Maternal Smoking During Pregnancy and Offspring Birth Weight: A Genetically-Informed Approach Comparing Multiple Raters

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Abstract Maternal smoking during pregnancy (SDP) is a significant public health concern with adverse consequences to the health and well-being of the fetus. There is considerable debate about the best method of assessing SDP, including birth/medical records, timeline follow-back approaches, multiple reporters, and biological verification (e.g., cotinine). This is particularly salient for genetically-informed approaches where it is not always possible or practical to do a prospective study starting during the prenatal period when concurrent biological specimen samples can be collected with ease. In a sample of families (N = 173) specifically selected for sibling pairs discordant for prenatal smoking exposure, we: (1) compare rates of agreement across different types of report—maternal report of SDP, paternal report of maternal SDP, and SDP contained on birth records from the Department of Vital Statistics; (2) examine whether SDP is predictive of birth weight outcomes using our best SDP report as identified via step (1); and (3) use a sibling-comparison approach that controls for genetic and familial influences that siblings share in order to assess the effects of SDP on birth weight. Results show high agreement between reporters and support the utility of retrospective report of SDP. Further, we replicate a causal association between SDP and birth weight, wherein SDP results in reduced birth weight even when accounting for genetic and familial confounding factors via a sibling comparison approach.

Keywords Birth weight · Genetics · Sibling comparison design · Multiple reporters · Smoking during pregnancy

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Introduction

Maternal smoking during pregnancy (SDP) continues to be a major public health concern. According to the pregnancy risk assessment and monitoring system (PRAMS) and the Centers for Disease Control (CDC), 12.3 % of women in the United States report SDP (Tong et al. 2013). While there has been some decrease in prevalence of SDP during recent years, the change is non-significant (13.3 % in 2000 to 12.3 % in 2010). This is despite a large literature suggesting undesirable outcomes in children exposed to SDP and warnings encouraging women to stop smoking while pregnant. SDP is associated with multiple adverse birth related outcomes, such as preterm delivery (Castles et al. 1999; Shah and Bracken 2000), increased risk for spontaneous abortion (Castles et al. 1999), and lower birth weight (e.g., Kuja-Halkola et al. 2014; Benjamin-Garner and Stotts 2013; Marceau et al., under review). It has also been associated with prenatal ischemia-hypoxia (see Smith et al., under review), respiratory disease (Cook and Strachan 1999), cancer later in life (Doherty et al. 2009), and a host of neurodevelopmental and behavioral outcomes

(Knopik 2009; see Bidwell et al., under review and Palmer et al., under review in this special issue for reviews). Findings also suggest that there are a variety of placental complications linked to prenatal exposure to cigarette smoke (e.g., alterations to the development and function of the placenta; Einarson and Riordan 2009), which could effectively translate into a number of sequelae (e.g., intrauterine growth retardation and later behavioral problems; Huizink and Mulder 2006; Knopik 2009; Joya et al. 2014).

Due to the large literature suggesting adverse effects of SDP and research showing that SDP is correlated with a host of other maternal behaviors that could also increase risk for offspring outcomes (Agrawal et al. 2008; Knopik 2009), a handful of research groups are using genetically-informed approaches to begin to disentangle SDP effects from other genetic/familial influences. These genetically informed analyses, primarily of non-US based datasets, support a contributory effect of SDP on birth-related outcomes, such as birth weight (D'Onofrio et al. 2003; Thapar et al. 2009; Kuja-Halkola et al. 2014; Marceau et al., under review), but are more mixed when it comes to behavioral outcomes, such as criminal behavior and ADHD (D'Onofrio et al. 2010; Rice et al. 2009; Kuja-Halkola et al. 2014). Replicating these results in a US-based study purposefully designed to disentangle genetic effects from SDP influences is key.

Quality of SDP assessment: the utility of multiple reporters

An important consideration for all studies of prenatal exposures is the quality of the prenatal assessment. There is continued debate about the best method of assessing maternal SDP. These methods include birth/medical records, timeline follow-back approaches, retrospective reporting, multiple reporters, and biological verification (e.g., cotinine). It is generally well accepted that, when possible, biological verification is the ideal. However, cotinine assessment has its own challenges which can impede the direct comparison to other measures and may prove infeasible for some types of studies. For example, there is no single level of cotinine or nicotine that can be uniquely associated with a specific number of cigarettes smoked (Land et al. 2012), which makes comparisons to findings measuring number of cigarettes smoked and public health recommendations difficult. Moreover, pregnancy changes the metabolism of nicotine and thus, cotinine (Land et al. 2012; Dempsey et al. 2002), and more work is needed in order to establish how differences in drug metabolism (both of mother and fetus) can affect later outcomes. Of particular salience for population-based, epidemiological studies, including genetically-informative studies such as the one used in this report, is the feasibility of collecting cotinine prospectively. In studies that require large sample sizes or difficult-to-predict samples (e.g., where mothers choose to smoke in one pregnancy and not the other, particularly when the first pregnancy is the non-smoking pregnancy), it may not be possible or practical to collect prospective data including cotinine verification.

