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Direct and Passive Prenatal Nicotine Exposure and the Development of Externalizing Psychopathology

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Abstract The association between maternal smoking during pregnancy and childhood antisocial outcomes has been demonstrated repeatedly across a variety of outcomes. Yet debate continues as to whether this association reflects a direct programming effect of nicotine on fetal brain development, or a phenotypic indicator of heritable liability passed from mother to child. In the current study, we examine relations between maternal smoking and child behavior among 133 women and their 7–15-year-olds, who were recruited for clinical levels of psychopathology. In order to disentangle correlates of maternal smoking, women who smoked during pregnancy were compared with (a) those who did not smoke, and (b) those who did not smoke but experienced significant second-hand exposure. Second-hand exposure was associated with increased externalizing psychopathology in participant mothers' offspring. Moreover, regression analyses indicated that smoke exposure during pregnancy predicted conduct disorder symptoms, over and above the effects of income, parental antisocial tendencies, prematurity, birth weight, and poor parenting practices. This is the first study to extend the findings of externalizing vulnerability to second hand smoke exposure.

Keywords Maternal smoking · Conduct disorder · Aggression · Second hand smoke · ADHD

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Introduction

Maternal smoking during pregnancy is associated with a wide range of externalizing outcomes among exposed children. This adversity is expressed across the lifespan, and includes conditions such as aggression in preschool [1], attention deficit/hyperactivity disorder (ADHD) in childhood [2–4], conduct disorder (CD) and delinquency in adolescence [5, 6] and criminality in adulthood [7]. Behavioral effects have been reported to increase linearly with the number of cigarettes smoked during pregnancy [8]. These associations appear specific to externalizing psychopathology, with no increased risk for internalizing outcomes among exposed children [9, 1].

While this observation has been supported consistently, the association cannot be considered causal, and the exact mechanism(s) through which maternal smoking affects behavioral outcomes remain(s) poorly understood. Retrospective research with human participants is replete with social, biological, and genetic confounds, weakening any assumptions of causality between smoking and externalizing outcomes [10]. Because smoking can not be randomly assigned to expectant mothers, naturalistic maternal behavior is inevitably correlated with genetic vulnerability for substance use, familial behavior problems, lower levels of socioeconomic status, and IQ, and with increased likelihood of assortative mating with antisocial males. These and related confounds are illustrated by research comparing mothers who continued to smoke during pregnancy to smokers who quit after becoming pregnant. This research indicates that women who continue to smoke are psychologically distinct from women who smoke yet choose to quit during pregnancy. The former mothers are more likely than quitters to have a lifetime history of poor relationships, adaptive functioning, and risky health behaviors, and are more likely to have a childhood history of CD [11, 12]. Given these findings, some have suggested that a direct genetic effect may explain the association between maternal smoking and childhood antisocial behavior [13].

Several studies have addressed this concern by examining prenatal smoking behavior in large samples of twins. When controlling for the correlated traits of maternal antisocial status, assortative mating with antisocial men, and deprived environmental conditions, the direct effects associated with smoking are greatly reduced, or disappear completely. This observation has lead some authors to suggest a heritable latent trait for antisocial tendencies that is passed from mother to child as a mechanism for the effects of maternal smoking on externalizing outcomes [10]. Using structural equation modeling, Silberg and colleagues [13] compared models of latent trait transmission with that of a direct environmental transmission, and found that the models did not differ. However, other researchers have found that maternal smoking predicts ADHD symptoms independently of the prediction offered by genetic effects [4]. Indeed, most authors who have found an association have reported that it withstands statistical controls for variables such as socioeconomic status, parental antisocial traits, pregnancy risk factors, and parenting practices [6].

Although the evidence supporting a heritable latent trait warrants caution in interpreting maternal smoking effects, experimental research also supports the biological plausibility of a direct programming effect of nicotine on the developing fetal brain. Nicotine used by the mother reaches fetal circulation, potentially in higher levels of blood concentration than found in the mother [14]. Nicotine binds with and stimulates nicotinic cholinergic receptors, allowing it to mimic the effects acetylcholine neurotransmission [15, 16]. Depending on the contextual state of the cell, nicotine may then affect such processes as

promotion of cell replication, cell differentiation, cell growth, cell death, and establishment of cell sensitivity to future stimulation [16].

