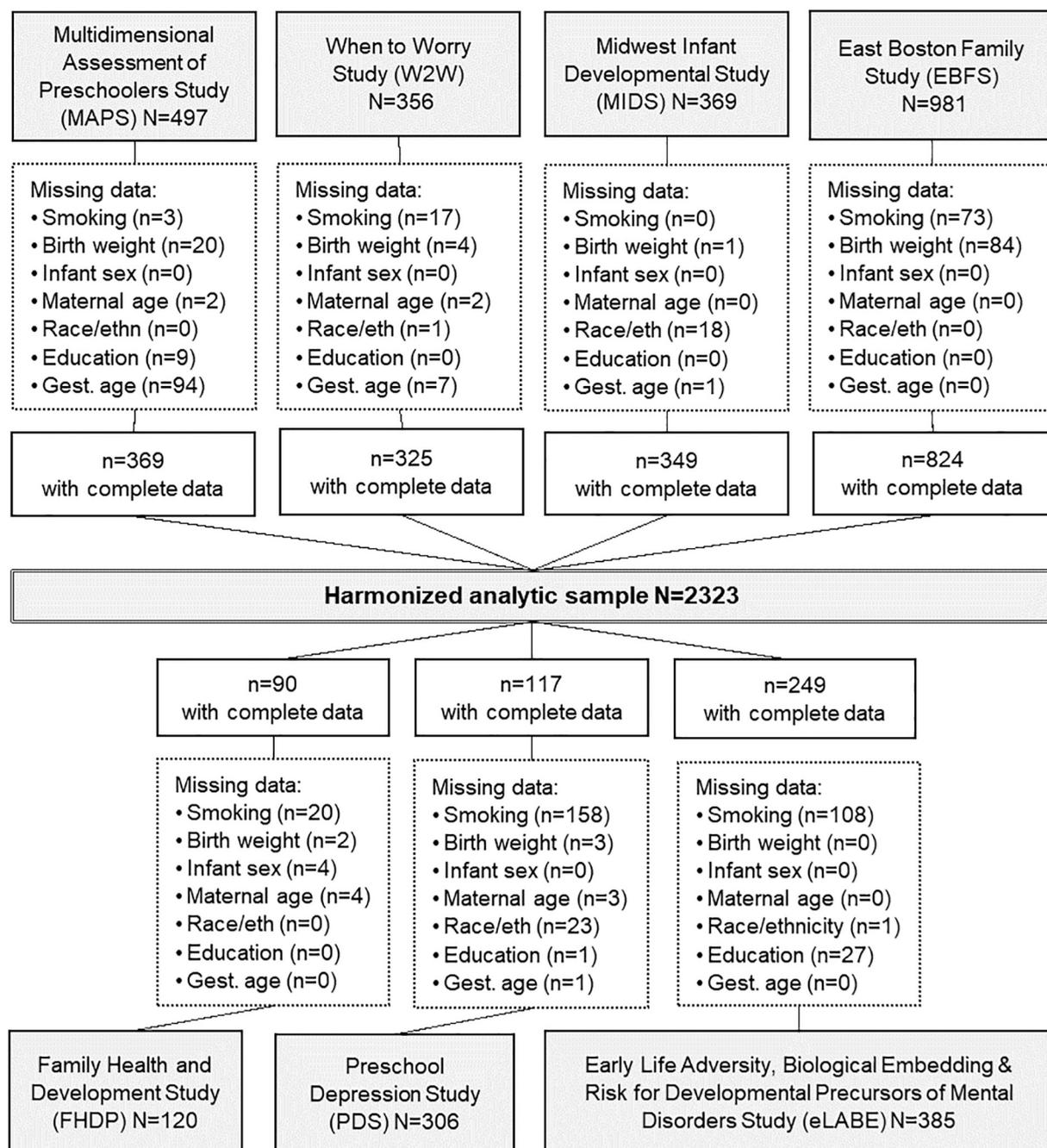


Fig. 1. Derivation of the analytic sample ($N = 2323$) from seven original cohorts.

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 g 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 and 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 MIDS-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

Table 1

Descriptive characteristics by prenatal tobacco exposure (PTE) characterized by fetal exposure and maternal smoking behavior frameworks.

	Fetal exposure framework		Maternal smoking behavior framework				Total N = 2323
	No exposure (ref.) n = 1616	Any exposure n = 707	Did not smoke at any time during pregnancy (ref.) n = 1598	Quit smoking n = 370	Did not quit n = 355		
					Smoked Intermittently n = 51	Smoked persistently n = 304	
% within framework	69.6%	30.4%	68.8%	15.9%	2.2%	13.1%	100%
Maternal age (years)	28.4 (5.8)	26.1 (5.3)*	28.4 (5.8)	26.3 (5.5)*	26.7 (5.3)*	26.2 (5.5)	27.7 (5.8)
<High school education	133 (8.2)	85 (12.0)*	133 (8.3)	40 (10.8)*	6 (11.8)*	39 (12.8)*	218 (9.4)
High school/some college	923 (57.1)	572 (80.9)	906 (56.7)	301 (81.4)	38 (74.5)	250 (82.2)	1495 (64.4)
Bachelor's Degree	311 (19.3)	40 (5.7)	312 (19.5)	20 (5.4)	5 (9.8)	14 (4.6)	351 (15.1)
Graduate Degree	249 (15.4)	10 (1.4)	247 (15.5)	9 (2.4)	2 (3.9)	1 (0.3)	259 (11.1)
Non-Hispanic white	726 (44.9)	521 (73.7)*	721 (45.1)	260 (70.3)*	25 (49.0)	241 (79.3)*	1247 (53.7)
Male infant	815 (50.4)	355 (50.2)	808 (50.6)	178 (48.1)	25 (49.0)	159 (52.3)	1170 (50.4)
Length, gestation (weeks)	38.5 (2.3)	38.5 (2.1)	38.5 (2.3)	38.4 (2.2)	38.3 (2.3)	38.5 (2.1)	38.5 (2.3)
Birthweight (grams)	3328 (567)	3313 (559)	3332 (566)	3388 (574)	3014 (598)*	3255 (516)	3323 (564)

* Indicates a statistically significant difference ($p < .05$) 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),

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 ($N = 2323$) 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 , $p = .54$).

