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Prenatal Smoke Exposure Predicts Hyperactive/Impulsive but Not Inattentive ADHD Symptoms in Adolescent and Young Adult Girls

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We examined the longitudinal associations between prenatal tobacco smoke exposure (PSE) and attention-deficit hyperactivity disorder (ADHD) symptom domains in adolescence and young adulthood. A sample of girls with ADHD combined presentation ($N = 93$), ADHD predominantly inattentive presentation ($N = 47$), and matched comparisons ($N = 88$) was assessed prospectively. Symptoms of hyperactivity/impulsivity (HI), inattention (IA), and oppositionality (oppositional defiant disorder) were measured via multiple informants 5 (M age = 14 years; retention rate = 92%) and 10 years (M age = 20 years; retention rate = 95%) following childhood ascertainment. PSE was captured via maternal self-report. We used linear regressions to examine the prediction from PSE to both HI and IA in adolescence and early adulthood after stringent control of relevant confounding variables. PSE significantly predicted HI during adolescence and young adulthood across multiple informants but did not predict IA at either wave. Symptoms of HI may have partial etiological independence from IA symptoms. Copyright © 2015 John Wiley & Sons, Ltd.

Key words: attention-deficit hyperactivity disorder (ADHD); prenatal nicotine exposure; longitudinal; presentation aetiology

Attention-deficit hyperactivity disorder (ADHD) is a prevalent, child-onset behavioural disorder characterized by developmentally extreme symptoms of inattention (IA) and hyperactivity/impulsivity (HI) (American Psychiatric Association, 2013). It yields major impairments across multiple domains including educational and vocational problems, social relationships, and family interaction

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patterns (e.g. Barkley, 2006; Hinshaw, 2002a). Although ADHD is highly heritable (Burt, 2009; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002), multiple aetiologies are likely. Existing research implicates combinations of genetic and environmental risk factors in the development of the disorder (for a review, see Nigg (2006)).

Individual differences in behaviour patterns and severity yield differentiable presentations of ADHD, including predominantly IA (ADHD/IA), predominantly hyperactive-impulsive (ADHD/HI), and combined (ADHD/C) forms (American Psychiatric Association, 2013). Despite these categorical diagnoses, continuous measures of ADHD symptoms better reflect the dimensional nature of ADHD-related symptomatology (e.g. Marcus & Barry, 2011) and facilitate research on the causal mechanisms of psychopathology as outlined by the National Institute of Mental Health Research Domain Criteria (RDoC) (Insel et al., 2010). Research using twin and adoption designs suggests that symptoms of IA and HI have both shared and distinct aetiological determinants (Nikolas & Burt, 2010). Yet most research examining the aetiology of ADHD symptoms utilizes primarily male samples (Levy, Hay, Bennett, & McStephen, 2005). Research within a well-characterized female sample may reveal divergent causal mechanisms in the development of ADHD symptom clusters.

One potential aetiological determinant is prenatal exposure to tobacco smoke (prenatal smoke exposure or PSE), with many investigations reporting a robust association between PSE and ADHD (for a review, see Linnet et al. (2003)). In a case–control study, Mick et al. (2002) found a twofold increased risk for ADHD in participants whose mothers reported smoking tobacco during pregnancy. In the Multimodal Treatment Study of Children with ADHD, Arnold et al. (2005) also found that PSE was predictive of ADHD status. Yet through (i) comparison of participants with or without any presentation of ADHD (Mick et al., 2002) or (ii) examination of participants with only the combined presentation (Arnold et al., 2005), neither study can elucidate the potential differential impact of PSE on IA versus HI symptom domains. The aetiological dissimilarity between these domains is supported by higher rates of comorbid oppositional defiant disorder (ODD) in children with ADHD/HI and ADHD/C than ADHD/IA, a finding that may be stronger in girls than boys (Levy et al., 2005). Because PSE is widely linked to externalizing disorders (Wakschlag, Pickett, Cook, Benowitz, & Leventhal, 2002) and because externalizing disorders such as ODD and conduct disorder (CD) tend to be comorbid with ADHD presentations that include HI, it is plausible that PSE is more closely associated with HI than IA symptoms in isolation. Mechanistic explanations include the teratogenic effects of PSE, gene-environment interactions, and passive gene-environment correlations that link tobacco use to heritable personality characteristics (Knopik, 2009).

