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Smoking During Pregnancy and ADHD Risk: A Genetically Informed, Multiple-Rater Approach

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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 developing child, including behavioral outcomes such as Attention-Deficit Hyperactivity Disorder (ADHD). There is substantial interest in understanding the nature of this reported association, particularly in light of more recent genetically informed studies that suggest that the SDP-ADHD link is less clear than once thought. In a sample of families (N = 173) specifically selected for sibling pairs discordant for prenatal smoking exposure, we use a sibling-comparison approach that controls for shared genetic and familial influences to assess the effects of SDP on ADHD symptom dimensions. ADHD was measured by both parent and teacher report on the Conners report forms and the Child Behavior Checklist/Teacher Report Form (CBCL/TRF). Results for the CBCL/TRF Total ADHD score are consistent with prior genetically informed approaches and suggest that previously reported associations between SDP and ADHD are largely due to familial confounding rather than causal teratogenic effects. However, results from the Conners parent report suggest a potentially causal effect of SDP on hyperactive/impulsive and, to a lesser extent, total ADHD symptoms; SDP results in increased parent-reported hyperactive/impulsive and total ADHD symptoms even after accounting for genetic and familial confounding factors. This suggests that the Conners assessment (parent-report) may provide a sensitive measure for use in studies examining child specific SDP effects on continuous and dimensional aspects of ADHD.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Keywords

ADHD; CBCL; Conners; genetics; sibling comparison design; multiple reporters; smoking during pregnancy

INTRODUCTION

Smoking during pregnancy (SDP) is a serious public health concern despite continued reports of the detrimental effects of SDP exposure on the fetus and intervention efforts aimed at reducing rates of smoking. SDP is associated with a wide range of offspring outcomes [Knopik, 2009; Knopik et al., 2012], in particular, numerous studies supporting an SDP-externalizing behavior relationship [Tiesler and Heinrich, 2014]. SDP has been linked to increased risk for conduct disorder [Wakschlag et al., 2002], criminality [Brennan et al., 1999], and ADHD [Thakur et al., 2013]. There is substantial interest in understanding the nature of these reported associations, particularly in light of more recent genetically informed studies that suggest that the SDP-externalizing link is less clear. Some genetically sensitive approaches suggest SDP is causally linked to disruptive behavior. For example, Gaysina et al. [2013] examined the association between SDP and offspring conduct problems among children reared by genetically related and genetically unrelated mothers and found an association even when controlling for postnatal environmental factors and postnatal genotype-environment correlation. However, others suggest that certain SDP-externalizing associations may be due to an inability to adequately control for shared familial influences, including genetic and shared family environmental factors, particularly when examining an effect of SDP on offspring conduct problems [D’Onofrio et al., 2008; Jaffee et al., 2012], criminality [D’Onofrio et al., 2010; Kuja-Halkola et al., 2014], and ADHD [Thapar et al., 2009; Skoglund et al., 2014]. With such variability across studies and debate in the field [Slotkin, 2013], it is challenging to determine how best to resolve these inconsistencies. Our report takes one approach to examine this issue further, specifically for the SDP-ADHD association. We present data from a family study of sibling pairs discordant for SDP. This study was purposefully designed to examine the effects of SDP within a genetics context, and thus offers different, and in many cases, more refined, types of family and individual data than those of larger medical registries that have been used to examine similar questions.

To date, most genetically informed approaches looking at the relationship between SDP and childhood ADHD have focused on either medical registry-based record of ADHD diagnosis (using data from countries that provide a national registry; e.g., Skoglund et al., [2014]) or parental report of child behavior. In the latter case, this is typically in the form of maternal report. To our knowledge, while the general ADHD literature has incorporated multiple reporters of child behavior, few genetically informed studies focused on effects of SDP on ADHD also incorporated information from other reporters of child behavior, such as teachers. Using data from the Avon Longitudinal Study of Parents and their Children (ALSPAC), Langley et al. [2012] recently examined the effects of both maternal and paternal SDP on child ADHD, as measured by parent and teacher report when the children were between 7 and 8 years of age. Their results support a growing body of work suggesting

that the association between maternal SDP and offspring ADHD symptoms (and possibly diagnoses) are due to unmeasured familial confounds rather than to a direct causal intrauterine effect; however, they could not rule out intrauterine risk effects of maternal SDP on teacher-reported symptoms. They concluded that additional studies using multiple informants of ADHD were needed [Langley et al., 2012], particularly because parent and teacher report of ADHD might not necessarily measure the same construct [Sherman et al., 1997; Mitsis et al., 2000].

In fact, DSM-IV field trials and other studies have suggested that parent and teacher reports of ADHD symptoms may indeed reflect important and valid differences in behavior and functional impairment across home and school settings [Hart et al., 1994; Gomez et al., 2003; Gomez et al., 2005; Goulardins et al., 2015; Narad et al., 2015]. Further, there is evidence that parent and teacher ratings account for unique variance in functional impairment [Hart et al., 1994]. Thus, each reporter has a unique behavioral and clinically relevant perspective that is important to capture. In particular, when examining an effect of SDP on child behavioral outcomes, examining parent and teacher ratings separately is critical as parents have personal knowledge of their own smoking behavior during each child's pregnancy, which has the potential to bias their ratings. In addition, based on data supporting important and valid differences across parent and teacher ratings, the DSM-IV field trials used an algorithm in which each symptom reported by either the parent or teacher during a structured interview was counted as a positive symptom [Lahey et al., 1994]. This "or" rule was used to determine optimal symptom counts and ADHD subtypes in DSM-IV and has been commonly adopted when combining parent and teacher ratings [Bidwell et al., 2011; Willcutt et al., 2014]. Thus, an approach that tests associations with a composite "or" rule measure would most accurately reflect clinical symptom levels across home and school settings from a DSM-IV perspective. Surprisingly, it has been rarely used within genetically informed studies of the association between SDP and ADHD.