The critical period for nicotine-induced damage to the central nervous system (CNS) appears to correspond to the second and third trimester, when nicotinic receptors maximally influence neurodevelopment, with no effects noted when exposure is limited to early gestation [17]. Because nicotine binds optimally with receptors in the CNS, it demonstrates cognitive and behavioral effects at doses below those required to affect peripheral systems [18, 16]. As such, by the time nicotine demonstrates its highly publicized effect on birth weight, it has almost certainly affected the developing CNS. Despite the rather broad implications for damage to the developing brain, prenatal exposure to nicotine, as noted above, is associated specifically with externalizing psychopathology. This may result from disruption in the development of striatal dopaminergic neurons [15] thought to be critical in the pathogenesis of ADHD and CD [19, 20]. In a study of rats exposed prenatally to nicotine, hyperactivity in the exposed animals was associated with reduced mesolimbic and nigostriatal dopamine [21].

Resolving this issue is critical as it may have important implications for prevention and intervention. Unfortunately, disentangling genetic and neurodevelopmental effects is especially difficult with humans as ethics preclude experimental designs for dissociating maternal smoke exposure from the numerous confounds outlined above. Yet testing neurodevelopmental effects within the limits of scientific ethics may be accomplished by comparing mothers who chose to smoke during pregnancy, with all of the associated confounds, with mothers who did not choose to smoke but were exposed to substantial second-hand smoke either at home or at work.

Recent research, summarized in a report by the Surgeon General, has revealed a substantial risk of passive smoke exposure to the general health of those who breathe the smoke, as well as to the fetuses of pregnant women [22]. Animal research demonstrates that environmental, or passive smoke exposure, affects fetal brain development in the same manner as exposure through direct maternal routes [23]. In humans, second hand smoke exposure during pregnancy results in the same degree of negative pregnancy outcomes as direct maternal use, including genotoxic effects [24], decreased fertility [25], neonatal antioxidant status [26], and increased fetal mortality, preterm births, and reduced fetal growth [27, 28, 29]. Given that nicotine exposure affects neural development at doses lower than those required to affect physical growth, the finding that birth weight and other physical correlates of nicotine exposure are impacted in fetuses whose mothers were passively exposed to smoke suggests that CNS correlates are likely to be implicated. Preliminary studies support this conjecture. Second hand smoke exposure among pregnant women predicts neuropsychological performance decrements in children that are intermediate to those found among smoking and non-smoking mothers, providing further evidence for a dose dependent response between smoke exposure and adverse outcomes [30].

Although less is known about the psychological characteristics of mothers exposed to second hand smoke, they are likely to be significantly different from those of maternal smokers. Findings regarding second hand smoke exposure have emerged only recently, and mothers who deliberately chose not to smoke during pregnancy may not have realized that passive exposure is also problematic. Additionally, they may have held jobs necessary for financial stability where exposure was unavoidable. In either case, nicotine exposure occurs, yet without many of the confounds associated with the choice to smoke during pregnancy. Therefore, in this study, we compare patterns of psychopathology among 7- to 15-year-old children with significant behavioral and/or emotional problems

who either (a) experienced no smoke exposure during gestation, (b) whose mothers smoked during pregnancy, or (c) whose mothers experienced only second hand smoke exposure during pregnancy. It was hypothesized that neural programming effects of nicotine would affect offspring regardless of maternal choice, providing support for an environmental transmission model of risk. Smoke exposure was also hypothesized to increase risk for all externalizing behaviors, showing no diagnostic specificity within the externalizing spectrum. Diagnostic specificity was expected with externalizing as opposed to internalizing disorders, consistent with the biological effects of nicotine on neural development.