Our purpose is to examine the differential associations between PSE and ADHD symptom domains longitudinally, in an all-female sample ascertained during childhood. Although we do not utilize a genetically informative design and although we assess PSE retrospectively, we control for key confounding variables (maternal psychopathology, socio-economic status (SES), youth oppositional symptoms, and substance use) in an attempt to ascertain whether PSE differentially predicts the core dimensions of ADHD (i.e. HI versus IA) in both adolescence and young adulthood. Although prior longitudinal research (Nigg & Breslau, 2007) did not find significant relations between PSE and ADHD of any type, it may be that more specific associations will emerge by examining the underlying domains separately. Indeed, using symptom counts to form separate dimensions of ADHD, we hypothesize that PSE will significantly predict ADHD HI symptoms

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but not IA symptoms. Although oppositional symptoms appear to be influenced by PSE, we do not expect these oppositional behaviours to explain this predicted relation (Mick et al., 2002).

METHOD

Participants

The study sample was drawn from a naturalistic, longitudinal study of 140 girls with ADHD—those with the combined presentation ($N = 93$) and predominantly IA presentation ($N = 47$)—and a matched comparison group ($N = 88$), all aged 6–12 years. The ADHD and comparison samples were recruited in parallel format from health maintenance organizations, mental health centres, pediatric practices, and local school districts in the San Francisco Bay Area, as well as direct advertisements. Participants attended one of three summer research programmes in 1997, 1998, or 1999. The study sample was ethnically diverse (53% Caucasian, 27% African American, 11% Latina, and 9% Asian American) and drawn from varied socioeconomic backgrounds. See Hinshaw (2002b) for more detailed demographics and recruitment information.

Procedures

Participants with ADHD met full *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) (American Psychiatric Association, 1994) criteria for ADHD via parental report on the Diagnostic Interview Schedule for Children Version IV (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), supplemented with up to two symptoms from the teacher-rated Swanson, Nolan, & Pelham Questionnaire-4th (SNAP-IV) (Swanson, 1992). Multi-method/multi-informant follow-up assessments were conducted both 5 (Wave 2: mean age = 14 years, range = 11–18 years; retention rate = 92%) and 10 years later (Wave 3: mean age = 20 years, range = 17–24 years; retention rate = 95%). Attrition analyses revealed that compared with the retained sample, the 19 girls lost at the adolescent (Wave 2) follow-up reported significantly higher baseline internalizing symptoms and came from a higher proportion of single-parent homes (Hinshaw, Owens, Sami, & Fargeon, 2006). Of the 19 girls lost at Wave 2, seven girls were re-engaged by young adulthood, leaving 12 lost at the Wave 3 follow-up. They had lower baseline family incomes and full-scale IQ scores as well as higher teacher-rated externalizing, internalizing, and ADHD symptoms (Hinshaw et al., 2012) than those retained.

Initial assessments, observations during the summer research programmes, and follow-up assessments were conducted while any medicated girls with ADHD were not receiving stimulant medication (45% of the ADHD/C sample and 27% of the ADHD/IA sample had been receiving stimulant medication during the interval between Waves 1 and 2 (Hinshaw et al., 2006), along with 58% of the ADHD/C sample and 44% of the ADHD/IA sample between Waves 2 and 3; Hinshaw et al., 2012). Caregivers and (during young adulthood) participants provided informed consent at all phases of the study.

Of the 228 original participants, 23 cases were missing data on PSE and six cases were missing data on maternal ADHD symptoms (Ward, Wender, & Reimherr, 1993). Symptoms of hyperactivity, impulsivity, and oppositionality were reported by 154 teachers and 199 parent informants at Wave 2 (from

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the 209 families retained) and by 178 parents and 197 young adult informants at Wave 3 (from the 216 families retained). Missing values analysis revealed that girls with teacher-reported symptoms at Wave 2 reported higher SES at baseline than girls without teacher-reported symptoms at Wave 2. Participants with mother-reported symptoms at Wave 3 reported higher SES at baseline than girls without mother-reported symptoms at Wave 3. There were no other significant differences with regards to demographics or other key variables used in the present analysis.

Measures

Prenatal smoke exposure

Prenatal exposure to tobacco smoke (PSE) was captured as a dichotomous variable during baseline assessment. As part of a developmental history questionnaire, biological mothers were asked to self-report on smoking tobacco during pregnancy, yielding a dichotomous response of 'yes' or 'no'. PSE was coded as a binary variable for data analysis.