There are studies (e.g., Reich et al. 2003; Buka et al. 2004; Pickett et al. 2009), however, that lend support to the use of reliability of retrospective interview-based recall methods for assessing SDP. Pickett et al. (2009), for example, compared SDP data from women that was collected both prospectively (self-report and cotinine) and retrospectively (when children are in adolescence) and suggest that women's ability to recall their smoking behavior in pregnancy more than a decade after the event is generally both accurate and reliable, particularly for the second and third trimester of pregnancy. Several studies have also compared maternal recall of prenatal events and behaviors to birth or medical records (e.g., Land et al. 2012; Liu et al. 2013; Neiderhiser et al., under review) in order to assess validity of retrospective recall. In general, these studies suggest very strong agreement between medical records and maternal recall when SDP is a dichotomous yes/no indicator, yet reports still caution against using maternal report as the sole source of information (e.g., Liu et al. 2013).

Interestingly, there is a paucity of studies measuring SDP that have collected additional reporters of maternal SDP, such as paternal report of maternal smoking behaviors during pregnancy. This additional data collection can be costly and time-consuming, but it does offer another level of information that can be used to assess reliability of maternal recall. In the present report, we compare three types of SDP report: birth records, maternal retrospective self-report, and paternal retrospective report of maternal SDP in order to determine reliability of SDP assessment. We then use this information to attempt to replicate the robust association between SDP and birth weight found using both genetically-informed and non-genetically-informed samples.

The SDP-birth weight association

It is well documented that birth weight is associated with multiple outcomes later in life. These include educational achievement, cognitive abilities, job performance related outcomes (e.g., earnings), and disruptive behaviors (see Chatterji et al. 2014 for a review). For example, low birth weight and fetal growth are predictors of developmental delays and speech impairments (Chatterji et al. 2014) as

well as antisocial, oppositional, and hyperactive behaviors (Chatterji et al. 2014; Datta Gupta et al. 2013). The association between SDP and birth weight is particularly salient due to evidence that birth weight might mediate the effects of SDP on later neurobiological and behavioral outcomes (Agrawal et al. 2010). The biological processes underlying the reported associations between SDP and birth weight in humans remain largely unknown and may be due, at least in part, to teratological effects of smoke exposure, gene-environment interplay, or epigenetic modifications which affect gene expression. In addition to using multiple reporting methods to assess SDP, the present study uses a sibling-comparison approach which can begin to tease apart causal vs non-causal effects of SDP on offspring birth weight. In other words, is the effect of SDP on offspring birth weight due to the teratogenic effects of SDP (i.e., a causal SDP effect) or background familial factors (i.e., non-causal SDP effect)? While not providing information on specific mechanisms, results can offer insight into potential targets for intervention and prevention efforts (i.e., smoking cessation vs more comprehensive, whole person/whole family approaches).

Present study

For the present report, in a sample of US families specifically selected for sibling pairs discordant for prenatal smoking exposure (i.e., according to birth records, mothers smoked during one pregnancy and not during another), we (1) compare rates of agreement across birth record, retrospective maternal, and retrospective paternal reports of any SDP and quantity of SDP, (2) examine the predictive utility of birth record, maternal, and or paternal reports of SDP for child birth weight in order to begin to establish the most informative reporter(s) of SDP; and (3) use a sibling comparison approach to examine the association between SDP and offspring birth weight while controlling for genetic and familial influences that siblings share.

Method

Study design

Data for the current study were obtained from the Missouri Mothers and Their Children study (MO-MATCH), an ongoing data collection collaboration between Rhode Island Hospital/Brown University and Washington University, St. Louis MO (see Knopik et al. 2015). The Institutional Review Boards of Rhode Island Hospital, Washington University and the State of Missouri Department of Health and Senior Services approved the study. Families were identified using birth records obtained from the Missouri Department of Health and Senior Services Bureau of Health Informatics. Birth records (BR) in Missouri for birth years 1998–2005 were examined for mothers who, according to the birth record, changed smoking behavior between any two pregnancies. Over 4000 mothers were identified. In cases where more than two siblings were identified, the two siblings closest in age were chosen. After 1520 initial screening interviews to verify BR information (i.e., mom smoked during one pregnancy but not the other), only 27 % of mothers agreed via screening with the BR [the majority (57 %) reported smoking during both pregnancies, and 16 % were non-smokers for both pregnancies]. Women who disagreed with the BR were not contacted further. Mothers who consented to being a part of the study completed a diagnostic interview about their pregnancies (including life events surrounding pregnancy) along with information on their mental health status and the mental health status of their children. Fathers were also included when available. Families were excluded from the study if: (1) mothers failed to understand the elements of informed consent, (2) English was not the primary language spoken in the home, or (3) if the children had a history of head trauma, neurological disorders or uncorrected visual or auditory acuity deficits. Based on evidence (e.g., Morales-Suarez-Varela et al. 2006) suggesting that offspring of nonsmokers who used nicotine substitutes (NRT) during pregnancy are at increased risk for congenital malformations, mothers who report using nicotine substitutes in the 'nonsmoking' pregnancy were also excluded.

