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Within-family effects of smoking during pregnancy on ADHD: the importance of phenotype

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Abstract

We sought to test within- and between- family associations of smoking during pregnancy (SDP) and attention deficit-hyperactivity disorder (ADHD) symptoms using a structured interview based on the conventional Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) symptoms and the Strengths and Weaknesses of ADHD-Symptoms and Normal-Behavior (SWAN) scale, which is a population based measure that grew out of the notion that an ADHD diagnosis exists on the extreme end of a continuum of normative behaviors and includes both

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above- and below- average performance on attention and activity. We used a sibling-comparison approach in a sample of 173 families including siblings aged 7-16 years (52% male) drawn from the state of Missouri, USA, wherein mothers smoked during one pregnancy but not the other. There was a within-family effect of smoking during pregnancy on SWAN hyperactivity/impulsivity and SWAN total ADHD behaviors. The associations between SDP and DSM-IV-based ADHD symptom dimensions as well as SWAN inattention were explained by familial confounds. These findings suggest that SDP exerts a potentially causal effect on increased ADHD hyperactive/impulsive behaviors and that this SDP effect is best captured when hyperactivity/impulsivity is assessed more normatively across the population, rather than specifically assessing problematic behaviors via DSM symptoms. Thus, any potentially causal effect of SDP on ADHD symptom dimensions may be restricted to hyperactive/impulsive behaviors rather than inattention, and normative, non-DSM-IV based behavioral measures may provide a more sensitive test of mechanisms of SDP-ADHD symptom associations, particularly in non-clinical samples.

Keywords

Attention Deficit Hyperactivity Disorder; DSM-IV; Family research; Prenatal exposure; Smoking

Depending on sampling designs, between eight and thirteen percent of women in the United States report smoking during pregnancy (SDP), making SDP a significant public health concern (Tong et al., 2013). While the prevalence has decreased from rates reported prior to 1980, a relatively high rate of SDP persists despite continued reports of the detrimental effects of SDP exposure on the fetus and intervention efforts aimed at reducing rates of smoking (Benjamin-Garner & Stotts, 2013; Castles, Adams, Melvin, Kelsch, & Boulton, 1999; Cook & Strachan, 1999; Knopik, Heath, Bucholz, Madden, & Waldron, 2009; Knopik, Marceau, Bidwell, et al., 2016; Knopik, Marceau, Palmer, Smith, & Heath, 2016; Kuja-Halkola, D'Onofrio, Larsson, & Lichtenstein, 2014; Marceau et al., 2016; Marceau et al., in press; Shah & Bracken, 2000; Smith, Schmidt-Kastner, McGeary, Kaczorowski, & Knopik, 2016). Of the offspring behavioral phenotypes that have been linked to SDP, the association with attention deficit-hyperactivity disorder (ADHD) symptoms appears the strongest (Knopik, 2009; Knopik, Maccani, Francazio, & McGeary, 2012; Thakur et al., 2013; Tiesler & Heinrich, 2014).

Potential pathways of SDP exposure for ADHD symptoms

Evidence in rodent models of prenatal nicotine exposure (Ernst, Moolchan, & Robinson, 2001; Shea & Steiner, 2008; Slikker Jr, Xu, Levin, & Slotkin, 2005) and human research on SDP (Bublitz & Stroud, 2012; Ekblad, Korkeila, & Lehtonen, 2015; Paus et al., 2008; Toro et al., 2008) suggest that there are plausible biological pathways by which prenatal nicotine act on neural pathways and the developing brain in such a way that could lead to deficits in later learning, memory, behavior, and development (e.g., by binding to nicotinic cholinergic receptors and potentially resulting in premature onset of cell differentiation leading to brain cell death, structural changes in regional areas, and altered neurotransmitter systems; Knopik, 2009). Despite evidence from animal models suggesting that prenatal exposure may exert a unique and specific influence on ADHD symptoms, there is substantial debate

(Slotkin, 2013) as to whether this association is potentially causal (Knopik, Marceau, Bidwell, et al., 2016) or whether the association arises because of an inability to adequately control for shared familial influences, including genetic and family environmental factors (Estabrook et al., 2015; Lindblad & Hjern, 2010; Obel et al., 2015; Skoglund, Chen, D'Onofrio, Lichtenstein, & Larsson, 2014; Thapar et al., 2009). Thus, although the literature generally suggests the potential of a specific SDP effect on ADHD-type behaviors, due to sampling designs that do not always account for other confounding factors, it is impossible to say whether these effects are specific to SDP or due to other potentially correlated variables, such as genetic transmission, other shared familial factors, or other prenatal exposures.

Without controlling for confounding factors, either statistically or via sampling design, the literature could also be interpreted as suggesting that SDP may index a more general prenatal mechanism encompassing multiple prenatal complications. For example, exposure to SDP has been linked to placental complications (Einarson & Riordan, 2009) that may lead to a variety of developmental problems, including intrauterine growth retardation and behavior problems (Huizink & Mulder, 2006; Joya et al., 2014; Knopik et al., 2009). Further, it has been hypothesized that cumulative exposure to multiple prenatal risks may, via fetal programming, impart risk for behavioral problems including ADHD symptoms (Williams & Ross, 2007). SDP exposure may contribute to more general pathways, but also may have a unique effect on some outcomes, including ADHD symptoms.

Several genetically-informed approaches (e.g., in-vitro studies, twin studies, children-of-twin studies, and sibling case-crossover designs; D'Onofrio et al., 2008; Estabrook et al., 2015; Knopik et al., 2006; Knopik, Marceau, Bidwell, et al., 2016; Knopik et al., 2005; Lindblad & Hjern, 2010; Thapar et al., 2009) have been used to attempt to understand whether the link between SDP and ADHD symptoms is potentially causal or explained by familial confounds, often finding evidence of familial confounding rather than potentially causal effects. However, genetically informed studies that have examined SDP-ADHD associations have generally focused on either medical registry-based records of ADHD diagnosis and/or medication use (Lindblad & Hjern, 2010; Obel et al., 2015; Skoglund et al., 2014) or Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM)-based symptom assessments (D'Onofrio et al., 2008; Estabrook et al., 2015; Knopik et al., 2006; Knopik et al., 2005). These methods lend themselves to assess severe problems, often in samples that do not necessarily have large distributions of youth with ADHD. Thus, careful consideration of measurement may shed further light on potential SDP-ADHD symptom associations.