Symptom domains

Continuous measures of hyperactive, impulsive, IA, and oppositional symptoms were established at Wave 2 and Wave 3 assessments using the SNAP-IV rating scale (Swanson, 1992). Population studies and clinical trials have documented the reliability and validity of this measure (e.g. MTA Cooperative Group, 1999). Parent-rated SNAP-IV was shown to have good to excellent internal consistency in elementary school children ($N = 1613$; parent: IA $\alpha = 0.90$; HI $\alpha = 0.79$; teacher: IA $\alpha = 0.92$; HI $\alpha = 0.96$) (Bussing et al., 2008). In the current sample, internal consistency was excellent (mother: IA $\alpha = 0.96$; HI $\alpha = 0.91$; teacher IA $\alpha = 0.94$; HI $\alpha = 0.92$). The SNAP-IV was administered to mothers and teachers at Wave 2 and to mothers and young adults at Wave 3. We analysed informants separately at each wave, given previous evidence of rater effects (McLoughlin, Rijsdijk, Asherson & Kuntsi, 2011). Indeed, we used a multi-method/multi-informant approach to prevent response bias and increase validity and reliability of the symptoms (Silverman & Eisen, 1992). Detailed diagnostic procedures may be found elsewhere (Hinshaw, 2002b). SNAP-IV items measuring hyperactivity ($N = 3$) and those measuring impulsivity ($N = 6$) were averaged to create a combined HI symptom subscale. Items corresponding to IA ($N = 9$) and oppositionality (ODD) ($N = 8$) were also averaged, to form separate symptom dimensions.

Covariates

SES was calculated using family income and mother's level of education. Pretax income was measures on a 9-point scale, where 1 = 'less than $10 000 per year' and 9 = 'more than $75 000 per year.' Education level was measured using a 6-point scale on which 1 = '8th grade or less' and 6 = 'advanced graduate or professional degree'. Scores were standardized and then averaged to create the SES covariate. Maternal ADHD symptomatology was measured using the Wender Utah Rating Scale (Ward et al., 1993) completed by biological mothers at baseline. A five-factor solution for female adults with ADHD is reported (Stein et al., 1995). We utilized the impulsive/conduct and attention/organizational factors, as these items overlap with DSM-5 (American Psychiatric Association, 2013) HI and IA symptoms respectively. Substance use was measured using a structured self-report

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questionnaire that was designed for use in an ADHD sample (Molina & Pelham, 2003). The total number of substances endorsed at Waves 2 and 3 was used as a proxy for substance use in adolescence and young adulthood respectively.

Statistical Analysis

We utilized Mplus version 7.2 (Muthén, L.K. & Muthén, B.O. (1998–2012)) for all analyses, using the robust maximum likelihood estimator. This method of handling missing data allowed usage of the full covariance matrix of available data for all 228 participants. Linear regressions were computed to examine the predictive power of PSE with respect to ADHD symptom domains at Wave 2 (adolescence) and at Wave 3 (young adulthood). Eight separate models were created using two separate informants for HI and IA symptoms: maternal-report and teacher-report at Wave 2 and maternal-report and young adult-report at Wave 3. In all models, maternal ADHD symptoms, SES, participant ODD symptoms by congruent informant, concurrent participant-reported substance use, and PSE were entered simultaneously. To further evaluate the hypothesis that PSE predicted HI but not IA symptoms in adolescence and young adulthood, we specified path models to examine the direct and indirect effects of PSE on ADHD symptom domains in adolescence and young adulthood. We were particularly interested in whether PSE directly predicted ADHD symptoms and/or if these relations could be explained by concurrent ODD symptoms. For indirect effects, we provide an estimate of the product coefficients ($\alpha\beta$) (i.e. the 'Sobel test') as an index of gross effect size. However, we also present the bootstrapped confidence intervals of these effects, as bootstrapped results have been shown to provide additional statistical power and provide less biased estimates as they are less dependent on the likely non-normal distribution of the product term (Hayes, 2009).