Sample

Formal interviews were completed with 173 families in which mom had agreed (via screening interview) with the BR that she changed her smoking behavior between two pregnancies. Mother-reported data was available on 344 pregnancies and father-reported data was available on 181 pregnancies. In order to obtain a sample in which siblings within the same family were discordant for maternal SDP, the sample was selected, using the birth record indicator of any SDP in one pregnancy but not in the other pregnancy, when youth were age 7–16 years [child 1 average age = 12.99 (standard deviation (SD) = 1.95), 53 % male; Child 2 = 10.19 (SD = 1.80), 51 % male]. The mean age of mothers and fathers at the time of interview was 39.83 years (SD = 5.62) and 44.04 years (SD = 6.34), respectively. Parents were primarily of Caucasian ancestry (96 %, n = 250; three individuals refused to provide ancestral information). See Table 1 for additional sample characteristics.

Of the 173 participating families, 94 fathers provided data. We examined possible differences between families

Table 1 Sample characteristics

	Mean	(SD)	Min	Max
Maternal age	39.83	5.62	29	54
Paternal age	44.04	6.34	33	60
Child 1 age	12.99	1.95	9	16
Child 2 age	10.19	1.80	7	14
Child age difference	2.79	1.54	1	7
	N	%		
Maternal education				
Less than HS	7	4		
HS	30	18		
1–2 years college	50	30		
3–4 years college	46	27		
More than college	29	17		
Not reported	7	4		
Paternal education				
Less than HS	9	10		
HS	19	20		
1–2 years college	14	15		
3–4 years college	17	18		
More than college	21	22		
Not reported	14	15		
Marital status				
Never married	6	4		
Married	130	77		
Separated	5	3		
Divorced	26	15		
Widowed	2	1		

where fathers did versus did not participate using Wilcoxon–Mann–Whitney tests (i.e., non-parametric analog to independent samples *t* tests) on demographic and study variables (marital status, maternal age, maternal employment status, maternal education, age difference between siblings, sex, birth weight, and the SDP severity variables described below for child 1 and 2). There were only two differences. First, mothers were slightly older in families where fathers participated than in families where fathers did not participate, $\chi^2 = 25.09$, $p < .05$. Second, families where fathers participated were more likely to have a "married" status (96 and 52 % among families with and without participating fathers, respectively), whereas families with fathers who did not participate had a higher proportion of "divorced" (2 and 32 % in families with and without participating fathers, respectively), "separated" and "widowed" mothers, $\chi^2 = 12.89$, $p < .05$. The remainder of demographic variables and all study variables did not differ for families where fathers did versus did not participate, $\chi^2 < 2.91$, $p > .05$.

Measures

Smoking during pregnancy (SDP)

Maternal report of SDP was obtained using a modified version of the Missouri Assessment of Genetics Interview for Children–Parent on Child (MAGIC-Parent on Child; Todd et al. 2003). All mothers completed the MAGIC-Parent on Child via telephone for each child in the family. Paternal report of SDP was obtained from the MAGIC-Adult on Self interview (Todd et al. 2003). All mothers and 54 % of fathers (i.e., 94 of 173 families) completed the MAGIC-Adult on Self. The computerized version of the MAGIC-Adult on Self was conducted in the presence of a trained interviewer. Parental reports provided information on maternal smoking behavior before and during each pregnancy and for the first 5 years of life for each child. The MAGIC interview was selected for this study because of high reliability and stability of maternal reporting about their pregnancies, including smoking and drinking (kappas $\sim$.60–.66 for reliability; kappa = .95 for stability) that was observed in a Missouri twin sample using the MAGIC (Todd et al. 2003; Reich et al. 2003).

The present study uses information on 'any SDP' (yes/no indicator) and 'quantity smoked' during pregnancy available from the birth records, as well as mother and father retrospective report of mothers' SDP as assessed via the MAGIC both overall, and specific to each trimester. *Any SDP* was assessed via birth record (BR-SDP), maternal report (MR-SDP), and paternal report (PR-SDP) on discrete indicators (0-no, 1-yes) of SDP across each pregnancy as a whole. Only mothers and fathers reported any SDP specific to each trimester via the MAGIC-Adult on Self and MAGIC-Parent on Child assessments. *Quantity smoked during pregnancy* was assessed via BR-SDP, MR-SDP, and PR-SDP on an ordinal scale (0 = no SDP, 1 = 21 or less, 2 = 21–99, 3 = 100 + cigarettes). Finally, only mothers and fathers reported the number of cigarettes smoked per day in each trimester (a continuous variable ranging from 0 to 98 per day across trimesters).