In addition to the general focus on maternal report or national medical registry record report of ADHD, the majority of genetically informed approaches to the SDP-ADHD association have focused primarily on combined type ADHD (or total ADHD symptoms) without considering the ADHD symptom dimensions separately. There is strong evidence suggesting that ADHD may exist on the extreme end of a continuum of behavior [Levy et al., 1997] and that there are clear distinctions between the inattentive (IN) and hyperactivity-impulsive (HI) symptom facets of ADHD [DuPaul et al., 1997], such that each symptom dimension is associated with a unique pattern of clinical and neuropsychological impairment [Willcutt et al., 2012]. There is also behavior genetic data to suggest that, while there is some genetic overlap between HI and IN, there are also distinct genetic influences specific (and unshared) between the two subtypes [Larsson et al., 2006; Nikolas and Burt, 2010]. Given this information, considering symptom dimensions rather than overall ADHD symptomatology might be useful to further understanding of the SDP-ADHD association. In a study that examined the influence of prenatal and familial risk factors on externalizing behaviors in female adolescent twin pairs, Knopik et al. [2009] analyzed dimensional ADHD symptom counts separately and did find that after adjustment for prenatal (smoking and alcohol use during pregnancy) and parental risk factors (alcohol dependence, alcohol abuse, and regular smoking) higher HI scores were more likely in girls whose mothers reported smoking 1–10

cigarettes/day throughout pregnancy. There was a similar trend, although non-significant for IN symptoms [Knopik et al., 2009]. This study, while informative and suggestive of potentially differing results for ADHD subtypes, was not ideal for investigating prenatal exposure effects due to the fact that twins largely share the prenatal environment. Moreover, the 2009 study was not designed to disentangle prenatal effects from genetic and other familial effects. Thus, it is important to consider whether there are differential associations with SDP and continuous measures of IN and HI symptom dimensions, particularly using a genetically informed approach that can disentangle in utero effects from broader familial effects.

The goal of the present study was to critically investigate the reported causal association between SDP and offspring ADHD, using a US-based family study specifically designed to attempt to disentangle the effects of SDP on ADHD and associated neurocognitive deficits. Family history, ADHD, and behavioral data were collected from siblings who are discordant for maternal smoking during pregnancy. This design has the unique benefits of allowing a direct comparison of siblings within families that differ on SDP exposure but, by nature of the design, are matched on confounding familial and parental risk factors that siblings share, such as parental education and mental health history. Data from sibling pairs discordant for maternal SDP exposure were modeled to explore the association of SDP and: (i) parent-reported ADHD symptoms, including HI and IN subtypes; (ii) teacher-reported ADHD symptoms, including HI and IN subtypes; and (iii) combined-report ADHD symptoms in order to investigate whether, once controlling for genetic and familial associations that siblings share, the association between SDP and ADHD differs across reporters.

MATERIALS AND METHODS

Data for the current study were drawn from the Missouri Mothers and Their Children study (MO-MATCH; see Knopik et al. [2015a] for details). Families were identified using birth records obtained from the Missouri Department of Health and Senior Services Bureau of Health Informatics. Birth records obtained for birth years 1998–2005 from the Missouri Department of Health and Senior Services Bureau of Health Informatics in Missouri were examined for mothers who changed smoking behavior between two pregnancies ($N > 4,000$ identified). Screening interviews were conducted with 1,520 mothers and were used to verify SDP information from the birth record (i.e., mom smoked during one pregnancy but not another); 27% of these mothers agreed via screening with the birth record and were invited to participate in the study. After consent, mothers completed a diagnostic interview about their pregnancies (including life events surrounding pregnancy) and both parents provided information on their own mental health history. This included DSM-IV alcohol abuse/dependence, smoking and tobacco dependence, illicit drug use and dependence, depression and anxiety disorders, antisocial behavior, childhood ADHD, and childhood conduct disorder. Mothers also completed diagnostic interviews about each child, including mental health and behavioral history, such as ADHD. Age-appropriate versions of the Missouri Assessment of Genetics Interview for Children (MAGIC) were used during the structured interviews [Todd et al., 2003]. Exclusion criteria included: (i) mothers failed to understand the elements of informed consent; (ii) English was not the primary language spoken in the home; (iii) children had a history of head trauma, neurological disorders, or

uncorrected visual or auditory acuity deficits; and (iv) mothers used nicotine substitutes in the “nonsmoking” pregnancy. The study was approved by the Institutional Review Boards of Rhode Island Hospital, Washington University and the State of Missouri Department of Health and Senior Services.

Formal interviews were completed with 173 families in which mom had agreed (via screening interview) with the birth record that she changed her smoking behavior between two pregnancies. The demographics of the MO-MATCH sample are consistent with the demographics of the state of Missouri in terms of marriage rates (75% census vs. 77% MO-MATCH). MO-MATCH parents show slightly lower rates of stopping at a high school education (31.6% census vs. 18% of mothers and 20% of fathers in MO-MATCH) and completing at least “some graduate school” (26.2% census vs. 17% of mothers and 22% of fathers in MO-MATCH), but are consistent with rates of completing “some college” (30% of mother and 15% of fathers in MO-MATCH). The MO-MATCH sample also appears to have lower rates of children and families served by food stamps (20–30% in the state of Missouri and 11% in MO-MATCH). MO-MATCH shows higher rates of tobacco usage than state averages, which is expected given the nature of sample selection [Knopik et al., 2015a]. Mother-and teacher-reported data on ADHD outcomes were assessed when youths were age 7–16 years (Child 1 age: Mean = 12.99, SD = 1.94, 53% male; Child 2 age: Mean = 10.19, SD = 1.80, 51% male). Parents were primarily of Caucasian ancestry (96%, n = 250; three individuals refused to provide ancestral information). See Table I and Knopik et al. [2015a] for further detail on the sample.