Measurement of ADHD symptoms

There are a range of instruments that may be used to assess ADHD symptoms. DSM-based diagnostic measures are among the most commonly used in research studies (Achenbach, 1991a; Todd, Joyner, Heath, Neuman, & Reich, 2003). Symptom counts from DSM-based measures can be used as a continuous measure in order to map onto a theoretical assumption that ADHD symptoms in the population are dimensional. Notably, one potential concern related to this approach arises from the fact that even when defined dimensionally, measures

based on DSM symptoms often result in highly skewed phenotypic counts, with much of the population receiving a score of zero for all or nearly all ADHD symptoms – a problem that has been highlighted in the literature (Conners, 2008; Swanson et al., 2012).

In part to address this limitation of DSM-based ADHD symptom scales, Swanson and colleagues developed the Strengths and Weaknesses of ADHD-Symptoms and Normal-Behavior (SWAN) scale, which was designed tap the full range of ADHD behaviors across the population and provide a more normally distributed phenotype (Swanson et al., 2012). While also based on the 18 ADHD items in the DSM-IV (American Psychiatric Association, 1994) the SWAN attempts to measure a wider range of population variation by framing the assessment in terms of both the positive and negative aspects of each ADHD symptom (e.g., “Gives close attention to details” vs. “Fails to give close attention to details”). Genetic investigations have suggested that although there is substantial overlap among the underlying genetic constructs assessed by DSM-based assessments and the SWAN, the SWAN may provide a more realistic description of the ADHD symptom phenotype for family-based genetic studies (Arnett et al., 2013; Hay, Bennett, Levy, Sergeant, & Swanson, 2007; Polderman et al., 2007).

A recent analysis using the present sample focused on the association of SDP and ADHD symptoms using multiple raters (i.e., parent and teacher) of ADHD symptoms and found potentially causal effects of SDP on parent-reported (as opposed to teacher- or multi-rater composites) hyperactive/impulsive ADHD (but not inattentive or combined) symptoms as assessed by the Conners Parent Rating Scale (2008). The Conners Parent scale is a gold standard clinical measure of ADHD symptoms focused on assessing a range of ADHD symptoms in a dimensional fashion in order to provide nuanced information in a clinical setting. In comparison, a non-causal association with SDP was suggested on the parent-report Child Behavioral Checklist (CBCL, Achenbach, 1991a) or teacher-report version of the CBCL (Teacher Report Form, TRF, Achenbach, 1991b), two widely used child behavior rating scales developed as screening tools for child behavior problems and DSM-based symptoms (Knopik, Marceau, Bidwell, et al., 2016). These findings led us to hypothesize that within parent-reported ADHD symptoms, the type of measure (DSM-IV measures targeted towards problematic and impairing behaviors vs. measures reflecting a more continuous distribution of the range of ADHD behaviors, both positive and negative) may have implications for SDP-ADHD symptom associations. Given that refined measurement of ADHD symptoms in genetically-informed and specialized samples seeking to understand the association of SDP and ADHD behaviors are rare, this hypothesis must be explored further before a distinction based on phenotyping can be concluded. Because additional ADHD parent-report measures were also assessed in this sample, we can test this hypothesis in the current study as a means to replicate this pattern of findings – that is, that we expect to see SDP-ADHD symptom associations when using measures that are designed to capture a more continuous distribution and range of behaviors, particularly in non-clinically ascertained samples. In addition to replication of prior findings, we also aim to expand the current literature by comparing a standard DSM-based interview and the SWAN scale, a newer measure to the ADHD symptom assessment ‘toolkit.’

Present Study

We sought to examine associations of SDP and ADHD behaviors on both a DSM-based interview and the SWAN, which is thought to assess a more dimensional distribution of the full range of ADHD behaviors across the population. In order to begin to understand whether associations of SDP and ADHD were potentially causal or reflected familial confounds, we used a sibling comparison approach in addition to controlling for a number of child-specific and family-level covariates. We conducted a family study of sibling pairs who were discordant for SDP (mothers smoked in one pregnancy but not the other). This US-based sibling case-crossover sample was purposefully designed to examine the effects of SDP within a genetics context. Thus, our sample offers more refined family and individual-level data than samples drawn from larger medical registries that have been used to examine similar questions. A strength of this design is that causality can be ruled out when associations are attributable to familial confounding, and any within-family associations can be concluded as *potentially* causal (e.g., causality has not been ruled out, but neither has it been confirmed, as other non-familial confounders could still explain the association; Kendler, 2017). We hypothesized that SDP-ADHD behavior associations will be explained by familial confounds when assessed using a DSM-based symptom measure (Estabrook et al., 2015; Lindblad & Hjern, 2010; Obel et al., 2015; Skoglund et al., 2014; Thapar et al., 2009), but that a within-family, potentially causal effect will be found when ADHD behaviors are assessed using the SWAN, specifically for hyperactivity/impulsivity (Knopik, Marceau, Bidwell, et al., 2016). Results will have implications for understanding the potential importance of assessment and phenotype operationalization when considering the potentially teratogenic effects of SDP. Further, findings will contribute to distilling mixed results currently found in the field regarding the potentially causal role of SDP on ADHD symptoms.

Method

Participants and Procedure

Data for the current study were drawn from the Missouri Mothers and Their Children study (MO-MATCH; Knopik et al., 2015). Families in which mothers changed smoking behavior between two pregnancies were identified using birth records (years 1998-2005) obtained from the Missouri Department of Health and Senior Services Bureau of Health Informatics ($N > 4000$ identified). After 1520 screening interviews, 27% of mothers ($N = 413$) agreed with the birth record via a screening interview conducted by research staff at the Washington University in St. Louis and were recruited. The overarching goals of the study were to understand the potential influence of SDP on youth ADHD symptoms and associated neuropsychological functioning (e.g., reading/language skills, executive function, response inhibition, memory, and fine motor skills), as well as substance use initiation.