SDP Severity was assessed via a single severity score per child for MR-SDP based on the quantity of overall MR-SDP and MR-SDP by trimester (this variable is hereafter referred to as "child-specific" MR-SDP). The operationalization of this variable is based on the following: (1) literature suggesting different, and potentially more harmful, effects of SDP later into pregnancy (e.g., Dwyer et al. 2009; Hebel et al. 1988), and (2) attempts to be consistent

with our prior work (e.g., Knopik et al. 2005, 2009). To do this we used MR-SDP given that MR-SDP is available for every child and, relative to BR-SDP, is a more detailed assessment of SDP (i.e., quantity and timing across pregnancy) available in the dataset. The values were as follows:

1 = did not smoke during pregnancy
2 = smoked during first trimester only, 1–10 cigarettes/day
3 = smoked during first trimester only, 11–19 cigarettes/day
4 = smoked during first trimester only, 20+ cigarettes/day
5 = smoked beyond first trimester, 1–10 cigarettes/day (max of all three trimesters)
6 = smoked beyond first trimester, 11–19 cigarettes/day (max of all three trimesters)
7 = smoked beyond first trimester, 20+ cigarettes/day (max of all three trimesters)

Birth weight

Birth weight was assessed using the birth weight recorded on the birth record for each child. Birth weight was recorded in pounds and ounces, and converted into grams for analyses.

Covariates

The following covariates were used in the sibling comparison models (described below) to control for other maternal and family characteristics that potentially confound the association of SDP and birth outcomes. Birth order and prematurity were determined from interview and birth record data. Marital status, maternal age and maternal education were reported in the demographic section of the MAGIC-Adult on Self. An indication of whether or not mothers were on food stamps at the time of delivery was collected from the birth report. Finally, father's SDP (as a measure of secondhand smoke exposure) was assessed via father report on the MAGIC-Adult on Self.

Analytic strategy

Determining most informative SDP report

We first examined cross-tabulation tables to obtain information on the prevalence and percent agreements on categorical study variables for sample description (objective 1). In order to judge concordance across raters, tetrachoric correlations (for dichotomous variables) and Pearson correlations (for continuous variables) were also estimated using MPlus (Version 7, Muthén and Muthén 2012) while accounting for the fact that participants within the sample are clustered within families (i.e., MPlus computed standard errors that accounted for the non-independent nature of the observations). To demonstrate the predictive utility of the three ratings of SDP (Objective 2), we predicted child birth-weight using BR-SDP, MR-SDP, and PR-SDP in separate models using the Huber-White estimator in STATA (StataCorp. 2015) for dealing with clustered observations. The first three models estimated the independent effects of BR-SDP, MR-SDP, and PR-SDP on child birth-weight, respectively (Eq. 1).

$$\mathrm{Y_i}(\text{birth weight}) = \beta_{01} + \beta_1 \mathrm{X_i}(\text{SDP}) + \varepsilon_\mathrm{i} \quad (1)$$

where SDP is BR-SDP, MR-SDP, or PR-SDP in each of three initial models. The final model was a multiple regression analysis that tested for independent effects of BR-SDP, MR-SDP, and PR-SDP (above and beyond the influence of the others) on child birth-weight (Eq. 2).

$$\begin{aligned}\mathrm{Y_i}(\text{birth weight}) = {} & \beta_{01} + \beta_1 \mathrm{X_i}(\text{BR} - \text{SDP}) \\ & + \beta_2 \mathrm{X_i}(\text{MR} - \text{SDP}) \\ & + \beta_3 \mathrm{X_i}(\text{PR} - \text{SDP}) + \varepsilon_\mathrm{i}\end{aligned} \quad (2)$$

Within- and between-family comparisons of SDP-birth weight associations

We then examined the between and within-family associations of SDP and birth weight (Objective 3) via the following steps:

(1) An 'intercept only' model was fitted to the data. This model was used to decompose the variance in birth weight into within- and between-family variation.
(2) A series of hierarchical linear models (HLM; using PROC MIXED in SAS), following the method laid out in D'Onofrio et al. 2008 to account for non-independence of data as well as assess within- and between- family associations of MR-SDP and birth weight were then fitted to the data. Thus, each HLM included two variance parameters: the family-level variance and the individual-level or residual level variance.
    a. In **Model 1**, child-specific MR-SDP was entered as a predictor of birth weight. This model compares children whose mothers smoked (or smoked more) during pregnancy vs those whose mothers did not smoke (or smoked less).
    b. **Model 2** added in measured covariates to help statistically account for within-family confounds: the standard approach to control for differences between mothers who differ in their MR-SDP.

c. **Models 3 and 4** used slightly different variables to assess both within- and between-family associations of MR-SDP and birth weight. First, the average score for MR-SDP (across both siblings) was computed to obtain an estimate of the family-average MR-SDP for each family. Next, the family average MR-SDP was subtracted from each child-specific MR-SDP variable. Thus, if mothers smoked the exact same amount for both pregnancies, both siblings in the family would have a "child-specific relative to family average" score of zero. The sibling for whom mothers smoked, or smoked more, would have a positive score, whereas the sibling for whom mothers did not smoke, or smoked less, would have a negative score. The effect of the family average MR-SDP on birth weight assesses the between-family effect of MR-SDP on birth weight. The effect of the child-specific relative to family average MR-SDP on birth weight assesses the within-family effect of MR-SDP on birth weight. In **Model 3**, both of these scores were entered as predictors of birth weight (child-specific relative to family average at level 1 and the family average at level 2). In **Model 4**, the covariates were added. All covariates for Model 4 were centered within family. Both individual values on each covariate as well as family average values were included in the Model 4.