Measures

Smoking during pregnancy (SDP)—Maternal report of SDP was obtained using a modified version of the MAGIC—Parent on Child [Todd et al., 2003]. A recent investigation of these data [Knopik et al., 2015b] compared the predictive utility of maternal report of SDP relative to both birth record report and paternal report of maternal SDP, and determined that retrospective maternal SDP, both any SDP (absent/present) and quantity smoked, was found to be the best assessment of SDP. Thus, to be consistent with prior reports, we focus here on maternal report of SDP. Any SDP was assessed via maternal report on discrete indicators (0 = No, 1 = Yes) of MSDP across each pregnancy as a whole, and specific to each trimester. *Overall quantity smoked during pregnancy* was assessed via maternal report on an ordinal scale (0 = No smoking during pregnancy, 1 = 21 or less, 2 = 21–99, 3 = 100 + cigarettes), and via mothers’ estimate of the number of cigarettes smoked in each trimester (a continuous variable ranging from 0 to 98 cigarettes smoked across trimesters). From these data, we created a single SDP *severity* score for each child (e.g., a child-specific SDP severity score). The operationalization of this variable was based on the following: (i) literature suggesting different, and potentially more harmful, effects of SDP later into pregnancy [Hebel et al., 1988; Dwyer et al., 2009]; and (ii) attempts to be consistent with our prior work [Knopik et al., 2009, 2005, 2015b].¹ The values were as follows:

¹In order to test these assumptions, the following variables were created in sensitivity analyses: 1. SDP yes/no: a binary indicator of whether mothers smoked during a given pregnancy 2. Sum quantity across trimesters: a continuous sum score of the quantity variables for each trimester 3. Number of Trimesters smoked: an ordinal variable indicating the number of trimesters in which mother reported SDP (0, 1, 2, or 3) 4. Maximum quantity: a continuous variable which was equal to the quantity for the single trimester in which the

- 1 = did not smoke during pregnancy (N = 143).
- 2 = smoked during first trimester only, 1–10 cigarettes per day (N = 50).
- 3 = smoked during first trimester only, 11–19 cigarettes per day (N = 80).
- 4 = smoked during first trimester only, 20+ cigarettes per day (N = 14).
- 5 = smoked beyond first trimester, 1–10 cigarettes per day (max of all three trimesters) (N = 83).
- 6 = smoked beyond first trimester, 11–19 cigarettes per day (max of all three trimesters) (N = 15).
- 7 = smoked beyond first trimester, 20+ cigarettes per day (max of all three trimesters) (N = 29).

Sample descriptive statistics are presented in Table I.

ADHD symptoms—ADHD symptoms were assessed with multiple raters and measures. Total ADHD symptoms, hyperactive/impulsive (HI) symptoms, and inattentive (IN) symptoms were assessed via parent- and teacher-report on the Conners [Conners, 2008]. Total ADHD symptoms were also assessed using the child behavior checklist (CBCL; parent report; Achenbach [1991a]) and teacher report form (TRF; Achenbach [1991b]). These measures are reliable and commonly used measures in assessing ADHD with high external and discriminate validity. In some cases, the teacher reports were available from two different teachers (99 children for the Conners, 95 children for the TRF). In these cases, we applied the “or” rule for each item assessed by two teachers (e.g., we used the score where a symptom was reported as present or more severe) to obtain a single, maximum teacher-rated ADHD symptom score per child.

The Conners–Parent assesses the presence of symptoms over the past 3 months and includes six items to assess IN symptoms and six items to assess HI symptoms on a scale of 0 (not at all) to 3 (very much). The Conners–Teacher includes six items to assess IN symptoms and five items to assess HI symptoms on the same 0–3 scale over the same time period. IN items are summed to form the Conners-IN subscales (parent report: $\alpha = 0.91$; teacher report: $\alpha = 0.93$). HI items are summed to form the Conners-HI subscales (parent report: $\alpha = 0.88$; teacher report: $\alpha = 0.92$). All IN and HI items are summed to form the Conner-Total ADHD symptom scales (parent report: $\alpha = 0.92$; teacher report: $\alpha = 0.93$). We used the DSM-IV syndrome scales for the CBCL and TRF, which assess total ADHD symptoms over the past 6 months. ADHD symptoms on the CBCL is the sum of seven items ($\alpha = 0.84$) that assesses total ADHD symptoms on a scale of 0 (not true) to 2 (very true/often true). ADHD symptoms on the TRF is the sum of 13 items ($\alpha = 0.89$) on the same 0–2 scale. The correlations between parent and teacher reports were moderate for the Conners scales

mother reported smoking the most. The correlations between our SDP Severity measure and each of these alternative SDP variables were as follows: SDP severity with SDP yes/no ($r = 0.80, P < 0.05$); SDP severity with Sum quantity ($r = 0.75, P < 0.05$); SDP severity with N trimesters smoked ($r = 0.94, P < 0.05$); SDP severity with Max quantity ($r = 0.69, P < 0.05$). See also Supplementary Table SXIII.

(Conners-IN: $r = 0.44$, Conners-HI: $r = 0.35$, Conners-Total ADHD: $r = 0.43$), whereas parent and teacher report were uncorrelated for the CBCL/TRF ($r = -0.06$).

