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Prenatal tobacco exposure, birthweight, and offspring psychopathology

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Abstract

Although prenatal tobacco exposure (PTE) is associated with several adverse offspring mental health outcomes, mechanisms remain unclear. We test whether associations between PTE and offspring psychopathology are explained by birthweight, one of the earliest-occurring outcomes of PTE. The analysis focuses on 238 offspring from a family study of depression with (1) collected prenatal histories and (2) at least one clinical interview in adulthood to assess psychiatric problems. Exposure was categorized by maternal smoking of 10 cigarettes daily/nearly daily; diagnostic outcomes were confirmed by clinicians using the best-estimate procedure, blind to exposure. After adjusting for potential confounders, PTE was associated with 0.7 lb(9%) lower birthweight ($p=0.0002$), increased rates of disruptive behavior disorders [males: $OR=2.66(1.15,6.16)$, and (trend) substance use disorders [females: $OR=2.23(0.98,5.09)$], and decreased rates of mood disorders (males: $OR=0.42(0.17,0.98)$]. Birthweight was not independently associated with diagnoses and did not mediate the association between exposure and psychopathology. Maternal smoking has long-term adverse consequences for offspring. Although birthweight cannot be manipulated, smoking is a modifiable risk factor. Thus, cessation efforts focused on pregnant women may not only improve maternal wellbeing, but also mitigate adverse proximal (e.g., birthweight) and long-term (psychopathology) outcomes in offspring.

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1. Introduction

Fetal exposure to maternal smoking in pregnancy has been associated with a number of psychiatric problems (Fried et al., 1987; Williams et al., 1998) and disorders in the offspring (Nigg and Breslau, 2007; O'Callaghan et al., 2009). Despite a plausible biological framework for modulation of neurodevelopment by nicotine (Slotkin et al., 2006), the degree to which observed offspring problems represent a *direct* effect of exposure remains unclear (Al Mamun et al., 2006; D'Onofrio et al., 2010; Knopik, 2009).

Because most psychiatric diagnoses do not fully emerge until several years after the exposure period, examining intermediate factors that lie closer to exposure could help clarify etiological pathways. One such factor is birthweight. Children born to mothers who smoke in pregnancy are typically about 5% smaller than their unexposed counterparts, and twice as likely to be classified as low-birthweight (<2500g) (Bernstein et al., 2000; Churchwell and Yurgelun-Todd, 2013). While several factors control birthweight, nicotine is thought to do so by constricting placental blood flow, thereby increasing fetal risk for malnutrition (Ernst et al., 2001; Lips et al., 2005). Other cigarette ingredients (carbon monoxide, beta-carbolines) can also impede growth by disrupting fetal access to oxygen (Lambers and Clark, 1996). Though other factors such as maternal alcohol consumption and nutrition affect birthweight as well, maternal smoking in pregnancy is estimated as one of the biggest determinants of low birthweight in developed countries (Bada et al., 2005). At the same time, birthweight is a risk factor itself for subsequent developmental, cognitive, and emotional problems (Breslau et al., 2000; Indredavik et al., 2004; Rimol et al., 2016). Although prenatal tobacco exposure and birthweight each contribute independent risks, there may also exacerbate the effects of each other. For example, the impairments in neural development resulting from tobacco exposure may further prevent the brain from corrective efforts (such as increasing blood flow) to counter the effects of low birthweight, further exacerbating the effects of exposure on long-term outcomes (El Marroun et al., 2014).

Although gestational exposures to smoking and low birthweight have each been independently associated with psychopathology, it is less clear as to whether birthweight lies on a *causal* pathway linking tobacco exposure and subsequent pathology. One study found birthweight to account for 6.6% of the association between *in utero* exposure and parent or teacher ratings of child externalizing behaviors (Parker et al., 2016). However, offspring in that study had not passed through the age of risk (age range, 5–12yrs), and psychiatric diagnoses were not examined. Another study reported that while both tobacco exposure and birthweight were independently associated with disruptive behaviors, birthweight did not account for the effects of exposure (Nigg and Breslau, 2007).