Results

Objective 1. Prevalence and concordance of SDP across reporters

Since participants were only selected for the study if the birth records indicated that the mother smoked during one pregnancy but not the other, birth record reports indicated SDP in 50 % of the total pregnancies. Mothers indicated SDP in 58 % ($n = 199$) of pregnancies. Fathers indicated SDP in 52 % ($n = 94$) of pregnancies. Across all pregnancies, the percent agreements for mothers' SDP behavior were 74 % for MR-SDP and PR-SDP, 80 % for MR-SDP and BR-SDP, and 74 % for PR-SDP and BR-SDP. Findings indicating concordance across raters (e.g., correlations and χ^2 estimates) are presented in Table 2. BR-SDP, MR-SDP, and PR-SDP were highly correlated for any SDP ($r = .70$–$.83$, $\chi^2 > 41.94$, p's $< .001$) and the ordinal overall quantity of SDP ($r = .64$–$.80$, $\chi^2 > 41.79$, p's $< .001$). MR-SDP and PR-SDP were highly correlated within each trimester for any SDP ($r = .69$–$.79$, $\chi^2 > 41.49$, p's $< .001$) and moderately correlated within each trimester for the number of cigarettes mothers smoked in each trimester ($r = .41$–$.61$, p's $< .001$). All effects were of large size (Kotrlik et al. 2011; see Table 2). BR-SDP assessment did not include a breakdown of smoking behavior on a trimester-by-trimester basis.

Concordance of change in SDP status across pregnancies

Because of the sampling strategy, birth records necessarily indicated *change* in SDP status across pregnancies within the same family. However, of the 171 mothers who provided smoking data (via MAGIC-Parent on Child interview) for both pregnancies, only 76 % (n = 130) endorsed smoking during one pregnancy but not the other (i.e., completely quitting); 20 % (n = 34) endorsed smoking during both pregnancies (albeit often at different quantity and frequency), and 4 % (n = 7) did not endorse smoking during either pregnancy. Similarly, of the 89 fathers reporting on maternal SDP for both pregnancies (via MAGIC-Adult on Self interview), 71 % (n = 63) endorsed maternal smoking during one pregnancy but not the other, 16 % (n = 14) indicated maternal smoking during both pregnancies, and 13 % (n = 12) did not indicate smoking during either pregnancy. Across families, the percent agreements for mothers' SDP status change were 72 % for MR-SDP and PR-SDP, 77 % for MR-SDP and BR-SDP, and 71 % for PR-SDP and BR-SDP.

Objective 2. Associations with child birth weight

In order to garner evidence of which reporter may provide the most informative or predictive assessment of SDP, we conducted regression models wherein each of the SDP variables examined thus far predicted birth weight for each reporter individually, and then with all reporters together (to see which reporter was the best predictor). All parameter estimates and model fitting statistics are presented in Table 3. Individual regression models suggested that any BR-SDP, MR-SDP, and PR-SDP each predicted lower birth weight. However, when all three reporters were entered simultaneously into the regression model, only MR-SDP remained significant. For quantity of SDP (i.e., number of cigarettes smoked) over the whole pregnancy, parallel results were found: the quantity of SDP reported by BR-SDP, MR-SDP, and PR-SDP each predicted lower birth weight, but only MR-SDP remained significant when the three reporters were examined together.

We also examined whether any SDP and the number/quantity of cigarettes smoked by mothers predicted low birth weight in each trimester using MR-SDP and PR-SDP (BR-SDP did not include a trimester-by-trimester breakdown). Results indicated that MR-SDP and PR-SDP during

Table 2 Concordance across raters for SDP indicators and quantity

	PR-SDP			φ	*n*	BR-SDP			φ	*n*
	r	(SE)	χ^2 (df)			*r*	(SE)	χ^2 (df)		
Overall										
SDP indicated										
MR-SDP	.70*	(.09)	41.94* (1)	.48	180	.83	(.05)	119.41* (1)	.61	325
PR-SDP						.70	(.08)	42.07* (1)	.49	176
Quantity SDP										
MR-SDP	.68*	(.07)	56.77* (9)	.56	178	.80	(.04)	124.74* (6)	.63	319
PR-SDP						.64	(.08)	41.79* (6)	.49	171
Trimester 1										
SDP indicated										
MR-SDP	.69*	(.09)	41.49* (1)	.47	186					
# of cigarettes										
MR-SDP	.41*	(.11)			171					
Trimester 2										
SDP indicated										
MR-SDP	.73*	(.08)	46.81* (1)	.50	188					
# of cigarettes										
MR-SDP	.61*	(.14)			134					
Trimester 3										
SDP indicated										
MR-SDP	.79*	(.07)	54.56* (1)	.54	188					
# of cigarettes										
MR-SDP	.56*	(.11)			99					