In order to create cross-rater composite measures of ADHD symptoms, we applied the “or” rule [Lahey et al, 1994] for each item across all raters for whom data was available. Some items were asked only of parents or of teachers; these were included in the maximized cross-rater composite. Thus, the Conners-IN composite score consisted of seven items, the Conners-HI composite score consisted of eight items, the Conners-Total composite score consisted of 15 items, and the CBCL/TRF composite score consisted of 13 items. The reliability of these cross-rater composite measures was excellent (Conners-IN: $\alpha = 0.92$, Conners-HI: $\alpha = 0.89$, Conner-Total: $\alpha = 0.93$, CBCL/TRF: $\alpha = 0.87$). See Table I for sample descriptive statistics on each of the measures.

Covariates—Covariates were chosen to be consistent with other genetically informed studies of the SDP-ADHD relationship [Skoglund et al, 2014]. Maternal report of her marital status (at birth of each child), maternal age at birth of each child, maternal education at birth of each child, child birth order, child sex, second-hand smoke exposure during pregnancy (by the father), and an indication of whether or not families qualified for food stamps at the time of delivery collected from the birth record were used to control for other maternal and family characteristics that potentially confound the association of smoking during pregnancy and ADHD symptoms. In our data, birth order was significantly (and negatively) correlated with age ($r = -0.87$), which lends to a multicollinearity problem when modeling these data. We were primarily concerned with birth order given the fact that we have sibling pairs discordant for exposure and the majority of our sibling pairs are pairs where the mother smoked in the first pregnancy (64%) but not the second. Thus, we included birth order as a covariate rather than age.

Analysis Plan

Our sibling comparison approach examined the between and within-family associations of SDP and each measure of ADHD symptoms using a series of hierarchical linear models (HLM) using SAS PROC MIXED for each ADHD outcome variable. Hierarchical linear models account for non-independence of data in addition to assessing the within- and between-family associations of SDP and ADHD. Prior to all analyses, all ADHD outcomes were log-transformed and standardized in order to normalize distributions and get the variables on a more comparable metric. In the first step, an unconditional “intercept only” model was fitted to the data. This model was used to decompose the variance in the ADHD measure into within-family (e.g., individual child-level) and between-family (e.g., family level) variation via intra-class correlations. Thus, each unconditional HLM included two variance parameters: the family level variance and the individual-level or residual level variance. Specifically, the percentage of between-family variation is calculated as the (family level variance/[family level variance + individual child-level variance]) [Snijders and Bosker, 1999]. This unconditional model provides a baseline against which to compare subsequent models in order to understand how much within-family (and therefore potentially causal) variance SDP and covariates explain in each measure of ADHD symptoms.

We then fit a series of two hierarchical linear models for each ADHD symptom dimension. Model 1 can be thought of as an approximation of the standard comparison seen in the literature and compared children whose mothers smoked (or smoked more) during pregnancy to those whose mothers who did not smoke (or smoked less). This model does not capitalize on the family structure (or sibling comparison aspect) of the data but does adjust for the fact that we have multiple children per family and thus non-independent observations. Model 1 is specified by Equation (1),

$$\begin{aligned} \text{ADHD}_{ij} &= \beta_{0i} + \beta_{1i}(\text{SDP}_{ij}) + \beta_{2i} \dots \beta_{8i}(\text{covariates}) + e_{ij} \\ \beta_{0i} &= \gamma_{00} + u_{0i} \\ \beta_{1i} &= \gamma_{10} + u_{1i} \end{aligned} \quad (1)$$

where ADHD_i was individual i 's ADHD symptoms (Conners-IN, Conners-HI, Conners-Total, CBCL, or TRF), nested in family j . The effect of SDP (using the child-specific SDP values described above) was modeled at level 1 (the child level). Thus, ADHD_{ij} was modeled as a function of child-specific coefficients β_{0i} (intercept level of ADHD symptoms), β_{1i} (association of SDP severity and ADHD symptoms), and e_{ij} a series of residuals (one per child in each family). Additionally, child sex (β_{2i}), child birth order (β_{3i}), mother education (β_{4i}), maternal age (β_{5i}), marital status (β_{6i}), food stamp usage at birth (β_{7i}), and prenatal second-hand smoke exposure (by fathers) (β_{8i}) were included as covariates. Random effects were not included on the level-1 covariates as these were not of primary import for hypothesis testing. Child-specific coefficients β_{0i} and β_{1i} were, in turn, modeled where γ_{00} and γ_{10} were sample means for the intercept and SDP association with ADHD symptoms, respectively. u_{0i} was the variation in intercepts between families, and u_{1i} was the individual child-level variation within families for the SDP effect.

Importantly, this more general model examines SDP-ADHD associations in the entire sample and is representative of how SDP effects and associated familial confounds are typically modeled in non-sibling based samples. That is, in this model, we do not test whether SDP is operating at a within-family level (e.g., contributing to differences in ADHD symptoms in one sibling vs. another, within families) or between-family level (e.g., contributing to differences in overall, average levels of siblings' ADHD symptoms in across families). These questions are addressed by Model 2.