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,

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)).

Fetal exposure	Birthweight (g) Estimated marginal mean (SE)	95% C.I.	Difference from unexposed	95% C.I.	p
Not exposed (ref.)	3326 (16.1)	3294–3358	–		
Exposed	3201 (24.6)	3153–3249	–125.2	–173.7, –76.6	<0.001
Maternal smoking behavior	Birthweight (g) Estimated marginal mean (SE)	95% C.I.	Difference from non-smokers	95% C.I.	p
Non-smokers (ref.)	3328 (16.0)	3297–3360	–		
Quitters	3297 (30.1)	3239–3357	–30.6	–88.7, 27.4	0.30
Intermittent smokers	3040 (67.6)	2907–3173	–288.4	–421.9, –154.9	<0.001
Persistent smokers	3122 (32.5)	3059–3186	–206.0	–269.9, –142.1	<0.001

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

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 per 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 g, 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-g 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-g increase in birth weight (SE = 37.4, $p < .001$, $R^2 = 0.29$). Relative to non-persistent smoking, persistent smoking was associated with a 135.8-g decrement in birth weight (SE = 37.5, $p < .001$, $R^2 = 0.28$).

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 ($p = .17$), mean daily cigarettes smoked ($p = .53$), quitting smoking (versus not quitting) ($p = .07$), and persistent smoking (versus non-persistent smoking) ($p = .11$). 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% C.I. (161.7 to 282.0)]. The PTE-related difference in birthweight when quitters were included was 125.2 g (SE = 24.8, $p < .001$, $R^2 = 0.31$).

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., 2021). 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

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.

	All infants (N = 2323)			Male infants (N = 1170)			Female infants (N = 1152)			interaction p-value
	B (SE)	p-value	R ²	B (SE)	p-value	R ²	B (SE)	p-value	R ²	
<i>Fetal exposure</i>										
Any PTE	-125.2 (24.8)	<0.001	0.31	-167.1 (36.2)	<0.001	0.28	-86.3 (33.9)	0.01	0.33	0.17
Each cig/d, mean exposure	-14.1 (2.4)	<0.001	0.28	-14.0 (4.3)	0.001	0.27	-14.3 (4.0)	<0.001	0.30	0.53
<i>Maternal smoking behavior</i>										
Quitting smoking (vs. not quitting)	167.7 (37.4)	<0.001	0.29	239.3 (54.4)	<0.001	0.30	114.0 (52.4)	0.03	0.31	0.07
Persistent smoking (vs. non-persistent smoking)	-135.8 (37.5)	<0.001	0.28	-216.4 (54.4)	<0.001	0.29	-70.7 (52.7)	0.18	0.30	0.11

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.

	Birthweight estimated marginal mean (SE)	95% C.I.	Difference from not exposed	95% C.I.	p-value
<i>Quitters included (N = 2323)</i>					
Exposed	3201 (24.6)	3153–3249	-125.2	-76.6 to -173.7	<0.001
Not exposed	3326 (16.1)	3294–3358	-		
<i>Quitters excluded (N = 1953)</i>					
Exposed	3116 (30.6)	3056–3175	-221.8	-161.7 to -282.0	<0.001
Not exposed	3337 (16.6)	3305–3370	-		

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

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 and Quinn, 2004).

Our results are strikingly consistent with prior characterizations of between-individual variability in PTE and birth weight (Cornelius and Day, 2009; Vardavas et al., 2010). The similarity between the 14.1-g decrement in birth weight associated with each mean cigarette per day smoked during pregnancy estimated from the current study and the 12.2-g decrement estimated from an integrated analysis of three different prenatal exposure cohorts (Massey et al., 2018b) 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 = 6039) when PTE was defined dichotomously as a mean of 10 or more cigarettes/day across pregnancy (Talati et al., 2017), but not when PTE was defined as 6 cigarettes/day (N = 6039)(Brannigan et al., 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 and 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 et al., 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 -g, -206 -g, and -168 -g 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 and Compton, 2012; Massey et al., 2011; Massey et al., 2012) and ways they relate to their children after delivery (Massey et al., 2018a; 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. 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 et al., 2018b) 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 et al., 2009b). Yet, in a different within-family design sample, integration of biomarkers with maternal report using our previously described “best estimate” algorithm (Pickett et al., 2009b; 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 et al., 2018b). 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 and Compton, 2012; Massey et al., 2011; Massey et al., 2018a; Massey et al., 2012; 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 et al., 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 et al., 2018a). 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.

Funding sources

This work was supported by grants K23DA037913 (Massey); R01DA050700 (Massey & Allen); K08DA000330 (Wakschlag); R01DA014661 (Espy); R01DA023653 (Espy & Wakschlag); R01DA023653-03S1 (Wakschlag); R01DA015223 (Wakschlag), R34DA050266 (Wakschlag) and R34DA050272 (Smyser & Rogers) from the National Institute on Drug Abuse (NIDA); and R01MH121877 (Wakschlag), R01MH107652 (Wakschlag) and R01MH113883 (Smyser) from the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH). The NIDA, NIMH, and NIH had no role in the study design, data collection, analysis or interpretation of the data, or the decision to submit this manuscript for publication.

Declaration of Competing Interest

Authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ntt.2021.107035>.

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