Exclusion criteria included: (1) mothers' failure to understand the elements of informed consent, (2) English not being the primary language spoken in the home, (3) children's history of head trauma, neurological disorders or uncorrected visual or auditory acuity deficits, (4) mothers' use of nicotine substitutes in the 'nonsmoking' pregnancy, (5) children not having the same biological father, (6) mother not having custody of the children, and (7)

one of the children was deceased. Seventy (of 413) mothers were excluded due to those criteria, and an additional 117 declined to participate. The study was approved by the Institutional Review Boards of Rhode Island Hospital, Washington University in St. Louis, and the State of Missouri Department of Health and Senior Services. After providing consent, mothers completed a diagnostic interview about their pregnancies (including life events surrounding pregnancy), diagnostic interviews about each child (including mental health and behavioral history), and both parents provided information on their own mental health history. A total of $N=173$ families completed the consent process and all parts of the study. Assessments occurred when youth were age 7-16 years (Child 1, older sibling, age: $M=12.99$, $SD=1.94$, 53% male; Child 2, younger sibling, age: $M=10.19$, $SD=1.80$, 51% male). Parents were primarily of Caucasian ancestry (96%, $n=250$). We assessed food stamp usage as an index of low income: 7% of families used food stamps at the time of the birth of the 1st child, whereas 11% of families used food stamps at the birth of the 2nd child. On average, mothers had a high school education (M years = 13) at the birth of both children, and education generally did not increase between children. See Table 1 and Knopik et al., (2015) for further detail on the sample.

Missing Data—The analytic sample included 152 families (19 families were not included because of missing data on demographic controls from the birth record, 3 families were not included because only 1 child had outcome data). Non-parametric one-way tests suggested that the excluded sample had, on average, slightly higher secondhand smoke exposure, and fewer married mothers, but did not differ on maternal age or education. Excluded participants had higher total and inattentive scores on the SWAN, but there were no differences in family average or child specific SDP, any MAGIC ADHD scores, or SWAN hyperactive/impulsive scores.¹

Measures

SDP—Maternal report of SDP was obtained using a modified version of the Missouri Assessment of Genetics Interview for Children (MAGIC)—Parent on Child (Todd et al., 2003). The following items were used to create a SDP severity score (described below): *Any SDP* (0=No, 1=Yes) across each pregnancy as a whole as well as specific to each trimester, and *overall SDP quantity* assessed via mothers' estimate of the number of cigarettes smoked in each trimester. Here, we focus on maternal report of SDP severity because prior reports have suggested that (i) maternal report of SDP (absence/presence and quantity/severity) has more predictive validity than paternal report and birth record reported SDP (Knopik, Marceau, Palmer, et al., 2016), (ii) the severity of SDP, including SDP later in pregnancy, imparts additional risk above and beyond the absence/presence of SDP (Dwyer, McQuown, & Leslie, 2009; Estabrook et al., 2015; Hebel, Fox, & Sexton, 1988), and (iii) in order to be consistent with our prior work using this and other samples (Knopik et al., 2009; Knopik, Marceau, Bidwell, et al., 2016; Knopik, Marceau, Palmer, et al., 2016; Knopik et al., 2005;

¹Results available upon author request. We also conducted the main study analyses in Mplus (Muthén & Muthén, 2010) using list-wise deletion and then using Full Information Maximum Likelihood, the pattern of findings were identical. Thus, despite small differences in the few children that were excluded, list-wise deletion appears to be fine in this sample for this analysis. We continue to use this strategy, as it is what was used in the paper we attempt to replicate and extend (Knopik, Marceau, Bidwell et al., 2016), and in other papers from other groups investigating similar questions in the literature.

Marceau et al., in press). A single *SDP severity* score was created for each child according to the following criteria:

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

Sample descriptive statistics are presented in Table 1.

ADHD symptom dimensions—ADHD symptoms were assessed via mother report on the MAGIC–Parent on Child (Todd et al., 2003) and the SWAN (Swanson et al., 2012).

The MAGIC is a DSM-IV structured interview where mothers endorsed (yes/no) whether the child exhibited each of the nine DSM-IV ADHD-inattention and nine ADHD-hyperactivity/impulsivity symptoms within the past year. We created sum scores indicating the number of symptoms endorsed within the inattention cluster ($\alpha = .92$), the hyperactivity/impulsivity cluster ($\alpha = .87$), and total ADHD symptoms ($\alpha = .93$).

The SWAN was designed to capture a more normative range of behaviors such that symptom counts would be normally distributed in the population (reflecting the underlying dimensionality of ADHD symptoms), but still include the standard 18 symptoms (nine symptoms tapping inattention and nine symptoms tapping hyperactivity/impulsivity over the past 6 months). Items are positively worded (e.g., Modulates motor activity [inhibits inappropriate running or climbing]; Gives close attention to detail and avoids careless mistakes). Investigations of the reliability and validity of the SWAN have showed good internal consistency (Chronbach's alphas $> .80$), test-retest reliability (coefficients $> .70$), longitudinal stability (r 's between $.51$ and $.76$), convergent validity (r 's and Craemer's V agreements $> .50$ with other measures of ADHD symptoms), discriminant validity, and factor analyses have shown that the SWAN is more sensitive to individual differences at the positive ends of the ADHD behavioral dimensions (“strengths”) than other measures of ADHD symptoms (Arnett et al., 2013; Lakes, Swanson, & Riggs, 2012; Swanson et al., 2012). The most recent iteration of the SWAN offers a 7-point scoring method ranging from -3 to 3 , with 0 being average, and a more traditional dichotomous scoring method with 0 reflecting average and 1 reflecting a weakness in that particular behavior (Swanson et al., 2012). Notably, in non-clinical populations, even when using the truncated dichotomous scoring, the positively worded SWAN is more effective at picking up individuals with scores in the “normative” range of the ADHD spectrum (i.e., those with average or better than average ADHD scores). As per standard scoring instructions at the time of assessment, *Not at all and just a little*, responses were scored 1 ; *Quite a bit* and *very much* responses were scored 0 ; scored item responses were summed into inattention ($\alpha = .87$), hyperactivity/

impulsivity ($\alpha = .86$), and total ADHD symptoms ($\alpha = .91$) scales with good internal consistency. Thus, high scores indicate higher levels of ADHD symptoms/problem behaviors whereas lower scores indicate the child has better than average attention behaviors (as opposed to no attention problems as in other measures of ADHD symptoms). ADHD symptoms as measured by the MAGIC and SWAN were associated (inattentive: $r = .62$, hyperactive: $r = .63$, total: $r = .65$, p 's $< .05$), suggesting good convergent validity. As expected, ADHD symptoms were slightly more skewed on the MAGIC than SWAN.²