Model 2, our sibling comparison approach, used slightly different variables to specifically assess both within- and between-family associations of SDP and ADHD, allowing for a direct test of unique SDP exposure effects on child behavior while controlling for genetic and environmental variables that siblings share [Lahey and D'Onofrio, 2010; Ellingson et al., 2014]. First, the average score for SDP severity (across both siblings) was computed to obtain an estimate of the family average SDP severity for each family. Next, the family average SDP was subtracted from each child-specific SDP severity score (e.g., the SDP severity scores used in Model 1). 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 SDP severity on ADHD symptoms assessed the between-family effect of SDP severity on ADHD (i.e., the overall effects of SDP and related familial factors on ADHD outcomes, comparing across families). The effect of the child-specific relative to family average SDP severity on ADHD assessed the within-family effect of SDP on ADHD (i.e., comparing across siblings within a family, a test of any unique effect of SDP on child specific outcomes over and above familial and genetic factors that siblings share). Thus, in the Model 2 sibling-comparison approach, we specifically examine within-family associations of SDP and ADHD, as well as the between-family analog to traditional research (and Model 1). The child-specific relative to family average SDP severity score was entered as a level 1 predictor, whereas the family average SDP severity score was entered as a level 2 predictor (specified in Equation 2):

$$\begin{aligned} \text{ADHD}_{ij} &= \beta_{0i} + \beta_{1i}(\text{Child-specific SDP}_{ij}) + \beta_{2i} \dots \beta_{8i}(\text{covariates}) + e_{ij} \\ \beta_{0i} &= \gamma_{00} + \gamma_{01}(\text{family average SDP}_j) + u_{0i} \\ \beta_{1i} &= \gamma_{10} + u_{1i} \end{aligned} \quad (2)$$

Again, ADHD_{ij} was modeled as a function of person-specific coefficients β_{0i} (intercept level of ADHD symptoms), β_{1i} (linear relationship of SDP severity, this time using the child-specific relative to the family average SDP severity score, and ADHD symptoms), and e_{ij} a series of residuals. Person-specific coefficients β_{0i} and β_{1i} were, in turn, modeled where γ_{00} and γ_{10} were sample means for the intercept and SDP severity association with ADHD symptoms, respectively. Additionally, γ_{01} was included to capture the level 2 (family level) effect of family average SDP severity on ADHD symptoms. As in Model 1, u_{0i} was the variation in intercepts between families, and u_{1i} was the individual child-level variation within families for the child-specific relative to family average SDP severity effect. The covariates were included in the same way as described in Model 1, with the exception that covariates that differed non-systematically for siblings 1 and 2 (mother age at childbirth, education, food stamp use, secondhand smoke exposure, child sex) were separated into child-specific relative to family average and family average components in the same way that smoking during pregnancy was (described above). Thus, both the within- and between-family effects of covariates were controlled (with separate variables). Within-family covariates were also centered within-family. Marital status did not differ for any participants, and thus was not separated into within- and between-family components.

In sum, for each outcome variable, we fit one unconditional model and two conditional models (Models 1 and 2; See Supplemental material for detailed results from all models). In order to quantify how much of the within-family variance is explained by each conditional model, we computed the percentage of the explainable (within-family) variance explained: $([\text{unconditional individual child-level variance} - \text{conditional, e.g., Model 1, individual child-level variance}] / \text{unconditional individual child-level variance})$ [Singer, 1998].

RESULTS

Due to the scope of our approach and our testing of multiple informants of ADHD, we provide our main findings in Table II, and more specific information in Supplemental

Materials. Specifically, beta weights from the SDP variables for all outcomes are presented in Table II and more detailed models providing the full context of models (all parameter estimates, including covariates, variance estimates, and model fit statistics) are shown in Supplemental Tables SI–SXII. Birth order and child sex were generally significant predictors of ADHD symptom dimensions throughout all models, with boys exhibiting higher symptoms than girls, and second-born (i.e., younger siblings) exhibiting higher symptoms than first-born, older siblings (with the exception of the TRF and the cross-rater composite of the CBCL and TRF).

Parent Report

Decompositions of the variance estimates from the unconditional model revealed that the majority of the variance in parent-reported ADHD symptoms manifested as within-family differences (i.e., at the individual level: Conners-IN: 82%; Conners-HI: 72%; Conners-Total: 71%; CBCL: 80%), though a substantial proportion (18–29%) manifested as between-family differences. This suggests that more of the variability in ADHD was explained by differences between siblings than differences across families. When comparing children whose mothers smoked versus those who did not (Model 1), SDP severity predicted more Conners-IN ($b = 0.07, P < 0.05$), Conners-HI ($b = 0.10, P < 0.05$), and Conners-Total symptoms ($b = 0.09, P < 0.05$). However, this effect did not reach significance when examining total ADHD symptoms on the CBCL ($b = 0.04, P = 0.14$). Model 1 explained a substantial proportion of the within-family variance in all measures of ADHD symptoms (Conners-IN: 12%; Conners-HI: 19%; Conners-Total: 16%; CBCL Total: 37%).

Next, using the sibling comparison approach, we examined the within-family effect (child specific SDP exposure relative to family average) and between-family effect (family average SDP exposure) of SDP on ADHD symptoms (Model 2). Relative to the unconditional model, Model 2 explained a substantial proportion of the within-family variance of all measures of ADHD symptoms: Conners-IN: 11%; Conners-HI: 17%; Conners-Total: 15%; CBCL Total: 39%. There was a significant within-family effect of SDP on parent-reported Conners-HI ($b = 0.07, P < 0.05$). The sibling exposed to more SDP was rated as having more HI symptoms than their un- (or less) exposed sibling. The within-family effect of SDP was trend-level significant for Conners-Total ADHD ($b = 0.06, P = 0.07$) and did not reach significance for parent-reported Conners-IN ($b = 0.06, P = 0.13$) or the CBCL Total ADHD ($b = 0.01, P = 0.82$). However, there was a consistent family average effect such that children in families with higher cumulative exposure to SDP had higher ADHD symptoms than children in families with lower cumulative SDP exposure even after controlling for several confounding variables and influences that siblings share.