Method

Participants

Participants for the current analysis were collapsed across two different studies, one in which children were recruited with clinically significant levels of emotional and/or behavioral disturbance as a part of an investigation into mechanisms of comorbidity for CD and depression (Study 1). The other study was a functional imaging investigation of ADHD and CD (Study 2). Although the aggregated sample was not drawn directly from a clinic, it was similar in many respects to the sample used by Wakschlag and colleagues [5], who originally proposed a relationship between maternal smoking and CD. Participants included 171 (136 male) children between the ages of 7 and 15, and one participant parent, who was the mother in all but two cases. For both studies, recruitment took place primarily in urban Seattle neighborhoods through advertisements placed in radio spots, newspapers, city busses, school newsletters, and flyers posted at clinics and community centers, and by flyers placed in psychiatrist's offices. Ads described the characteristics of children with the particular disorder being recruited. Interested parents responded to the advertisements by telephoning the laboratory and completing a 30 min structured interview to assess their child's appropriateness for the study. Qualified families were invited to the laboratory to participate in the study.

Procedure

One hundred thirty-six participants were drawn from Study 1 in which families were enrolled in a larger longitudinal study spanning three years. Diagnostic data were collected as a part of the initial laboratory visit, whereas questions regarding prenatal smoke exposure were asked as a part of a one-year follow up visit. Participants were paid $75 for the initial visit and $100 for the follow-up visit. Thirty-five participants were drawn from Study 2 in which parents provided both diagnostic data and data on prenatal smoke exposure during the same initial visit, for which they were paid $50. All procedures were approved by the University of Washington Institutional Review Board. All participant parents signed informed consent documents and participant children signed assent forms. Data from both studies were protected by Certificates of Confidentiality issued by the National Institute of Mental Health.

Smoking status

Maternal participants in both studies were asked to fill out a questionnaire regarding their pregnancy with the participant child and any health problems that the child had during the course of his or her life. In this questionnaire participants were asked to report on their own prenatal smoking habits for each trimester of pregnancy. In two cases, the biological father accompanied the child and filled out the questionnaire on behalf of the mother. Categorical options included: (1) smoked regularly, half a pack of cigarettes per day or less; (2) smoked regularly one half to one pack of cigarettes per day; (3) smoked regularly more than a pack of cigarettes per day; (4) smoked occasionally, but not every day; (5) did not smoke during the pregnancy; and (6) do not recall or decline to answer. These classifications are similar to those used by Wakschlag et al. [5], although in our study women were able to classify each trimester individually rather than responding for their pregnancy as a whole. This allowed for the identification of women who quit during the first trimester after learning of their pregnancy. In addition, women were also asked about second hand exposure with the following question: ''For each trimester of your pregnancy, did you spend a lot of time indoors in an environment where someone smoked regularly? (for instance partner at home, worked in a restaurant or bar where smoking regularly took place)''. Data from experimental studies suggest that first trimester exposure is less detrimental as nicotine affects CNS functioning minimally in the state of development typical of the first trimester [17]. As such, only second and third trimester exposures were considered in classifying groups. Accordingly, nine women who reported smoking only in the first trimester, or reported only occasional smoking were not included in the analyses. Additionally, data were not available for 14 participants from Study 1 who did not complete the 1 year follow-up at the time of analysis, for 4 participants who had been adopted by the participant parent and for whom information about pregnancy was not known, or for 11 participants who skipped or declined one or more questions regarding smoking. Groups were created to reflect (1) no smoke exposure, (2) direct maternal smoking and (3) second hand exposure only. The non-smoking group consisted of 96 women who reported that they did not smoke during any trimester of their pregnancy and were not exposed to any significant second hand smoke during any trimester. The smoking group consisted of 21 women who reported smoking regularly during at least the second or third trimester. Any reported level of regular smoking was considered given the findings that CNS development is affected at doses lower than those required to affect birth weight, and that women generally tend to underreport their smoking behavior during pregnancy [31]. Finally, the second hand exposure group consisted of 16 women who endorsed exposure at home or at work for the second or third trimester of pregnancy and also denied any personal use of cigarettes (even occasional use). Mean ages for the smoking groups differed significantly F (2, 132) = 3.58, P = .031. Children in the non-smoking group were 10.43 years of age (SD = 1.92), children of smoking mothers were 11.14 (SD = 2.15), and children of second hand exposure mothers were 11.75 (SD = 2.32). Follow up comparisons indicated that only the second hand group and the non-smoking group differed significantly P = .016.