RESULTS

Table 1 displays means and standard deviations for the variables analysed, in both the total sample and the sample divided by presence versus absence of PSE. Compared with girls whose mothers did not report smoking during pregnancy, girls whose mothers reported such smoking were of significantly lower SES, reported less substance use in adolescence, and had greater maternal-reported and teacher-reported IA, HI, and ODD symptoms in adolescence and greater maternal-reported IA symptoms and maternal- and self-reported HI symptoms in young adulthood. Maternal-reported and teacher-reported IA, HI, and ODD symptoms at Wave 2 were moderately to highly correlated (IA = 0.54, $p < 0.001$; HI = 0.50, $p < 0.001$; ODD = 0.46, $p < 0.001$). Maternal-reported and self-reported symptoms at Wave 3 were also similarly associated (IA = 0.54, $p < 0.001$; HI = 0.59, $p < 0.001$; ODD = 0.51, $p < 0.001$).

Does Prenatal Smoke Exposure Differentially Predict ADHD Symptom Domains in Adolescence?

Table 2 depicts the linear regression models at Wave 2 for HI symptoms and IA symptoms by maternal and teacher informants. The linear combination of maternal ADHD impulsive/conduct and attention/organizational symptoms, SES, girl's concurrent ODD symptoms and substance use, and PSE accounted for 53%

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Table 1. Mean, standard deviations, and significance levels for total sample and by prenatal smoke exposure

	Total sample	Prenatal smoke exposure		
	Mean (SD)	Mean (SD)		
		No	Yes	*p*-value
SES	−0.07 (.78)	0.01 (.74)	−0.44 (.89)	**
Mom ADHD: impulsive/conduct	7.43 (5.98)	7.64 (6.06)	6.44 (5.54)	ns
Mom ADHD: attention/organization	8.50 (5.80)	8.47 (5.84)	8.62 (5.72)	ns
W2 substance use	0.77 (1.32)	0.86 (1.40)	0.28 (.53)	*
W2 IA Sx: maternal report	1.33 (.96)	1.26 (.96)	1.70 (.87)	*
W2 IA Sx: teacher report	0.93 (.81)	0.84 (.75)	1.38 (.95)	**
W2 HI Sx: maternal report	0.66 (.75)	0.56 (.70)	1.13 (.83)	***
W2 HI Sx: teacher report	0.41 (.60)	0.33 (.49)	0.82 (.88)	***
W2 ODD Sx: maternal report	0.95 (.83)	0.89 (.80)	1.28 (.91)	*
W2 ODD Sx: teacher report	0.39 (.63)	0.34 (.60)	0.65 (.75)	*
W3 substance use	3.02 (2.35)	2.96 (2.34)	3.27 (2.40)	ns
W3 IA Sx: maternal report	1.18 (.99)	1.09 (.98)	1.67 (.92)	**
W3 IA Sx: youth report	0.89 (.69)	0.85 (.66)	1.09 (.79)	†
W3 HI Sx: maternal report	0.55 (.68)	0.47 (.63)	0.96 (.80)	**
W3 HI Sx: youth report	0.63 (.59)	0.58 (.55)	0.87 (.74)	*
W3 ODD Sx: maternal report	0.93 (.85)	0.87 (.83)	1.21 (.91)	†
W3 ODD Sx: youth report	0.55 (.57)	0.53 (.56)	0.65 (.63)	ns

Note. ADHD, attention deficit hyperactivity disorder; HI, hyperactive-impulsive; IA, inattentive; Sx, symptoms.
SNAP, Swanson, Nolan, and Pelham Questionairre-4th Edition (Swanson, 1992); ODD, oppositional defiant disorder.
†$p < 0.10$.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

of the variance in maternal-reported offspring HI symptoms in adolescence. Both PSE and concurrent ODD symptoms were significant predictors in the model, such that girls with greater HI symptoms were more likely to be prenatally exposed to nicotine ($p = 0.002$) and presented with greater levels of concurrent ODD symptoms ($p < 0.001$). Second, 55% of the variance in teacher-reported HI symptoms was accounted for by the linear combination of maternal ADHD impulsive/conduct and attention/organizational symptoms, SES, girl's concurrent ODD symptoms and substance use, and PSE. Again, PSE was a marginally significant predictor and ODD symptoms were a significant predictor in the model, such that girls with greater HI symptoms were more likely to be prenatally exposed to nicotine ($p = 0.058$) and presented with greater levels of concurrent ODD symptoms ($p < 0.001$). Using both maternal-reported and teacher-reported HI symptoms, path models also indicated an indirect effect of PSE on HI symptoms via concurrent ODD symptoms by congruent informant (maternal report: $\alpha\beta = 0.13$, $p = 0.006$, bootstrapped 99% CI [0.01, 0.26]; teacher report: $\alpha\beta = 0.14$, $p = 0.032$, bootstrapped 95% CI [0.01, 0.27]).