Teacher Report

The vast majority of the variance in teacher-reported ADHD symptoms manifested as within-family differences in the unconditional models; Conners-IN: 86%; Conners-HI: 95%; Conners-Total: 91%; TRF Total: 76%. In contrast to parent-report, a slim proportion of the variance in the Conners-teacher measures manifested as between-family differences (5–15%), though a more substantial proportion of the variance in ADHD symptoms as assessed by the TRF (24%) was attributable to between-family differences. In Model 1, SDP severity

was unrelated to ADHD symptoms across measures ($b = 0.01-0.03$, $P > 0.05$). Nonetheless, Model 1 explained a substantial proportion of the within-family variance in the Conners' measures of ADHD symptom dimensions, but not the TRF; Conners-IN: 34%; Conners-HI: 38%; Conners-Total: 35%; TRF Total: 4%. The variance explained in the Conners' measures was driven by covariates rather than SDP (see Supplemental Tables SV-SVII).

Relative to the unconditional model, Model 2 also explained a substantial proportion of the within-family variance of all measures of teacher-reported ADHD symptoms, with the exception of the TRF; Conners-IN: 42%; Conners-HI: 46%; Conners-Total: 44%; TRF Total: 5%. As in Model 1, SDP severity was unrelated to ADHD symptoms across measures ($b = -0.001-0.05$, $P > 0.05$ for the within-family effects).

Multi-Rater Composites

The majority of the variance in the unconditional models of multiple rater composite ADHD symptoms manifested as within-family differences, Conners-IN: 93%; Conners-HI: 82%; Conners-Total: 85%; CBCL/TRF Total: 71%, though a small proportion (7–17%) manifested as between-family differences (except for the CBCL/TRF: 29%). In Model 1, the findings most closely matched findings from the parent-report: SDP severity predicted more Conners-IN symptoms ($b = 0.06$, $P = 0.06$), Conners-HI symptoms ($b = 0.05$, $P < 0.05$), and Conners-Total symptoms ($b = 0.07$, $P < 0.05$). However, this effect did not reach significance when examining CBCL/TRF Total ($b = 0.05$, $P = 0.14$). Relative to the unconditional model, Model 1 explained a substantial proportion of the within-family variance in the Conners' measures of ADHD symptoms, but not the CBCL/TRF; Conners-IN: 16%; Conners-HI: 38%; Conners-Total: 24%; CBCL/TRF Total: 9%. Model 2 explained a substantial proportion of the within-family variance of all composite measures of ADHD symptoms; Conners-IN: 18%; Conners-HI: 27%; Conners-Total: 23%; CBCL/TRF Total: 11%. In Model 2, the within-family effects of SDP for parent-reported ADHD symptoms were non-significant.

DISCUSSION

In a sample of sibling pairs discordant for exposure to SDP, we fit a series of sibling comparison models to examine the association between SDP and ADHD (including inattentive [IN] and hyperactive/impulsive [HI] symptom dimensions), as assessed via multiple assessments and multiple reporters. This sibling comparison 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 ADHD, once these shared effects are taken into account. Specifically, the design allowed us to quantify within family effects (assessing effects of SDP on child ADHD in sibling pairs discordant for levels of exposure). Indeed, in our study, analyses that did not incorporate the direct sibling comparison suggested a broad effect of SDP on maternal-reported ADHD and related symptom dimensions. Analyses that compared siblings discordant for SDP revealed more specific and nuanced SDP effects, suggesting the possibility of a direct effect of SDP on increased risk for maternal-reported ADHD symptoms, ADHD-HI in particular. Given the inconsistencies in the literature regarding whether SDP has a causal effect on offspring ADHD, this ascertainment and

analytical design is critical to begin to further examine and quantify the potential for causal effects of SDP exposure.

Our study incorporated multiple assessments of ADHD, including the Conners scales and the CBCL/TRF rating forms, the latter of which are the most widely used parent and teacher rated assessments of ADHD. Parent findings from the Conners scales were consistent with the hypothesized effects of SDP on increasing ADHD symptoms, primarily HI symptoms. When using a traditional approach (i.e., Model 1; non sibling-comparison), there were significant associations between maternal SDP and Conners-IN, Conners-HI, and Conners-Total ADHD symptom dimensions. Sibling comparison models (Model 2) allow for a more detailed assessment of SDP's effects on offspring ADHD. Specifically, maternal report of SDP (as assessed by the SDP severity score incorporating both quantity and timing of exposure) was significantly associated with Conners-HI symptom dimension with a trend effect with Conners-Total ADHD, suggesting that HI symptoms may be the primary drivers of the reported SDP effect on total ADHD reported in the literature. Specifically, SDP severity was associated with higher levels of HI in the sibling exposed to more SDP (within-family effect, i.e., Family average SDP—child-specific SDP exposure) as well as across both siblings in the homes where children were collectively exposed to higher amounts of SDP (between-family effect—i.e., family average SDP). Importantly, these models leverage the advantages of our discordant sibling sample and point to the presence of possible unique/direct effects of SDP after controlling for genetic and familial influences that siblings share. In contrast to the Conners maternal report, findings were not suggestive of any of effects of SDP on CBCL-Total ADHD ratings. Our sibling comparison (Model 2) results for the parent report CBCL-Total are consistent with those of prior genetically informed approaches (i.e., no within-family effect; e.g., Skoglund et al. [2014]), suggesting that SDP is non-causal and that the effects of SDP on CBCL Total ADHD are due to primarily to familial confounding. However, given that there were no effects of SDP on CBCL Total ADHD using the more traditional modelling approach (Model 1), it is possible that the null findings are because the CBCL is a less sensitive diagnostic measure than the Conners report form. For example, it has been suggested that the CBCL ADHD scale is somewhat limited in assessing severity and does not provide a direct match in DSM-IV symptoms in terms language [Ebesutani et al., 2010].