Smoke exposure score

In addition to assigning participants to groups, a continuous smoke exposure score was computed for each participant for use in regression analyses. Self-reported smoking categories were weighted for severity by coding occasional smoking as one, smoking less than half a pack a day classified as two, smoking half a pack to one pack per day as three, and

smoking more than a pack per day as four. Second hand exposure was coded as one because there was no reliable way to quantify exposure more specifically. Scores were then added across all three trimesters to create a total exposure score. Scores ranged from 0 to 15.

Substance use

Because base rates of self-reported alcohol and substance use during pregnancy were low, statistical comparison of the groups was not possible given the assumption of at least five participants per cell for χ^2 analyses. Of the 133 women assigned to a smoking classification, three reported having consumed more than four alcoholic drinks on a single occasion. Among those, two were classified as smokers and one as a non-smoker. Marijuana use was reported by seven participants, including three non-smokers, one smoker, and two who were second hand exposed. Cocaine use was reported by two participants, both in the smoking group. Heroin use was reported by one participant who was also in the smoking group. Finally amphetamine use was reported by one participant who was in the non-smoking group. No reports of hallucinogens, barbiturates, or PCP were made by anyone. A dichotomous variable was created to capture the presence versus absence of substance use in pregnancy. Women reporting having more than four alcoholic drinks on one occasion at any time during pregnancy, and women reporting any illicit substance use at any time during pregnancy were assigned a one, with all others assigned a 0.

Child psychopathology

For both studies, parents were asked to report on child symptoms during the initial structured phone interview, which was administered by a trained research assistant. Parents were administered the aggression, anxiety/depression, and attention subscales of the Child Behavior Checklist (CBCL) [32]. In addition, parents completed the ADHD, oppositional defiant disorder (ODD), CD, major depressive disorder (MDD), and dysthymia (DYS) subscales of the Child Symptom Inventory (CSI) [33]. The CSI is a dimensionalized checklist of DSM-IV-TR diagnostic criteria. CSI scales offer the advantage of providing a scale of symptom severity, thereby increasing power for testing linear associations among variables. Sensitivity and specificity of the scales used in this study are adequate to excellent.

Parent psychopathology

In order to control for the possibility that parental antisocial behavior would account directly for offspring externalizing scores, assessments of antisocial behavior in both the mother and the father were conducted for each participant child. The participant parent (the mother in all but two cases) was administered the antisocial personality disorder (ASPD) portion of the Structured Clinical Interview for DSM-IV (SCID II) [34] by a trained graduate level interviewer. The participant parent was then administered the Family Interview for Genetics Studies (FIGS) [35] to assess for (ASPD) in the child's other biological parent. A continuous score of symptom severity was created for both the parent antisocial measures for use in regression analyses. For the mothers, who were assessed using the SCID II, symptom counts were computed by summing their scores for each symptom. The minimum score possible was seven, which is equivalent to a 'one' or 'not

present' rating on each of the seven items of the antisocial interview. The maximum score possible was 21, which is equivalent to a 'three' or 'threshold' rating on each of the seven items. For fathers, who were assessed using the FIGS interview, a symptom count was computed by summing each item endorsed positively by the reporter, which are collected as zero 'not true' or one 'true'. Scores range from 0 to 6.

The decision to interview only one parent was driven by practical considerations. In addition to the added inconvenience and potential reduction in participation from requiring two parents, 52% of participant families did not have the father living at home with the child at the time of the interview, as is typical among low income families of children with behavior problems. Research on this topic has revealed that antisocial characteristics of offspring are higher in families where the father is not present in the home and cannot be recruited for research participation [36]. Therefore, requiring the participation of both biological parents would likely bias the sample toward lower symptom severity. Accordingly, only one parent was required to participate. These procedures have been used in several family history studies [e.g., 37–39] as well as other research studies examining correlates of maternal smoking [e.g., 10].