On the other hand, PSE did not significantly predict IA symptoms by either informant ($p > 0.10$), yet ODD symptoms remained a significant predictor ($p < 0.001$). The linear combination of maternal ADHD impulsive/conduct and attention/organizational symptoms, SES, girl's concurrent ODD symptoms and

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Table 2. Prenatal smoke exposure differentially predicts ADHD symptoms in adolescence

	Inattentive symptoms				Hyperactive-impulsive symptoms			
	Mother		Teacher		Mother		Teacher	
	B (*SE*)	*β*	*B* (*SE*)	*β*	*B* (*SE*)	*β*	*B* (*SE*)	*β*
SES	−0.03(0.07)	−0.03	−0.12(0.08)	−0.11	−0.02(0.05)	−0.02	−0.05(0.05)	−0.06
Mom ADHD: mpulsive/Conduct	−0.01(0.01)	−0.08	−0.003(0.01)	−0.02	0.01(0.01)	0.06	0.01(0.01)	0.06
Mom ADHD: Attention/Organization	0.01(0.01)	0.07	0.01(0.01)	0.06	−0.01(0.01)	−0.04	−0.003(0.01)	−0.03
SNAP ODD Sx	.79(0.05)	0.67***	0.72(0.08)	0.55***	0.60(0.06)	.65***	0.65(0.08)	0.70***
Substance Use	0.07(0.03)	0.10*	0.02(0.03)	0.04	0.05(0.03)	0.08	−0.02(0.02)	−0.03
Prenatal Smoke Exposure	0.13(0.16)	0.05	0.29(0.19)	0.13	0.36(0.11)	0.18**	0.24(0.13)	0.15†
Total R^2		0.52***		0.40***		0.53***		0.55***

Note. *N* = 228; SES, socio-economic status; ADHD, attention-deficit hyperactivity disorder; Sx, symptoms; SNAP, Swanson, Nolan, and Pelham Questionairre-4th Ed. (Swanson, 1992); ODD, oppositional defiant disorder;
†$p < 0.10$.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.01$.

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substance use, and PSE accounted for 52% of the variance in maternal-reported offspring IA symptoms and 40% of the variance in teacher-reported IA symptoms in adolescence. Although there were no direct effects of PSE on IA symptoms by either informant, path models indicated significant indirect effects of PSE on maternal-reported and teacher-reported IA symptoms via concurrent ODD symptoms (maternal report: $\alpha\beta = 0.14$, $p = 0.007$, bootstrapped 99% CI [0.01, 0.27]; teacher report: $\alpha\beta = 0.11$, $p = 0.035$, bootstrapped 95% CI [0.01, 0.21]).

Does Prenatal Smoke Exposure Differentially Predict ADHD Symptom Domains in Young Adulthood?

Table 3 reports parallel analyses at Wave 3 for HI and IA symptoms reported by maternal and young-adult informants. First, the linear combination of the previously described covariates accounted for 55% of the variance in maternal-reported offspring HI symptoms and 38% of the variance in self-reported HI symptoms in adulthood. Maternal-reported HI symptoms were significantly predicted by PSE ($p = 0.033$) and concurrent ODD symptoms ($p < 0.001$) and marginally by maternal ADHD impulsive/conduct ($p = 0.076$) and attention/organizational symptoms ($p = 0.051$). Self-reported HI symptoms were marginally predicted by PSE ($p = 0.076$) and significantly predicted by concurrent ODD symptoms ($p < 0.001$) and substance use ($p = 0.026$). Path models confirmed direct effects of PSE on ADHD/HI symptoms but did not indicate that PSE predicted these symptoms indirectly via concurrent ODD symptoms by either informant (maternal report: $\alpha\beta = 0.10$, $p = 0.092$, bootstrapped 95% CI [−0.02, 0.22]; young-adult report: $\alpha\beta = 0.03$, $p = 0.471$, bootstrapped 95% CI [−0.06, 0.12]).