In addition to multiple forms of assessment, our study incorporated information from multiple raters, specifically both parent and teacher ratings of ADHD, which are thought to tap somewhat distinct yet clinically relevant ADHD behaviors. This allowed for an in-depth examination of SDP on ADHD symptoms and dimensions across home and school settings. The findings from teacher reported measures of ADHD yielded no associations of SDP with ADHD. The pattern of findings from the parent/teacher composite measure was broadly consistent with the parent reported associations, particularly for the traditional approach (Model 1). However, due to the different patterns of results between parent- and teacher-reported models, it was not surprising to find that results from the composites were non-significant for the sibling comparison approach (Model 2). Differences among parent and teacher ratings are common and were expected in the current study given that they tap different aspects of inattention, hyperactivity, and impulsivity across unique settings [Goulardins et al., 2015; Narad et al., 2015]. Here, it appears that there may be a washing

out of measurable SDP effects when considering both parent and teacher reports as a composite using the “or” rule [Lahey et al., 1994].

In our teacher report data, the birth order and sex effects were much stronger predictors than SDP. Thus, we may be capturing a cohort effect that was not explicitly modeled (i.e., that older children are viewed by teachers as less hyperactive/impulsive than their younger siblings). However, this is unlikely given that the age difference between siblings is fairly small (2.79 years on average). Further, it is possible that children “hold it together” well in school (hiding/masking ADHD symptoms) only for them to be more readily apparent at home or that teachers see learning problems and question learning disability as opposed to ADHD. It is also, of course, possible that there is indeed no effect of SDP on teacher-reported ADHD symptom dimensions. There is little precedent for what to expect from models examining the relationship between SDP and teacher report of ADHD within a genetically informed approach. Existing genetically informed studies of the SDP-ADHD relationship rarely included teacher report. The only study that we are aware of [Langley et al., 2012] used a different sampling, assessment, and analytic design and could not rule out intrauterine risk effects of maternal SDP on teacher-reported ADHD symptoms using the Development and Well-Being Assessment (DAWBA). Consistent with Langley et al. [2012] conclusion, we also suggest that similar designs with larger samples including a wide range of ADHD severity, multiple assessments of ADHD, and multiple reporters of child behavior are needed to disentangle potentially unique SDP-ADHD symptom dimension associations as well as the direction of effects of ADHD behaviors across raters, sexes, and settings.

Although few studies have examined the role of SDP on the ADHD symptom dimensions separately, our results suggest a potentially causal relationship between SDP and increasing HI symptoms in offspring. This finding is consistent with some prior work implicating a role for SDP in increasing risk for HI symptoms (measured via DSM-IV criteria) after controlling for other prenatal and familial confounds in a sample of Missouri female twins [Knopik et al., 2009]. These two studies suggest that after controlling for familial influences, there may be a direct effect of SDP on increasing parent-reported HI symptoms, an effect which may at least partially drive the SDP-ADHD associations found in the literature. Given that differential associations with HI and IN symptom dimensions have been found with various forms of substance use outcomes [Elkins et al., 2007; Bidwell et al., 2014], that dimensions are differentially implicated in neuropsychological and clinical impairment [Willcutt et al., 2012], and that there is evidence from behavior genetics studies suggesting some distinct genetic influences specific (and unshared) between HI and IN [Larsson et al., 2006; Nikolas and Burt, 2010], additional studies are critical to understanding how prenatal exposure influences the ADHD symptom dimension risk pathway, taking into account genetic influences.

Limitations

This report is the first genetically informed examination of the SDP-ADHD association to consider multiple assessments of ADHD, including symptom dimensions, as well as multiple reporters. By incorporating teacher report, we are able to assess ADHD dimensions outside of the home setting. Further, teachers are, we assume, unaware of maternal SDP

status and thus may offer a more objective assessment of ADHD-behaviors. Despite these strengths, we note the following limitations. First, while we have shown that retrospective reporting of SDP in this study appears reliable and accurate [Knopik et al., 2015b], our results are reliant on the ability of the SDP assessment to correctly reflect the amount of SDP exposure. Second, 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 [Dwyer et al., 2009; Knopik et al., 2015b] we did conduct sensitivity analyses to test this assumption and found our findings to be consistent across different methods of defining and capturing SDP across the pregnancy (see Supplementary Table SXIII). Third, despite a carefully designed study that was purpose-built for targeting siblings discordant for prenatal exposure, our sample is limited in size and thus statistical power; moreover, there are undoubtedly unmeasured variables that differ between siblings that are not included in these analyses and could therefore, influence the sibling comparison [D'Onofrio et al., 2010]. Fourth, results from parent report models may be biased due to maternal report of both SDP and child ADHD. That is, because mothers rated both their own smoking and their children's ADHD behaviors, there may have been rater effects whereby mothers rate differentially exposed siblings differently. However, given that results did not suggest a causal SDP effect across all maternally rated assessments or across all symptom dimensions, we believe this to be an indication that maternal bias is likely minimal. Fifth, 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.

CONCLUSION

Our results add to a growing body of literature using genetically informed approaches to try to disentangle genetic effects from prenatal effects (in this case, SDP effects) on child behavior. While some of our findings (CBCL and TRF) are consistent with the literature suggesting that there is not a causal effect of SDP on Total ADHD symptoms, our findings using the Conners parent-report suggest the possibility of a significant and causal effect of SDP on Conners hyperactive/impulsive and, to a lesser extent, total symptom dimensions. This suggests that the Conners assessment (parent-report) may provide a more sensitive measure for use in studies examining child specific SDP effects on continuous and dimensional aspects of ADHD.