Demographic control variables

In addition to diagnostic variables, several perinatal factors that are related to maternal smoking behavior were evaluated in accordance with the recommendations of Wakschlag et al. [5]. These variables, which were used as statistical controls, included child's birth weight and gestational age in weeks. In addition, household income was used as a control variable as an indication of family economic function.

Parenting styles

Previous research has suggested that parenting practices are important mediators of child behavior problems and may differ among smokers and non-smokers, making the examination of such practices important in this context [5]. This possibility was evaluated using only a subset of the families, as data on parenting were only collected from participants in Study 1, who completed the Parenting Scale (PS) [40], designed to measure dysfunctional discipline practices. The PS includes subscales measuring laxness, or the failure to follow through with discipline; overreactivity, or extreme emotional reactions to child misbehavior including the use of physical punishment and name calling; and verbosity, or the tendency to engage in discussion rather than action. Higher scores on each subscale represent poorer parenting practices.

Analyses

To test the hypothesis that second hand smoke exposure would result in increased child externalizing symptoms, the three smoking groups were compared with two multivariate analyses of variance (MANOVAs), one for externalizing measures and one for internalizing measures, to control for inflated familywise Type I error rates. Significant Wilks' λs were followed up with one way analyses of variance (ANOVA). In turn, significant ANOVAs were followed up with Tukey HSD post hoc contrasts to evaluate the pattern of group differences while correcting for inflated Type I error rates. To test the hypothesis

that smoking would predict child antisocial behavior independent of parental and biological control variables, parental antisocial traits, income, birth weight, gestational age, and smoke exposure scores were entered simultaneously into a regression analysis predicting CD symptoms. In a simultaneous multiple regression, regression coefficients represent the significance of the independent increment in variance accounted for by each variable, as if it were entered last in the regression equation. Thus, a significant coefficient for smoke exposure would indicate a significant effect on children's externalizing scores, over and above the effects of the set of control variables. A second regression was also run for the participants of Study 1, which included the three subscales of dysfunctional parenting practices as additional control variables.

Results

The smoking, non-smoking, and smoke exposed groups were compared on CBCL and CSI measures of depression/anxiety, conduct problems/aggression, and inattention/hyperactivity to determine if smoke exposure was indeed specific to externalizing symptoms as reported previously. The result from the MANOVA with externalizing measures was significant, Wilks' $\lambda = .81$, $P = .003$, indicating that 19% of the variance in externalizing outcomes was accounted for by smoking group status. The result from the MANOVA with internalizing measures approached significance, Wilks' $\lambda = .911$, $P = .061$, indicating that 8.9% of the variance in internalizing outcomes was accounted for by smoking group status. Results from the omnibus ANOVAs run for each diagnostic measure are presented in Table 1. Significant group differences were found only for externalizing measures of psychopathology, including CBCL attention problems, CBCL aggression, CSI CD, and CSI ADHD. The result for the CSI ODD scale was significant only at the trend level, $P = .082$. Because the MANOVA including internalizing measures approached significance, follow-up ANOVAs were examined, yet no significant univariate effects were found.

Table 1 Group means (and standard deviations) on measures of child psychopathology

Psychopathology scale	Non-smoking($n = 96$)	Smoking ($n = 21$)	2nd hand exposure($n = 16$)	F (2, 132)
Externalizing measures				
CSI conduct disorder	4.98 (4.66)	9.05 (5.41)	9.69 (8.84)	8.63**
CSI ADHD	29.51 (11.67)	38.24 (9.75)	37.94 (11.07)	7.70**
CBCL attention problems	71.92 (10.51)	78.57 (10.67)	76.06 (9.21)	4.10*
CBCL aggression	71.34 (12.29)	77.14 (10.44)	77.56 (12.82)	3.27*
Internalizing measures				
CSI depression	6.77 (4.61)	9.29 (6.08)	8.44 (6.81)	2.44
CSI dysthymia	6.65 (3.86)	8.71 (5.18)	7.44 (5.20)	2.10
CBCL anxious/ depressed	73.51 (11.64)	71.57 (14.66)	73.44 (10.65)	0.23