Covariates—Covariates were chosen to be consistent with other genetically-informed studies of the SDP-ADHD symptom relationship (Knopik, Marceau, Bidwell, et al., 2016; Skoglund et al., 2014). Maternal and family characteristics that could confound the association of SDP and ADHD symptoms included maternal report of her marital status, age, and education at birth of each child, child birth order, child sex, second-hand smoke exposure during pregnancy (the number of cigarettes smoked by the father across the whole pregnancy: 0 = none, 1 = < 21 , 2 = 22-99, 3 = 100+), and qualification for food stamps (yes/no) at the time of delivery collected from the birth record. Birth order was significantly (and negatively) correlated with age in this sample ($r = -.87$), which leads to a multicollinearity problem when modeling these data; birth order was included as a covariate rather than age given that 1) mothers usually smoked in the first pregnancy (64%) but not the second, and 2) birth order was generally more highly associated with ADHD measures than was age (Knopik, Marceau, Bidwell, et al., 2016; Knopik, Marceau, Palmer, et al., 2016).

Statistical Analysis

Our sibling comparison approach included a series of hierarchical linear models (HLM) executed using SAS PROC MIXED in order to account for non-independence of data in addition to assessing the within- and between-family associations of SDP and ADHD symptoms, identical to the approach detailed in Knopik et al. (2015). First, an *unconditional* 'intercept-only' model was fitted to the data to decompose the variance in the ADHD symptom measure into within-family (e.g., individual child-level) and between-family (e.g., family-level) variation via intra-class correlations (Snijders & Bosker, 1999). This unconditional model provides a baseline against which subsequent models are compared 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 HLMs for each ADHD symptom dimension. The *Standard* model compared ADHD symptoms among children whose mothers smoked (or smoked more) during pregnancy to those whose mothers who did not smoke (or smoked less), controlling for covariates. The Standard model thus examines SDP-ADHD symptom associations in the entire sample and is representative of how SDP effects and associated familial confounds are typically modeled in non-sibling based samples, without capitalizing on the family structure (or the sibling comparison aspect) of the data. It does, however, adjust for the non-

²Results did not differ using the slightly skewed, raw versus square root transformed outcomes. MAGIC skewness was .98 for inattention, 1.57 for hyperactivity/impulsivity, and 1.18 for the total score. The SWAN skewness was .66 for inattention, 1.29 for hyperactivity/impulsivity, and .93 for the total score. Square-root transformed variables had skewness between .88 and 1.01 for the MAGIC and .67 to 1.00 for the SWAN.

independent observations of siblings nested within families. The Standard model is specified by Equation (1),

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

where $ADHD\ symptoms_{ij}$ was individual i 's ADHD symptoms, 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, $ADHD\ symptoms_{ij}$ 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_{0j} was the variation in intercepts between families, and u_{1j} was the individual child-level variation within families for the SDP effect.

Importantly, this Standard model is a more general model which examines SDP-ADHD symptom associations in the entire sample and is representative of how SDP effects and associated familial confounds are typically modeled in non-sibling samples. Therefore, the Standard model does not distinguish between whether SDP is operating at a within-family level (e.g., contributing to differences in ADHD symptoms in one sibling versus 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 the *Sibling Comparison* model, described below.

Sibling Comparison models were conducted in order to test whether SDP operates at a within-family (e.g., contributing to differences in ADHD symptoms in one sibling versus another, within families) or between-family level (e.g., contributing to differences in overall, average levels of siblings' ADHD symptoms across families). In the Sibling Comparison models, we specifically examined within-family associations of SDP and ADHD symptoms, allowing for a direct test of unique SDP exposure effects on child behavior while controlling for genetic and environmental variables that siblings share, as well as the between-family analog to traditional research (and the Standard models; Ellingson, Goodnight, Van Hulle, Waldman, & D'Onofrio, 2014; Knopik, Marceau, Bidwell, et al., 2016; Knopik, Marceau, Palmer, et al., 2016; Lahey & D'Onofrio, 2010). Two variables are used to capture SDP severity in Sibling Comparison models: *family-average SDP severity* for each family was the average score for SDP severity (across both siblings); *child-specific SDP severity relative to family average* for each child was the resulting value when the family average SDP was subtracted from each child-specific SDP severity score (e.g., the SDP severity scores used in

the Standard models). Thus, if a mother smoked the same amount for both pregnancies – regardless of total severity – then both siblings would have a child-specific SDP severity relative to family average of zero. In families where mothers changed her smoking behavior from one pregnancy to another, 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. For example, if a mother had a SDP severity score of 5 for one pregnancy and 0 (did not smoke) for the other, the family-average SDP severity score would be 2.5 (i.e., the average of 5 and 0), the child-specific SDP severity relative to family average score for the sibling for whom mothers smoked would be 2.5 (i.e., 5-2.5), and the child-specific SDP severity relative to family average score for the sibling for whom mothers did not smoke would be -2.5 (i.e., 0-2.5).