In contrast, although the linear combination of the previously described covariates significantly predicted maternal-reported ($R^2 = 0.49$) and self-reported IA symptoms ($R^2 = 0.40$), PSE was not a significant predictor in either model. Concurrent ODD symptoms and substance use significantly predicted IA symptoms in adulthood reported by both informants. Path models did not indicate significant indirect effects from PSE to IA symptoms via concurrent ODD symptoms by either maternal report ($\alpha\beta = 0.09$, $p = 0.120$, bootstrapped 95% CI [−0.02, 0.20]) or young-adult report ($\alpha\beta = 0.03$, $p = 0.487$, bootstrapped 95% CI [−0.06, 0.13]).

DISCUSSION

Extant research consistently links PSE to childhood ADHD (Linnet et al., 2003). Complicating this causal pathway is the occurrence of highly comorbid ODD/CD, which is also believed to be related to PSE. Research is limited both longitudinally and with respect to the partially independent behavioural dimensions of ADHD—namely HI versus IA. To clarify matters, we examined the longitudinal effects of PSE on symptoms of HI versus IA in a large and diverse sample of girls followed prospectively for 10 years. In linear regressions we found that PSE significantly predicted maternal-reported HI symptoms in both adolescence and young adulthood and marginally predicted teacher-reported and self-reported HI symptoms in adolescence and young adulthood respectively. These associations remained stable even after controlling for maternal ADHD impulsive/conduct and attention/organizational symptoms, family SES, and girl's concurrent ODD symptoms and substance use. On the other hand, PSE did not predict IA symptoms in either adolescence or young adulthood regardless of informant.

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Table 3. Prenatal smoke exposure predicts ADHD symptoms in adulthood

	Inattentive symptoms				Hyperactive-impulsive symptoms			
	Mother		Girl		Mother		Girl	
	B (*SE*)	*β*	*B* (*SE*)	*β*	*B* (*SE*)	*β*	*B* (*SE*)	*β*
SES	0.02(0.07)	0.01	0.06(0.04)	0.07	0.004(0.04)	0.01	−0.04(0.04)	−0.05
Mom ADHD: attention/organization	−0.02(0.01)	−0.11†	−0.004(0.08)	−0.04	−0.01(0.01)	−0.11†	−0.001(0.01)	−0.01
Mom ADHD: attention/organization	0.02(0.01)	0.11	0.01(0.01)	0.11†	0.02(0.01)	0.12†	0.01(0.01)	0.05
SNAP ODD Sx	0.74(0.05)	0.65***	0.72(0.07)	0.59***	0.57(0.06)	0.68***	0.56(0.08)	0.53***
Substance use	0.05(0.02)	0.11*	0.03(0.01)	0.10*	0.02(0.02)	0.06	0.04(0.02)	0.16*
Prenatal smoke exposure	0.25(0.15)	0.10	0.16(0.11)	0.09	0.30(0.14)	0.16*	0.20(0.11)	0.13†
Total R^2		0.49***		0.40***		0.55***		0.38***

Note. $N = 228$; SES, socioeconomic status; ADHD, attention-deficit hyperactivity disorder; inattentive; Sx, symptoms; SNAP, Swanson, Nolan, & Pelham Questionairre-4th Ed. (Swanson, 1992); ODD, oppositional defiant disorder;
$^{\dagger}p < 0.10$.
$^{*}p < 0.05$.
$^{**}p < 0.01$.
$^{***}p < 0.01$.

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Overall, smoking during pregnancy may play a role in the maintenance or development of ADHD HI symptoms specifically, over a 10-year period. This finding is especially salient as we understand ADHD symptoms to follow a normative decline in hyperactivity and impulsivity during adolescence (e.g. Martel, Nikolas, & Nigg, 2007).

Concurrent ODD symptoms were a consistent predictor of both IA and HI symptoms at both waves and for all informants. This finding may be explained by the high number of girls in the sample with the combined presentation of ADHD. Presenting with both IA and HI symptoms, these girls may represent a more extreme form of ADHD, characterized by high comorbidities with externalizing disorders such as ODD (for a review, see Frick & Nigg (2012). Thus, although the association between IA and ODD symptoms may appear surprising, this finding may reflect the diagnostic makeup of the sample. What is striking is that PSE directly predicts HI symptoms after accounting for the linear combination of ODD and substance use. We note, in addition, that replacing ODD symptoms and substance use with concurrent CD symptoms led to an identical pattern of overall findings (data not presented but available from authors upon request). Another plausible explanation lies in the relation between PSE and ODD symptoms, reported in our sample and elsewhere (Wakschlag et al., 2002). To address the possibility that PSE predicts ADHD symptomatology indirectly via its association with ODD symptoms, we modelled these indirect pathways using a robust bootstrapping technique in Mplus (Muthén, L.K. & Muthén, B.O. (1998–2012)). Results confirmed significant direct pathways from PSE to maternal-reported and teacher-reported HI symptoms in adolescence and maternal-reported and youth-reported HI symptoms in young adulthood. Additionally, we report significant indirect pathways from PSE to maternal-reported and teacher-reported HI and IA symptoms in adolescence—but not young adulthood—via concurrent ODD symptoms. Thus, there appears to be a *direct* prediction of HI symptoms by PSE as well as an *indirect* effect of PSE on ADHD symptoms more broadly, via ODD symptoms.