Notes. CBCL = Child Behavior Checklist (Achenbach, 1991); CSI = Child Symptom Inventory (Gadow & Sprafkin, 1997)

*$P < .05$. **$P < .01$

Tukey HSD post hoc comparisons indicated that both the smoking group and the second hand exposure group had significantly higher CD symptom scores than the non-smoking group, $P = .006$, $d = 0.81$ and $P = .005$, $d = 0.70$, respectively. These groups did not differ from each other, $P = .933$, $d = .09$. Similarly, both the smoking and second hand exposure groups had significantly higher ADHD scores than the non-smoking group, $P = .005$, $d = .82$ and $P = .018$, $d = .74$ respectively, yet they did not differ from each other, $P = .996$, d = .03. For the CBCL attention scale, group differences were only significant for the comparison of the smoking group to the non-smoking group, $P = .024$, $d = .14$. The second hand exposure group did not differ from the non-smoking group on the CBCL attention scale, $P = .305$, $d = .42$. Although the omnibus F-test for group differences on the CBCL aggression scale was significant, follow up comparisons were not significant for any individual contrast.

Next, regression analyses were run to determine if smoke exposure predicted CD symptoms, over and above the effects of control variables. Household income, maternal and paternal antisocial symptoms, child birth weight, child gestational age at birth, maternal use of alcohol and other substances during pregnancy, and maternal smoke exposure were all entered as predictors of CD symptoms. Results of the regression are shown in Table 2. With all variables entered into the equation, the model was significant, $R^2 = .14$, $P = .019$. Only smoke exposure yielded a significant coefficient. A parallel regression was then run with ADHD as the dependent variable. With all variables in the equation the model was significant, $R^2 = .144$, $P = .015$. Again, only the smoke exposure score yielded a significant coefficient.

Table 2 Simultaneous multiple regression analysis evaluating smoke exposure as a predictor of conduct disorder and ADHD symptoms

Variable	B	SE B	β	P
Conduct disorder				
Income	−0.02	0.02	−.14	.181
Maternal ASPD	0.16	0.18	.08	.377
Paternal ASPD	0.18	0.22	.08	.423
Birth weight	0.30	0.45	.07	.502
Gestational age	0.05	0.23	.02	.839
Substance use	−2.07	2.11	−.09	.328
Smoke exposure	0.44	0.17	.24*	.013
ADHD				
Income	−0.04	0.034	−.13	.194
Maternal ASPD	0.24	0.363	.06	.517
Paternal ASPD	0.17	0.456	.04	.709
Birth weight	−1.15	0.92	−.14	.215
Gestational age	.57	0.49	.13	.240
Substance use	−2.67	4.35	−.06	.540
Smoke exposure	.98	.36	.25	.007

Note. $N = 117$

*$P < .05$

A second simultaneous regression was run with the subset of participants from Study 1, which enabled us to control for parenting variables. The same predictors were entered as in the first regression while adding the PS subscales, including laxness, overreactivity, and verbosity. Results of the regression are reported in Table 3. With all variables in the regression equation, the model was significant, R^2 = .288, P = .007. Parental laxness, maternal ASPD, and smoke exposure provided independent prediction to CD symptoms. The same regression was repeated with ADHD as the dependent variable. Once again, the model was significant, R^2 = .25, P = .026. Smoke exposure was the only variable that provided independent prediction to ADHD symptoms.