* $p < .0001$. χ^2 values given only for dichotomous and ordinal variables. Sample *n*'s represent individual pregnancies. *r* represents tetrachoric correlations for dichotomous and ordinal variables, and Pearson's correlations clustered on family id in order to correct for family-wise non-independence. φ is an estimate of effect size for χ^2 tests (.1 = small, .3 = medium, .5 = large; Kotrlik et al. 2011). *BR-SDP* birth record report of SDP, *MR-SDP* maternal report of SDP, *PR-SDP* paternal report of SDP)

the first trimester each independently predicted lower birth weight, although the effect of PR-SDP disappeared when MR-SDP and PR-SDP were examined together. For the second trimester, only 'any MR-SDP' predicted lower birth weight, whether or not models included PR-SDP. The number of cigarettes smoked during the second trimester did not predict birth weight regardless of reporter. For the third trimester, 'any MR-SDP' and 'quantity smoked MR-SDP' each predicted lower birth weight whether or not PR-SDP was included in the model. Thus, across models, MR-SDP was frequently associated with low birth weight, in both indicator (y/n) and in terms of quantity. Thus, MR-SDP was very consistently the most predictive of child birth weight.

Objective 3. Within- and between-family comparisons of SDP-birth weight associations

In light of these results and given the increased detail provided in MR-SDP (i.e., quantity smoked and timing across pregnancy), we then examined between and within-family associations of SDP and birth weight using only MR-SDP. Recall that a child-specific severity score for MR-SDP was created for these analyses (see "Analytic Strategy" section). Results for these models are presented in Table 4.

We first ran an 'intercept only' model to decompose the variance in birth weight into within- and between-family variation. We calculated intra-class correlations to assess the percentage of variance accounted for by within- and between-family variation (*unconditional* column of Table 4). The percentage of between-family variation is calculated as the [(individual-level variance − family level variance)/individual-level variance] (e.g., Snijders and Bosker 1999). We found that 42 % of the variation in birth weight was attributable to between-family differences and 58 % was attributable to within-family differences (including residual error). In Model 1, higher severity of MR-SDP was associated with lower birth weight. This effect remained significant after controlling on other maternal characteristics (Model 2). In Model 3, only the within-family association was significant, suggesting a causal

Table 3 SDP status and SDP quantity predicting birth weight

Predictors	Individual models						Combined model					
	β	(SE)	*p*	F(*df*)	R^2	*n*	*β*	(SE)	*p*	F(*df*),*p*	R^2	*n*
SDP indicated												
MR-SDP	−207.66	(60.44)	.001	F(1172) = 12.45	.03*	343	−240.34*	(93.76)	.01	F(3,89) = 6.12, *<.001*	.07*	*175*
PR-SDP	−148.77	(74.45)	.07	F(1,91) = 3.99	.02*	180	3.12	(97.31)	.98			
BR-SDP	−212.67	(53.98)	<.001	F(1164) = 15.52	.03*	324	−65.26	(86.79)	.47			
Quantity SDP												
MR-SDP	−79.69	(20.87)	<.001	F(1172) = 15.28	.04*	343	−98.73	(34.33)	.005	F(3,88) = 7.33, *<.001*	.08*	*170*
PR-SDP	−58.32	(27.50)	.04	F(1,90) = 4.50	.02*	178	6.69	(36.98)	.86			
BR-SDP	−201.17	(51.77)	<.001	F(1164) = 15.10	.03*	320	−26.67	(81.84)	.75			
Trimester 1												
SDP indicated												
MR-SDP	−219.60	(59.30)	<.001	F(1172) = 13.72	.03*	343	−274.93	(81.22)	.001	F(2,93) = 10.13, *< .001*	.07*	*185*
PR-SDP	−157.27	(73.12)	.03	F(1,93) = 4.63	.02*	185	−27.10	(84.91)	.75			
# of cigarettes												
MR-SDP	−8.16	(3.55)	.02	F(1172) = 5.30	.02*	343	−12.94	(5.57)	.02	F(2,89) = 3.96, *.005*	.03*	*170*
PR-SDP	−6.75	(5.93)	.25	F(1,89) = 1.30	.01	170	−1.96	(6.38)	.76			
Trimester 2												
SDP indicated												
MR-SDP	−234.57	(61.52)	<.001	F(1172) = 14.54	.04*	343	−234.99	(78.56)	<.001	F(2,93) = 9.89, *.005*	.07*	*187*
PR-SDP	−107.73	(78.91)	.18	F(1187) = 1.86	.01	187	18.14	(91.57)	.18			
# of cigarettes												
MR-SDP	−7.82	(4.32)	.07	F(1172) = 3.28	.01	343	−13.98	(9.05)	.13	F(2,83) = 2.61, *.08*	.03	*134*
PR-SDP	−10.62	(6.96)	.13	F(1,83) = 2.33	.01	134	−5.08	(7.71)	.51			
Trimester 3												
SDP indicated												
MR-SDP	−170.69	(60.57)	.005	F(1172) = 7.94	.02*	343	−122.25	(87.68)	.17	F(2,93) = 1.81, *.17*	.02	*187*
PR-SDP	−120.66	(86.82)	.17	F(1,93) = 1.93	.01	187	−45.79	(99.15)	.65			
# of cigarettes												
MR-SDP	−14.27	(5.32)	.008	F(1162) = 7.19	.03*	252	−8.60	(10.50)	.42	F(2,74) = 2.67, *.08*	.05	*99*
PR-SDP	−13.47	(8.10)	.10	F(1,82) = 2.77	.02	123	−14.57	(9.90)	.15			