There are a number of plausible explanations linking PSE to HI symptoms in particular (Knopnik, 2009). First, PSE could induce teratogenic effects on the developing fetus directly as a neuroteratogen (Slikker, Xu, Levin, & Slotkin, 2005) or via gene by environment interactions (Nigg, Nikolas and Burt, 2010). In a prospective design, Kahn, Khoury, Nichols, and Lanphear (2003) showed that children whose mothers smoked during pregnancy had significantly higher HI and ODD symptoms than children whose mothers did not smoke during pregnancy. Furthermore, children with a dopamine transporter gene polymorphism plus PSE scored approximately one standard deviation (SD) higher on the HI scale than did children without the polymorphism but who also had exposure to prenatal tobacco smoke. In contrast, IA symptoms did not differ by dopamine transporter gene status or PSE.

Another possible explanation lies in passive gene-environment correlation, whereby women who smoke during pregnancy pass heritable traits (e.g. personality characteristics) to their offspring that increase the likelihood of developing HI symptoms. Thapar et al. (2003) used a twin design to control for additive genetic factors as well as shared and non-shared environmental influences; results showed that PSE was associated with ADHD symptoms after such control (see also Button, Thapar, & McGuffin, 2005). Yet in a later investigation Thapar and colleagues (2009) separated prenatal from genetic influences by investigating the offspring of women who were conceived using assisted reproductive technology. Although PSE was significantly associated with ADHD in the related mother–child pairs, the

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magnitude of the association between PSE and ADHD was attenuated in the unrelated pairs. Thus, PSE may not have a direct teratogenic effect on ADHD but could interact with genetic liability—or may serve as a marker of heritable maternal and familial characteristics.

Limitations

Our study had several limitations. First, PSE was coded retrospectively as a binary variable (i.e. with a 'yes/no' response). Extant literature, however, supports a dose–response relation between PSE and ADHD outcomes (Button et al., 2005). PSE was also captured by self-report, which may have yielded response bias. Notably, however, Neuman, Lobos, Reich, Henderson, Sun, and Todd (2007) found that a binary variable of PSE was no less predictive of univariate outcomes than PSE variables that captured trimester of exposure or dosage by number of cigarettes.

Second, without a genetic understanding of our sample, we cannot control for spurious or genetically mediated associations between PSE and ADHD symptoms. Social background, parenting characteristics, and behavioural characteristics of mothers who smoke during pregnancy may be of equal or greater etiological concern than the biological effects of PSE *per se* (Thapar et al., 2009). Despite this limitation, our finding that the relation between PSE and ADHD may be explained by the association with HI symptoms in particular could help to focus future research efforts.

Third, in each of our models predicting ADHD symptoms, SES and maternal ADHD symptoms were entered as covariates. These measures were gathered at baseline and used in the analyses to predict adolescent and young adult ADHD symptomatology. It is possible that SES changed over time. Indeed, SES is best understood as a multi-dimensional construct with considerable variability (Braveman et al., 2005). Similarly, maternal ADHD symptoms may not accurately reflect the psychiatric history of the mother throughout the study, as those measures were recorded only at baseline.

Implications for Research, Policy, and Practice

In line with the RDoC approach, to the study of psychiatric disorders, examination of ADHD aetiology by symptom domain may reveal causal mechanisms associated with clusters of symptoms. Our demonstration that PSE predicts HI but not IA symptoms fits with extant literature clustering HI symptoms with defiant, aggressive, and impulsive behaviours — and IA symptoms with dysexecutive behaviours and higher-order internalizing disorders such as anxiety (Frick & Nigg, 2012). Whether the relation between PSE and HI is teratogenic or a result of genetic liability for maternal and familial characteristics awaits further research.

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