Discussion

Results from this study support a direct role of cigarette smoke exposure in the transmission of risk for childhood externalizing behaviors. Children exposed in utero to cigarette smoke, regardless of whether or not the exposure was direct or second hand, showed more severe symptom scores for both CD and ADHD. The finding that this effect was not specific to CD, as previously reported [5], suggests that nicotinic programming influences

Table 3 Regression analysis of Study 1 evaluating smoke exposure as a predictor of conduct disorder and ADHD symptoms

Variable	B	SE B	β	P
Conduct disorder				
Income	0.02	0.02	.01	.906
Maternal ASPD	0.47	0.21	.24	.032
Paternal ASPD	0.13	0.26	.06	.621
Birth weight	−0.33	0.51	−.09	.517
Gestational age	0.39	0.25	.21	.128
Substance use	−1.67	2.01	−.09	.407
Laxness	0.17	0.07	.31	.016
Overreactivity	0.03	0.07	.05	.664
Verbosity	−0.15	0.10	−.20	.125
Smoke exposure	0.47	0.20	.25	.023
ADHD				
Income	−0.04	0.04	−.13	.309
Maternal ASPD	0.70	0.49	.16	.156
Paternal ASPD	−0.12	0.59	−.02	.839
Birth weight	−1.82	1.18	−.23	.127
Gestational age	1.06	0.58	.26	.073
Substance use	−2.02	4.59	−.05	.662
Laxness	−0.13	0.16	−.11	.396
Overreactivity	0.22	0.16	.18	.168
Verbosity	−0.20	0.22	−.12	.371
Smoke exposure	1.31	0.47	.31	.007

Note. N = 79

impart a general vulnerability for impulsive behavior rather than CD per se. Indeed, prenatal smoke exposure has been associated with the full range of externalizing behaviors, including the propensity of the offspring to abuse substances later in life [41]. It is likely that environmental factors that often differ among smokers and non-smokers, such as income, parental psychopathology, and parenting practices serve to shape impulsive tendencies into more specific diagnostic entities over the course of development, an interpretation supported indirectly by research indicating a single latent impulsivity trait as the substrate of a wide range of externalizing disorders [42].

The specificity of the relationship between maternal smoking and externalizing symptoms as opposed to internalizing symptoms follows from a large body of research linking nicotine to functional and structural brain changes in regions known to be critical in the development of externalizing psychopathology, including the mesolimbic dopamine system. Nicotinic receptors are abundant on dopamine terminals, particularly in the striatal regions, leading to the vulnerability of these cells to the toxic effects of nicotine [15]. Research has shown that prenatal administration of nicotine decreases the sensitivity of dopaminergic cells in the nucleus accumbens to administration of acute doses of nicotine later in life, indicating that these cells required higher levels of stimulation to instigate dopamine release [43]. Furthermore, both cell numbers and transcription rates of nicotinic receptors in dopaminergic cells of the ventral tegmental area (VTA) are reduced following prenatal nicotine administration, affecting dopaminergic action in both the VTA and its target regions including the nucleus accumbens and prefrontal cortex through adolescence [44]. This may serve as a mechanism for the increased drug and novelty seeking typically engaged in by externalizing individuals, whereby higher levels of stimulation are sought in order to achieve normative responses of the dopaminergic reward system [44]. In contrast, correlates of smoking such as low socioeconomic status, parental antisocial behaviors, perinatal complications, and poor parenting practices do not show diagnostic specificity and have been associated with both externalizing and internalizing disorders in offspring [45, 46, 47].

The current study provides both replication and extension of previous research demonstrating associations between smoking and externalizing outcomes [48, 2]. This consistent replication is remarkable given the inconsistencies across studies in defining the externalizing outcome variables of interest, and given methodological inconsistencies in defining maternal smoking. Moreover, retrospective reporting of a socially undesirable trait is likely to introduce substantial measurement error, and significant underestimation of the true degree of maternal smoking that occurred among study participants. Alternatively, the consistency of such findings could result from antisocial mothers being more willing to report an undesirable trait. However, by extending the association to that of second hand smoke, artifacts attributable to social desirability are likely eliminated. Thus, the strong association between smoke exposure and child externalizing symptoms remains regardless of maternal smoking behavior and as such, the role of nicotine exposure in the development of psychopathology warrants further investigation.