* $p < .05$. Sample *n*'s represent individual pregnancies. Standard errors for all regressions were clustered on family id using the Huber-White estimator in STATA in order to correct for family-wise non-independence. *BR-SDP* birth record report of SDP, *MR-SDP* maternal report of SDP, *PR-SDP* paternal report of SDP

Table 4 Between- and within-family associations of MR-SDP and birth weight

	Unconditional		Model 1		2		3		4	
	b	SE	*b*	SE	*b*	SE	*b*	SE	*b*	SE
Intercept	3444.90*	35.47	3620.12*	54.14	3525.67*	272.45	3520.02*	109.38	3716.79*	311.85
MR-SDP										
Child-specific			−59.00*	12.07	−42.71*	14.92				
Child-specific relative to family average							−240.29*	54.72	−154.11*	69.56
Family average							−215.38*	59.39	−144.54*	23.54
Controls										
Education (child specific)					30.78	19.64			17.51	41.54
Education (family average)									15.32	23.54
Food Stamps (child specific)					−11.28	7.72			59.00	184.63
Food stamps (family average)									16.66	174.09
Mother married					−14.36	109.35			18.30	114.26
Mother age (child specific)					42.06	125.41			0.76	34.06
Mother age (family average)									−10.15	8.36
Father SDP (secondhand smoke (child specific))					−26.52	23.31			−27.73	36.67
Father SDP (secondhand smoke (family average))									−42.38	30.87
Premature (<37 weeks (child specific))					−914.46*	117.95			−729.80*	166.34
Premature (<37 weeks (family average))									−1061.51*	197.28
Birth order					−45.08	60.92				
Variance										
Family-level	91,499*		169,154*		108,874*		120,281*		109,569*	
Individual-level (residual)	249,480*		203,982*		160,069*		199,733*		169,535*	
Model fit										
−2 Res Ln L	5320.4		5271.8		4114.7		5189.3		3986.2	
AIC	5324.4		5277.8		4120.7		5197.3		3992.2	

The child-specific SDP variable is defined as a 7-level variable capturing quantity smoked and timing of smoking across the pregnancies (see Analytic Strategy for details). For the sibling comparison models (3 and 4) the child specific (within-family centered) and family average values for the level 1 covariates are included

effect of MR-SDP severity on birth weight. The between-family association was also significant. These results held after controlling on other maternal characteristics (Model 4). Across all models, there was significant family-level and individual-level variability in birth weight.

Discussion

In a sample of families specifically targeted for sibling pairs discordant for exposure to SDP, we examined rates of agreement across birth record report of SDP, retrospective maternal report of SDP, and retrospective paternal report of SDP. Specifically, we compared reports for any SDP during pregnancy and for quantity of cigarettes smoked across each pregnancy. We then compared rates of agreement for changes in SDP behavior from one pregnancy to another. Once predictive utility of various reports of SDP was determined, we then fit a sibling comparison model to examine the association between SDP and birth weight. This approach controls for genetic and familial influences that make the siblings similar and can provide a test of whether SDP has an independent effect on birth weight once effects that siblings share are taken into account. This is among the first *specifically designed* US-based family studies to leverage the sibling comparison approach to prenatal smoke exposure.

Our findings suggest strong agreement across birth records, maternal retrospective report, and paternal retrospective report of any maternal SDP (yes/no) and overall

quantity of cigarettes smoked during the entire pregnancy. When considering trimester-by-trimester reports, maternal retrospective report and paternal retrospective report of any maternal SDP were also highly correlated within each trimester (birth records did not report on trimester specific data). When examining mother's change in smoking behavior across both pregnancies, we also found high agreement between all three reports. These findings are particularly important given the debate about the quality of retrospective reporting of exposures during pregnancy. First, they support the findings of, for example, Pickett et al. (2009) who examined data from the Maternal Infant Smoking Study of East Boston (Hanrahan et al. 1992; Tager et al. 1995) and subsequent follow-up study the East Boston Family Study (Wakschlag et al. 2010). Pickett and colleagues examined prospective data on SDP (interview and cotinine) that was collected at the time of the first prenatal visit (10–27 weeks gestation) and compared it to retrospective recall of SDP 11–18 years later. Overall, in comparison with both prospective self-report and prospective biological assessment of smoking status, they found that women's long term retrospective recall of smoking in pregnancy was accurate and reliable. Our own findings support the utility of retrospective reporting, particularly in the design of a sibling-comparison study, where it is impossible to predict or forecast whether a woman will change her smoking behavior from one pregnancy to the next. Second, these findings stress the importance of assessing exposure in a variety of ways. Because paternal report of maternal smoking behavior was also assessed, we were able to corroborate (in the subset of families where the father did participate) that maternal self-report of SDP was indeed reliable and accurate.