The effect of the family average SDP severity on ADHD symptoms assessed the between-family effect of SDP severity on ADHD symptoms (i.e., the overall effects of SDP and related familial factors on ADHD symptoms, comparing across families). The effect of the child-specific SDP severity relative to family average on ADHD symptoms assessed the potentially causal within-family effect of SDP on ADHD symptoms (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 Sibling Comparison model, the child-specific relative to family average SDP severity score was entered as a level 1 predictor, and the family average SDP severity score was entered as a level 2 predictor (as specified in Equation 2):

$$\begin{aligned}
 ADHD\ symptoms_{ij} &= \beta_{0i} + \beta_{1i}(Child - specific\ SDP_{ij}) + \beta_{2i} \dots \beta_{8i}(covariates) + e_{ij} \\
 \beta_{0i} &= \gamma_{00} + \gamma_{01}(family\ average\ SDP_j) + u_{0j} \\
 \beta_{1i} &= \gamma_{10} + u_{1j}
 \end{aligned} \tag{2}$$

Again, $ADHD\ symptoms_{ij}$ 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 the Standard model, u_{0j} was the variation in intercepts between families, and u_{1j} was the individual child-level variation within families for the child-specific relative to family average SDP severity effect. The covariates were included in a manner similar to that described in the Standard model (Equation 1), with the exception that covariates that could differ for sibling 1 and 2 (mother age at childbirth, education, food stamp usage at birth, 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). Within-family covariates were centered within-family, as is standard practice for these types of models (e.g., D'Onofrio et al., 2008; Knopik, Marceau, Bidwell, et

al., 2016). Thus, both the within- and between- family effects of covariates were controlled (with separate variables).

In sum, for each ADHD symptom variable, we fit one unconditional model and two conditional models (i.e., Standard and Sibling Comparison). In order to quantify how much of the total within-family variance is explained by each conditional model, we computed the percentage of the explainable (within-family) variance explained: ((unconditional individual child-level variance – conditional [e.g., Standard model] individual child-level variance) / unconditional individual child-level variance) (Singer, 1998). This was an omnibus test in order to judge the magnitude of the role of SDP and covariates for (within-family) differences in siblings' ADHD symptoms.

Results

A summary of our main findings (beta-weights from the SDP variables for all outcomes) is provided in Table 2. Child sex and birth order were generally significant predictors of ADHD symptom dimensions across models; when significant, boys exhibited more symptoms than girls and second-born (younger) siblings exhibited more symptoms than first-born, older siblings.

MAGIC DSM-IV ADHD Symptom Interview

See Table 3 for the full context of all models of the MAGIC (all parameter estimates, including covariates, variance estimates, and model fit statistics from the unconditional [panel A], Standard [panel B], and Sibling Comparison [panel C] models). Decompositions of the variance estimates from the unconditional model revealed that the majority of the variance in parent-reported ADHD symptoms on the MAGIC manifested as within-family differences (i.e., at the individual level: inattentive = 96%, Table 3, panel A; hyperactive/impulsive = 81%, Table 3, panel B; total = 84%; Table 3, panel C), suggesting that more of the variability in ADHD symptoms on the MAGIC was explained by differences between siblings than differences across families. When comparing children whose mothers smoked to those whose mothers did not smoke (Standard model; Table 3, panel B), SDP severity predicted more inattentive, hyperactive/impulsive, and total symptoms, $b's > .04$, $p's < .05$. The Standard model explained modest amounts of the within-family variance in MAGIC ADHD symptoms (inattentive: 8%, panel A; hyperactive/impulsive: 17%; total: 12%). In terms of total variance in ADHD symptoms, because the unconditional model revealed that 96% of the total variance in inattentive symptoms (for example) was attributable to within-family differences, and 8% of the within-family variance was explained by the full model, 7.68% of the total variance was explained (8% of 96% attributed to within-family differences). Eighty-eight percent (88.32%) of the total variance remains unexplained within-family differences (92% [100% - 8%] of 96% attributed to within-family differences); 4% of the total variance is between-family variance (e.g., 100% -96% attributed to within-family differences).

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 (Sibling Comparison model; Table 3, panel C).

Relative to the unconditional model, the Sibling Comparison model explained a similar proportion of the within-family variance in MAGIC ADHD symptoms as did the Standard model: inattentive: 8%; hyperactive/impulsive: 16%; total: 12%. There were no significant within-family effects of SDP on ADHD symptoms, $b's < .02$, $p's > .05$. 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, $b's > .13$, $p's < .05$.

Strengths and Weaknesses of ADHD-Symptoms and Normal-Behavior (SWAN) scale

See Table 4 for the full context of all models of the SWAN (all parameter estimates, including covariates, variance estimates, and model fit statistics from the *unconditional* [panel A], Standard [panel B], and Sibling Comparison [panel C] models). Decompositions of the variance estimates from the unconditional model revealed that the majority of the variance in parent-reported ADHD symptoms on the SWAN manifested as within-family differences (i.e., at the individual level: inattentive = 72%, Table 4, panel A; hyperactive/impulsive = 72%, Table 4, panel B; total = 64%, Table 4, panel C), suggesting that more of the variability in ADHD symptoms on the SWAN was explained by differences between siblings than differences across families. When comparing children whose mothers smoked vs. those who did not (Standard model; Table 4 panel B), SDP severity predicted more inattentive, hyperactive/impulsive, and total symptoms, $b's > .04$, $p's < .05$. The Standard model explained modest amounts of the within-family variance in SWAN ADHD symptoms (inattentive: 18%; hyperactive/impulsive: 42%; Total: 31%).

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 (Sibling Comparison model; Table 4, panel C). Relative to the unconditional model, the Sibling Comparison model explained a similar proportion of the within-family variance in SWAN ADHD symptoms as did the Standard model: inattentive: 22%; hyperactive/impulsive: 39%; total: 29%. There were significant within-family effects of SDP on hyperactivity/impulsivity and total symptoms, $b's > .05$, $p's < .05$, but not inattentive symptoms, $b = .04$, $p > .05$. The family average effect was significant for inattentive and total symptoms, $b's > .14$, $p's < .05$, but not hyperactive/impulsive symptoms, $b = .06$, $p > .05$.