Importantly, this sample has been used to demonstrate the causal effects of SDP on birth weight [Knopik et al., 2015b], a finding that replicates prior examinations of the SDP-birthweight relationship within a genetics context [Kuja-Halkola et al., 2014]. Thus, our design is strongly positioned to identify potentially causal intrauterine effects of SDP on developmental and behavioral child outcomes. However, multiple and differing designs and approaches are critical to expanding our understanding of the likely complex association between SDP and ADHD. In fact, our results emphasize the need for continued and more comprehensive family based efforts that can begin to disentangle the multifaceted relationship between SDP and ADHD symptom dimensions. Only through multiple, comprehensive, quasi-experimental approaches that address the role of genetic influences

[Knopik, 2009; D’Onofrio et al., 2010], can we begin to better test the assumptions that SDP has a direct, causal effect on child outcomes, including ADHD, and further 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Sample Characteristics

	Child 1			Child 2		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Study variables						
SDP severity	173	3.95	2.05	167	2.04	1.77
Conners-parent inattention (IN)	165	3.90	3.56	162	4.59	3.89
Conners-parent hyperactive (HI)	165	2.55	3.03	162	4.30	4.20
Conners-parent total ADHD	165	6.45	5.87	162	8.89	7.45
CBCL total ADHD	164	2.91	2.79	161	3.78	3.62
Conners-teacher inattention (IN)	110	3.46	2.90	113	4.70	3.33
Conners-teacher hyperactive (HI)	110	2.05	3.09	113	3.74	4.13
Conners-teacher total ADHD	110	5.51	5.43	113	8.44	6.71
TRF total ADHD	110	5.86	5.93	109	5.03	4.85
Conners-composite inattention (IN)	167	6.13	4.93	166	7.83	5.54
Conners-composite hyperactive (HI)	167	3.58	4.05	166	6.18	5.22
Conners-composite total ADHD	167	9.71	8.13	166	14.01	9.79
CBCL/TRF composite total ADHD	164	7.25	5.39	162	7.83	5.42
Covariates						
Maternal age at birth	143	26.64	5.40	145	29.48	5.60
Maternal education (in years) at birth	143	13.31	2.10	145	13.59	1.90
Second-hand smoke exposure by fathers	171	1.84	1.44	159	1.13	1.42
	N	%		N	%	
Marital status (percent married) at birth	143	85		145	85	
Food stamp usage at birth	142	7		142	11	
Family demographics (at assessment)						
Maternal age	162	39.83	5.62			
Paternal age	80	44.04	6.34			
Child 1 age	173	12.99	1.95			
Child 2 age	170	10.19	1.80			
Child age difference	170	2.79	1.54			

	Child 1		Child 2	
	N	Mean (SD)	N	Mean (SD)
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		
Mothers' marital status				
Never married	6	4		
Married	130	77		
Separated	5	3		
Divorced	26	15		
Widowed	2	1		

SDP, smoking during pregnancy; ADHD, attention deficit/hyperactivity disorder symptoms; CBCL, child behavior checklist; TRF, teacher report form; HS, high school.

* All ADHD variables are presented in this table as raw and unstandardized data for descriptive purposes; however, for analyses, they are log-transformed and standardized.

TABLE II

Summary of SDP-ADHD Associations

Outcome variable	Model 1	Model 2	
	Child-specific SDP severity	Child-specific SDP relative to family average Family average (within-family effect)	SDP (between family effect)
Parent report			
Conners Inatt (IN)	0.07* (0.03)	0.06 (0.04)	0.13 ⁺ (0.07)
Conners Hyp/Imp (HI)	0.10* (0.03)	0.07* (0.03)	0.20* (0.07)
Conners Total	0.09* (0.03)	0.06+ (0.03)	0.20* (0.07)
CBCL Total	0.04 (0.03)	0.01 (0.03)	0.19* (0.07)
Teacher report			
Conners Inatt (IN)	0.02 (0.04)	0.02 (0.05)	0.01 (0.08)
Conners Hyp/Imp (HI)	0.01 (0.04)	-0.01 (0.05)	0.09 (0.07)
Conners Total	0.01 (0.04)	-0.001 (0.05)	0.03 (0.07)
TRF Total	0.03 (0.05)	0.05 (0.06)	-0.01 (0.08)
Cross-rater			
Conners Inatt (IN)	0.06* (0.03)	0.05 (0.04)	0.07 (0.06)
Conners Hyp/Imp (HI)	0.06* (0.03)	0.05 (0.03)	0.12+ (0.06)
Conners Total	0.07* (0.03)	0.05 (0.04)	0.10 (0.07)
CBCL/TRF Total	0.05 (0.03)	0.02 (0.04)	0.13 ⁺ (0.07)

Unstandardized beta-weights are presented, followed by standard errors in parentheses. Each row represents a different outcome variable and summarizes only the SDP severity findings from the larger models noted along the top. All parameter and variance estimates and model fit information from each of the models are provided in supplemental materials. Model 1 includes the effect of child-specific SDP severity as a level 1 predictor of the ADHD symptom score labeled on the left, and the additional individual- and family level covariates (child sex, child birth order, maternal education, age, marital status, food stamps qualification at birth, and second-hand smoke exposure during pregnancy). Model 2 includes the within-family effect of child-specific SDP severity relative to the family average as a level 1 predictor, and the between-family effect of family average SDP severity as a level 2 predictor of the various ADHD symptom scores labeled on the left, as well as the covariates.

* $P < 0.05$;

⁺ $P < 0.10$.