Maternal report of SDP, both any SDP and quantity smoked, was found to be the most informative assessment of SDP when predicting birth weight, with neither BR-SDP nor PR-SDP explaining any additional variance of SDP above and beyond that of maternal report. Further, sibling comparison models suggest that maternal report of SDP (as assessed by the SDP severity score incorporating both quantity and timing of exposure) is significantly associated with lower birth weight, even when controlling for genetic and familial influences that siblings share. Thus, this association, consistent with prior genetically-informed non-US studies using various means of assessing SDP (D'Onofrio et al. 2003; Thapar et al. 2009; Kuja-Halkola et al. 2014), appears robust and is in line with a causal interpretation. However, the exact mechanism by which SDP influences birth weight in humans remains unknown. Nicotine crosses the placenta, and fetal concentrations of nicotine can be 15 % higher than maternal concentrations (Lambers and Clark 1996). Further, there are more than 4000 chemicals in cigarette smoke including benzo(a)pyrene, nicotine, and carbon monoxide (Thielen et al. 2008; US Department of Health and Human Services 2010), making it difficult to determine what biological pathways are contributing to the SDP-birth weight association. One potential theory is that smoking induces oxidative stress and initiates the prenatal ischemia-hypoxia response (Smith et al., under review). This response could alter signal transduction pathways, damage macromolecules, produce vasoactive compounds (e.g., isoprostanes), alter both placental morphology (e.g., placental calcification) and blood flow, and contribute to intrauterine growth retardation and low birth weight (Hutter et al. 2010; Stone et al. 2014). Additional evidence suggests the possibility of inflammatory pathways (Lin et al. 2014; Pringle et al. 2015) and epigenetic modifications (Knopik et al. 2012), but the mechanisms by which these effects are transmitted is poorly understood. Considerably more research, particularly prospective, genetically informed, and carefully designed animal and human studies that can address critical/sensitive periods of exposure, measurements or biomarkers of exposure effects (e.g., placental tissue) and longitudinal course of disease and behavior is needed to begin to disentangle the likely complex nature of this association.

Limitations and future directions

First, we compared maternal and paternal retrospective reports of SDP to birth records, which are subject to recording errors and additional inconsistencies, such as variation between hospitals in who completes and submits birth record information (Hewson and Bennett 1987). Second, while we have shown that retrospective reporting of SDP in this study appears reliable and accurate, our results are reliant on the ability of the SDP assessment to correctly reflect the amount of SDP exposure. Third, this study does not assess the accuracy of the birth record. That is, since the project is conditioned on obtaining consistent data from the birth record and the screening interview, women who are prone to giving inconsistent reports may be eliminated and thus, the accuracy of maternal report of SDP may be overestimated. We are unaware of other studies that compare birth record, maternal retrospective self-report, and paternal retrospective report of maternal behavior; however, given that our results from the sibling comparison models support similar studies conducted in other samples using different means of measuring SDP, we believe that our measure of SDP is sensitive, reliable, and accurate. Fourth, our SDP severity measure assumes that smoking beyond the first trimester is more extreme than smoking only in the first trimester. While there is literature from preclinical and human studies to support this assumption (e.g., Dwyer et al. 2009; Hebel et al. 1988), we did conduct sensitivity analyses

to test this assumption and found our findings to be robust to different methods of defining and capturing SDP across the pregnancy (results available upon request). Fifth, sibling comparison studies, while controlling for confounding factors that siblings share, do suffer from their own limitations. Despite a carefully designed study that was purpose-built for targeting siblings discordant for prenatal exposure, there are undoubtedly unmeasured variables that differ between the siblings that are not included in these analyses and could therefore, influence the sibling comparison (see D'Onofrio et al. 2013). Finally, we have not examined reasons why these sibling pairs differ in their exposure to SDP. More specifically, why have these mothers changed their smoking behaviors from one pregnancy to another? These data were indeed collected as part of the larger project and will be used in future extensions of this work.

In summary, these findings support the reliability of retrospective reporting of SDP and the utility of multiple reporters of maternal behaviors during pregnancy. Further, results of our genetically-informed models suggest a causal association between SDP and lower birth weight, even when genetic and familial influences are accounted for by the model. Thus, this report adds to a body of research supporting a causal pathway to this association and emphasizes the need for continued efforts that can begin to disentangle the complex relationship between SDP and birth weight. Results also stress the importance of studies that can begin to shed light on the motivating factors that influence women to change their smoking behavior from one pregnancy to the next as this might guide ultimate smoking cessation and prevention efforts.

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Compliance with ethical standards

Conflicts of interest Valerie S. Knopik, Kristine Marceau, Rohan H.C. Palmer, Taylor F. Smith, and Andrew C. Heath declare that they have no conflicts of interest.

Human and animal rights and informed consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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