Discussion

We used a sibling case-crossover design wherein mothers smoked during one pregnancy, but not another, to explore whether the association between SDP and ADHD symptom dimensions withstands rigorous control for familial confounds. Our analyses leverage the advantages of the 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, including specific family and individual-level covariates. This study is novel in that it examined the association of SDP with ADHD dimensions in two different measures- a structured DSM-IV interview (MAGIC) and the SWAN, which was specifically designed to

reflect the underlying range of behavior instead of the problematic extreme, mapping onto current theory regarding the continuous nature of ADHD symptoms across the population (Swanson et al., 2012). Consistent with our hypotheses and the existing literature, we found that SDP-ADHD symptom associations were explained by familial confounds for the DSM-IV symptom measure, but that there was a within-family effect of SDP on increased ADHD hyperactive/impulsive behaviors (such that SDP severity was associated with more hyperactivity/impulsivity in the sibling exposed to more SDP relative to his/her unexposed or less exposed sibling) using the SWAN (Table 2). This effect was also found for total ADHD symptoms on the SWAN, and was likely driven by hyperactivity/impulsivity (Table 2). Thus, our findings across measures within this non-clinical sample (e.g., the within-family effect for hyperactive/impulsive symptoms using the Conners presented in Knopik, Marceau, Bidwell, et al., 2016 and the SWAN found here vs. familial confounding using the MAGIC here and using CBCL in Knopik, Marceau, Bidwell, et al., 2016) are highly consistent, suggesting that ADHD scales designed to index a broader phenotypic range of underlying ADHD behaviors show a potentially causal effect of SDP with the hyperactive/impulsive dimension specifically.

Our findings highlight the importance of phenotyping for understanding specific potentially causal mechanisms linking SDP with ADHD symptoms. Theoretically (Swanson et al., 2012) and empirically (Hay et al., 2007), the SWAN reflects an underlying assumption that ADHD behaviors are normally distributed across the population, rather than adhering to a psychopathology-based symptom distribution (thus, by definition, rare and highly skewed) in the population. Because most of the studies examining SDP-ADHD symptom associations, including this one, draw from samples that are more normative in terms of ADHD behaviors (e.g., are not selected for extreme cases or clinical diagnoses), DSM-based symptom measures may not be as sensitive as alternative measures (e.g., SWAN, Conners). That is, DSM-based symptom measures may be more focused on the extreme ends of the ADHD spectrum and not sensitive enough to pick up on more normative, within-family SDP-ADHD behavior associations. Conversely, our community-based, non-clinical sampling design may lack the sensitivity to reveal true within-family SDP-ADHD *diagnosis* associations. Thus, in samples such as ours, that are expected to display a range of ADHD behaviors (including more normative and/or moderately severe ranges of ADHD symptoms), measures designed to reflect the broader range of distribution of ADHD behaviors may be more sensitive and appropriate than DSM-based measures.

Relatively few genetically informed studies have examined the role of SDP on the ADHD symptom dimensions separately (Estabrook et al., 2015; Knopik et al., 2009; Knopik, Marceau, Bidwell, et al., 2016). Nonetheless, finding a potentially direct relationship between SDP and hyperactive/impulsive symptoms is consistent with some prior work (Knopik et al., 2009; Knopik, Marceau, Bidwell, et al., 2016). Here, we provide additional evidence that after controlling for familial influences, there may be a direct effect of SDP on higher levels of parent-reported hyperactive/impulsive behaviors, an effect that may partially drive SDP-ADHD symptom associations found in the literature. This is consistent with evidence from behavior genetics studies that suggests distinct etiological differences between hyperactive/impulsive and inattentive symptoms (Larsson, Lichtenstein, & Larsson, 2006; Nikolas & Burt, 2010). Together, these findings suggest that at least some of the early

risk factors leading to the development of hyperactive/impulsive and inattentive symptoms may be distinct. Based on our findings, SDP may play a specific role in the development of variation across the full range of the distribution of hyperactive/impulsive behaviors as measured by the SWAN. Accordingly, it is important to use measures that are sensitive to the full range of ADHD behaviors across the population and, moreover, to separate hyperactivity/impulsivity behaviors from inattentive behaviors, when investigating etiological pathways of risk, including prenatal exposures, for later behavioral outcomes.

Implications

Our finding that SDP exposure may be associated specifically with increased hyperactivity/impulsivity is relevant to early assessment and intervention efforts. Our findings highlight the need for careful and early assessment of the full-range of variation in hyperactive/impulsive behaviors in individuals with SDP exposure. Given that the hyperactivity/impulsivity dimension is associated clinically with unique comorbidity and neuropsychological profiles relative to inattention (Willcutt et al., 2012), early assessment can help tailor intervention efforts towards the full clinical presentation. For example, even subclinical levels of hyperactivity/impulsivity early in life may be an indication of risk for the later development of more severe externalizing psychopathology and substance use outcomes (Bidwell, Ameringer, & Leventhal, 2014; Colder et al., 2013; Disney, Elkins, McGue, & Iacono, 1999; Elkins, McGue, & Iacono, 2007; Lansford et al., 2008). Thus, the SDP exposure pathway identified here underscores the need for early and fine-grained ADHD assessment in exposed children. Further, it suggests the importance of psycho-education to families and mental health providers on the links among elevated, but still subthreshold hyperactivity/impulsivity, and increased risk for future psychopathologies that may be particularly relevant to SDP-exposed individuals.

Limitations

The following limitations should be considered when interpreting the current study. First, recall bias is a risk when assessing specific details about the quantity smoked during two different pregnancies 7-16 years after the occurrence (Coughlin, 1990; Pickett, Kasza, Biesecker, Wright, & Wakschlag, 2009). Although retrospective reporting of SDP appears reliable and accurate in this sample and others (Estabrook et al., 2015; Knopik, Marceau, Palmer, et al., 2016; Pickett et al., 2009; Verkerk, Buitendijk, & Verloove-Vanhorick, 1994), our SDP assessment may not correctly reflect the amount of SDP exposure. Second, although we in no way limited enrollment by race/ethnicity and it was our goal to recruit families that would represent the racial makeup of the area, a lower percentage of minorities than expected ultimately participated, potentially limiting the representativeness of our sample. Third, despite a carefully designed study targeting siblings discordant for SDP exposure, our sample is limited in size and thus statistical power is also limited (e.g., post-hoc exact power analysis conducted via a Monte-Carlo simulation study in Mplus revealed that the SDP-SWAN hyperactive/impulsivity symptoms association was significant in only 53% of the simulations, indicating that we are underpowered to detect small effects). Further simulations showed that we are powered to detect medium and large effects. Our methodological approach included a series of models that are hierarchical in nature and overlapping. These models included multiple ADHD outcomes and multiple tests per