Future research should explore more fully the psychological characteristics of mothers exposed to second hand smoke. Interestingly, in the current study mother's who were exposed to second hand smoke did not differ from non-smoking mothers in level of education, whereas both groups were significantly higher than mothers who smoked during pregnancy. This finding is not surprising given that low education is a likely correlate of the decision to smoke during pregnancy, but it argues against the assumption that similar demographics may apply to women who are exposed second hand. Additionally, this pattern of findings suggests that maternal education is not likely to account for the pattern of increased externalizing symptom severity in smoke exposed offspring.

Another possibility is that mothers are exposed to significant amounts of second hand smoke when they associate with antisocial men who are more likely to smoke in their presence. Thus, even among women who do not smoke, a genetic explanation may apply through transmission via the father. The current study was not able to assess paternal ASPD directly as discussed. However, maternal reports of paternal ASPD did not diminish the relationship between smoke exposure and child externalizing behaviors. Although exposure in the home is likely to be associated with a genetic relative of the child's (either the child's father or grandparents if the mother lives at home with family) exposure in the workplace is independent of any genetic correlates and represents a purely environmental risk. Many workplaces, particularly restaurants, permit smoking and employees may be exposed to significant levels of smoke for 8 hours per day or more. Further research examining workplace exposure may be warranted.

Limitations of the current study include indirect assessments of fathers' contributions to child outcomes. No parenting variables were available for fathers, and fathers did not report on their own antisocial behavior. Although maternal reports of antisocial behavior are common in research, these reports may represent an underestimate of paternal antisociality, as some mothers may not have contact with antisocial fathers and thus may not have enough information to report on all antisocial behaviors. Inaccuracy in reporting paternal antisocial symptoms may have contributed to the failure of these symptoms to provide independent prediction to child conduct disorder as would be expected. Although parental antisocial behavior was controlled, parental ADHD was not assessed and may contribute to offspring externalizing behavior directly.

Furthermore, past research has suggested that chronicity of maternal smoking and not prenatal smoking exposure per se are more predictive of offspring antisocial traits (Maughan, et al., 2004). Such findings raise the possibility that passive exposure in the child's environment continues to impart a programming effect on neural development, suggesting that postnatal smoke exposure should also be explored for its role in neurodevelopment. In order to control optimally for all alternative routes of exposure, future studies should assess blood or urine levels of nicotine metabolites to establish smoking groups rather than relying on self report. Such assessments could be made of both the mother and the infant, thereby increasing precision in measurement by correcting for recall failures and biases, and by correcting for individual differences in metabolic factors affecting circulating levels of nicotine.

This is the first study to associate second hand smoke exposure with psychopathological outcomes in the offspring of pregnant women. The current findings should be considered preliminary given the small sample size, particularly in the second hand exposure group. However, the results support an environmental programming effect of nicotine and as such have important implications for public policies regarding healthy work environments for women of child bearing age, such as initiatives to eliminate indoor smoking in public settings. Further exploration of the effects of second hand exposure to environmental smoke is warranted.

Summary

The purpose of the present study was to examine the relationship between prenatal smoke exposure and offspring externalizing behavior with respect to the many psychosocial confounds that have been raised. Despite the fact that prenatal smoke exposure has been

robustly associated with a wide range of externalizing outcomes, concerns regarding potential genetic explanations accounted for by the unique characteristics of mothers who chose to smoke during their pregnancy has cast doubt on the veracity of this association. In an attempt to address this concern, we have examined women who did not smoke during their pregnancy, but who were exposed to significant levels of second hand smoke during that time. Findings indicate that regardless of route of exposure (direct or passive), smoke exposure was associated with significant increases in offspring externalizing symptoms in comparison to offspring of women who had no prenatal smoke exposure. Furthermore, regression analyses confirm this association even when controlling for demographic (household income), perinatal (birth weight, gestational age), and diagnostic (maternal and paternal ASPD) variables. Thus there is support for a direct association between prenatal smoke exposure and externalizing vulnerability that is consistent with experimental research with animals. Future examination of the psychological effects of second hand smoke exposure is warranted from both a psychological and public policy perspective.

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