outcome. Thus, depending on the multiple testing correction strategy used (i.e., correcting for number of outcomes, number of tests, or number of outcomes*number of tests), some of our results may not survive correction. We thus suggest that results should be interpreted cautiously and should also be replicated. Fourth, the beta-weights were similar for inattention and hyperactivity/impulsivity via the SWAN, and thus may not be significantly different from each other. While this is consistent with reports using other assessments of ADHD (Knopik, Marceau, Bidwell et al., 2016), caution in interpretation of different pathways to the subtypes is merited until these findings are more strongly replicated. Fifth, although we included several covariates, we could not measure or include all variables that differ between siblings; there are likely other variables not included in these analyses that could influence the sibling comparison. Sixth, the SWAN and MAGIC differed in the timing of assessment: the SWAN asks about symptoms in the past 6 months whereas the MAGIC asks about the past year. This limits the comparability of the measures. However, ADHD symptom presentation is generally a chronic condition and a six-month assessment is typically long enough to pick up the presence or absence of particular behaviors. Finally, results may be biased (if mothers rate differentially exposed siblings differently) or inflated (due to shared method variance) because mothers reported both SDP and child ADHD symptoms. Because results did not suggest a potentially causal SDP effect for all assessments or symptom dimensions, and given the consistency of the specific findings with other research, we believe that this maternal bias is likely minimal.

Conclusion

Despite these limitations, our findings are consistent with, and expand upon, the growing body of literature using genetically-informed approaches to understand the nature of SDP-ADHD symptom associations. We add an important observation and supporting evidence for the *potentially* causal role of SDP for specifically hyperactive/impulsive symptoms assessed with measures designed to tap a theoretically dimensional distribution within the population. Associations between SDP and DSM-based symptom measures (which provide a non-normal distribution of ADHD problems in the population) in the current study are consistent with the literature using DSM-based symptom measures and diagnoses supporting a non-causal role of SDP (Estabrook et al., 2015; Lindblad & Hjern, 2010; Obel et al., 2015; Skoglund et al., 2014; Thapar et al., 2009). Thus, measures such as the SWAN and Conners that reflect a theoretically more dimensional distribution of a range of ADHD behaviors may provide greater construct sensitivity for use in studies examining the potentially causal role of SDP on continuous and dimensional aspects of ADHD symptoms in future work, particularly in non-clinically ascertained population-based samples. Careful attention to the phenotype will continue to be crucial for testing assumptions that SDP has a direct, causal effect on child outcomes, including ADHD behaviors and diagnoses. Such future work may help to elucidate specific pathways, un-confounded by genetic and other familial influences, by which SDP exposure and subsequent behavioral development are implicated in risk for more severe forms of psychopathology and substance use.

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Table 1

Sample Characteristics

	Child 1			Child 2		
	N	Mean	(SD)	N	Mean	(SD)
Study Variables						
SDP severity	173	3.95	2.05	167	2.04	1.77
MAGIC inattentive	173	2.68	3.20	171	2.32	3.17
MAGIC hyperactive/impulsive	173	1.42	2.26	171	1.82	2.45
MAGIC Total ADHD	173	4.10	4.87	171	4.14	5.11
SWAN inattentive	159	2.84	2.74	156	3.28	3.06
SWAN hyperactive/impulsive	159	1.52	2.11	156	2.63	2.91
SWAN Total ADHD	159	4.36	4.24	156	5.90	5.50
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)						
	N	Mean	(SD)			
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			
	<i>Maternal</i>			<i>Paternal</i>		
	N	%		N	%	
Education						
Less than HS	7	4%		9	10%	

	Child 1			Child 2		
	N	Mean	(SD)	N	Mean	(SD)
HS	30	18%		19	20%	
1-2 years college	50	30%		14	15%	
3-4 years college	46	27%		17	18%	
More than college	29	17%		21	22%	
Not reported	7	4%		14	15%	
<i>Mothers' marital status</i>						
Never married	6	4%				
Married	130	77%				
Separated	5	3%				
Divorced	26	15%				
Widowed	2	1%				

Note. MAGIC = Missouri Assessment of Genetics Interview for Children; SWAN = Strengths and Weaknesses of ADHD-Symptoms and Normal-Behavior; SDP = Smoking during pregnancy; ADHD = attention deficit/ hyperactivity disorder symptoms; 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. N's reflect the sample size with valid data and vary due to random missing data in the birth record.

Table 2

Summary of SDP-ADHD associations

The Standard model			The Sibling Comparison model	
Outcome Variable	Child-specific SDP severity	Child-specific SDP relative to family average	Within-family effect	Family average SDP (Between family effect)
Parent Report				
MAGIC				
Inatt (IN)	.05* (.02)		.02 (.03)	.14* (.05)
Hyp/Imp (HI)	.04* (.02)		.02 (.02)	.13* (.04)
Total	.07* (.03)		.04 (.03)	.22* (.06)
Parent Report				
SWAN				
Inatt (IN)	.06* (.03)		.04 (.03)	.14* (.05)
Hyp/Imp (HI)	.05* (.02)		.05* (.02)	.06 (.04)
Total	.08* (.03)		.06* (.03)	.17* (.07)

* $p < .05$. 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. The *Standard* model 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). The *Sibling Comparison model* 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. Inatt (IN) = inattention symptoms; Hyp/Imp (HI) = hyperactive/impulsive symptoms; MAGIC = Missouri Assessment of Genetics Interview for Children; SWAN = Strengths and Weaknesses of ADHD-Symptoms and Normal-Behavior.

Table 3
Full results for models of SDP-ADHD associations using the MAGIC

	A: MAGIC Inattention						B: MAGIC hyperactive/impulsive						C: MAGIC total ADHD symptoms					
	Unconditional			Sib-Comparison			Unconditional			Sib-Comparison			Unconditional			Sib-Comparison		
	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE
Intercept	1.69 *	0.04	2.3	0.39	1.99 *	0.43	1.49 *	0.04	1.34 *	0.30	1.53 *	0.35	2.01 *	0.06	2.38 *	0.51	2.22 *	0.57
SDP																		
Child-specific SDP			0.05 *	0.02	0.02	0.03			0.04 *	0.02	0.02	0.02			0.07 *	0.03	0.04	0.03
Family average SDP					0.14 *	0.05					0.13 *	0.04				0.22 *	0.06	
Controls																		
Child-specific Sex			-0.31 *	0.09	-0.26 *	0.12			-0.23 *	0.07	-0.16	0.09			-0.43 *	0.11	-0.34 *	0.15
Family average Sex					-0.35 *	0.14					-0.33 *	0.11				-0.53 *	0.18	
Birth Order			0.00	0.10	0.21	0.21			0.25 *	0.07	0.26	.14,			0.17	0.13	0.35	0.24
Child-specific Mother Education			-0.01	0.03	-0.04	0.07			0.03	0.02	0.04	0.05			0.01	0.04	-0.01	0.09
Family average Mother Education					0.00	0.03					0.03	0.02				0.02	0.04	
Child-specific Mother			-0.01	0.01	-0.08	0.06			-0.01	0.01	-0.02	0.04			-0.01	0.01	-0.08	0.07
Family average Mother age					-0.01	0.01					-0.01	0.01				0.01	0.01	
Mother Marital Status			-0.02	0.14	0.02	0.15			-0.04	0.12	0	0.12			-0.04	0.19	0.03	0.2
Child-specific Food Stamps			-0.08	0.17	-0.47	0.30			-0.03	0.13	-0.28	0.21			-0.09	0.21	-0.56	0.36
Family average Food Stamps					0.11	0.20					0.14	0.16				0.2	0.26	
Child-specific Second-hand smoke exposure			-0.02	0.03	0.03	0.07			0.00	0.03	0.04	0.04			-0.01	0.04	0.07	0.08
Family average Second-hand smoke exposure					-0.04	0.04					-0.03	0.03				-0.06	0.05	
Variance																		
Family-level	0.0264		<0.0001		0.0399		0.0747 *		0.034		0.0806 *		0.1685 *		0.089		0.1849 *	
Random effect on SDP			0.0006		0.0007				<0.0001		<0.0001				<0.0001		<0.0001	
Individual-level (residual)	0.6146 *		0.5635 *		.5667 *		.3236 *		.2702 *		.2705 *		.9030 *		.7991 *		0.7907 *	
Model Fit																		

	A: MAGIC Inattention						B: MAGIC hyperactive/impulsive						C: MAGIC total ADHD symptoms					
	Unconditional			Sib-Comparison			Unconditional			Sib-Comparison			Unconditional			Standard		
	<i>b</i>	SE	<i>b</i>	SE	<i>B</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	<i>b</i>	SE	SE
-2 Res Ln L	826.3		724.9		726.8		657.2		560		565.3		998.5		858.5		853.5	
AIC	830.3		730.9		734.8		661.2		566		571.3		1002.5		864.5		859.5	

* $p < .05$. In the Sib-Comparison model, 2 "Child-specific" parameters are "child-specific relative to family average"

Table 4
Full results for models of SDP-ADHD associations using the SWAN

	A: SWAN Inattention						B: SWAN hyperactive/impulsive						C: SWAN total ADHD symptoms					
	Unconditional			Sib-Comparison			Unconditional			Sib-Comparison			Unconditional			Standard		
	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	SE	<i>b</i>	<i>b</i>	SE	SE
Intercept	1.88 *	0.05	2.01 *	0.37	2.38 *	0.41	1.61 *	0.04	1.48 *	0.32	2.39 *	0.39	2.26 *	0.07	2.29 *	0.50	3.23 *	0.59
SDP																		
Child-specific SDP		0.06 *	0.02		0.04	0.03			0.05 *	0.02	0.05 *	0.02			0.08 *	0.03	0.06 *	0.03
Family average SDP					0.14 *	0.05					0.06	0.04				0.17 *	0.07	
Controls																		
Child-specific Sex		-0.33 *	0.08		-0.25 *	0.10			-0.24 *	0.07	-0.19 *	0.08			-0.46 *	0.11	-0.37 *	0.13
Family average Sex					-0.45 *	0.14					-0.32 *	0.13				-0.63 *	0.19	
Birth Order		0.22 *	0.09		0.24	0.17			0.46 *	0.07	0.45 *	0.14			0.50 *	0.11	0.53 *	0.21
Child-specific Mother Education		0.01	0.03		0.09	0.05			-0.01	0.02	0.03	0.05			0.00	0.03	0.08	0.07
Family average Mother Education					0.00	0.03					-0.03	0.03				-0.03	0.04	
Child-specific Mother		-0.01	0.01		-0.03	0.05			-0.01	0.01	-0.01	0.04			-0.01	0.01	-0.04	0.06
Family average Mother age					-0.01	0.01					0.00	0.01				-0.01	0.01	
Mother Marital Status		-0.08	0.14		-0.01	0.14			-0.11	0.13	-0.09	0.13			-0.14	0.19	-0.06	0.20
Child-specific Food Stamps		-0.03	0.16		-0.33	0.24			0.11	0.13	0.01	0.21			0.04	0.21	-0.25	0.30
Family average Food Stamps					0.14	0.20					0.14	0.18				0.21	0.28	
Child-specific Second-hand smoke exposure		0.00	0.03		0.04	0.05			0.04	0.03	0.03	0.04			0.03	0.04	0.05	0.07
Family average Second-hand smoke exposure					-0.03	0.04					0.04	0.04				-0.01	0.07	
Variance																		
Family-level	0.1494 *		0.2166 *		0.1396 *		0.1298 *		0.3063 *		0.1568 *		0.3573 *		0.6095 *		0.3545 *	
Random effect on SDP		0.006			0.0079				0.0078		0.007				0.0139		0.0127	
Individual-level (residual)	0.3771 *		0.3077 *		0.2930 *		0.3256 *		0.1879 *		0.1987 *		0.6473 *		0.4481 *		0.4592 *	
Model Fit																		

$p < .05$. In the Sib-Comparison model, 2 “Child-specific” parameters are “child-specific relative to family average”