We followed a 3-generation cohort of offspring of families with and without major depressive disorder (MDD) over six assessment waves spanning up to 30 years (Weissman et al., 2006; Weissman MM, 2016). Although not originally designed to study prenatal exposures, several aspects allow us to examine the effects of prenatal smoking on offspring, including (1) detailed prenatal history that included reports of maternal smoking, substance, and medication use during pregnancy; (2) prospective assessments of psychiatric and

behavioral outcomes, blind to exposure status; and (3) lifetime psychiatric histories on both parents. On the other hand, because the study was originally designed to study depression, findings may not be representative of the population at large.

We previously noted, in a subsample of 147 offspring that females exposed to maternal smoking had increased rates of drug use, and males, higher rates of conduct disorder (Weissman et al., 1999). Since then, offspring have been followed for another 10–20 years, and new offspring have aged in. We now classify 238 offspring based on their prenatal tobacco exposure status, to examine the associations between exposure and birthweight; between exposure and psychopathology; and test whether birthweight accounts for the relationship between exposure and psychopathology.

2. Method

2.1 Background

The sample was originally recruited to study transmission of major depressive disorder (MDD) across generations, and has been detailed in previous publications (Weissman et al., 2006; Weissman MM, 2016). Briefly, the first generation probands (G1) were selected in 1982 from outpatient clinical specialty settings for the treatment of mood disorders, and had moderate to severe MDD. Non-depressed probands were selected concurrently from a sample of adults from the same community, and were required to have no lifetime history of psychiatric illness. Both groups were screened to eliminate subjects with primary diagnoses of substance use or antisocial personality disorders. Offspring of these probands (G2) were then followed prospectively for up to six waves spanning 30 years (time [years] ~1, 2, 10, 20, 30). Procedures were kept similar across waves, with minor exceptions, to avoid method variation bias. All procedures were approved by the institutional review board at New York State Psychiatric Institute/Columbia University, and informed consent was obtained from all study participants.

2.2 Sample

Offspring were classified based on whether or not their mother smoked during pregnancy as classified at the first wave of the study (time 1; 8/1982–2/1984). There were a total 240 eligible offspring, from 88 mothers. For the present study, we included the 238 (>99%) offspring who were also interviewed independently at least once at time 10, 20, or 30. The first interview assessed the lifespan to date; subsequent interviews assessed intervening time periods. The total assessment period, therefore, is always from birth to year of final interview, regardless of the number of interviews or the age at first interview. The average offspring age at time 1 (that is, when prenatal histories were collected) was 17.0 ± 4.8 yrs (range 6–23). At final interview, age was 44.7 ± 8.8 yrs, representing a mean follow-up of 27.7 years. Neither age varied by prenatal exposure status.

2.3 Maternal assessments

Mothers completed a parent-on-child report for each child, which included questions about the course of pregnancy, delivery, and the child's early developmental history. Mothers were asked whether they had smoked while pregnant, and if so, how frequently they smoked 10 or

more cigarettes per day: [1–2 times; 3–5 times; 6–10 times; every two weeks; weekly; or daily/nearly every day]. Because most mothers reported either not smoking at all (61%), or 10 cigarettes daily/nearly daily (28%), we generated a dichotomous variable based on whether or not the mother reported smoking 10 cigarettes/day. Similar classifications have been used in the psychiatric literature (Cornelius et al., 2000; Hoff et al., 1986), and findings were essentially unchanged when smoking was coded as a continuous variable, or when the intermediate smokers were excluded from the analysis.

2.4 Offspring assessments

Offspring were interviewed using the semi-structured Schedule for Affective Disorders and Schizophrenia (SADS)-Lifetime Version for adults (Mannuzza et al., 1986), or the child version for ages 6–17 (Kaufman et al., 1997). Assessments were administered by trained doctoral- and masters-level mental health professionals, blind to the clinical status of the parents. Final diagnoses were made using the best-estimate procedure (Leckman et al., 1982) by 1 experienced clinician not involved in the interviewing, and blind to parental exposure status. Inter-rater reliability scores, detailed elsewhere (Weissman et al., 1999), were high.

2.5 Statistical analyses

Analyses were conducted using Statistical Analysis Software (SAS 9.4/Carey NC). Initial comparisons were conducted using chi-square tests for categorical and two-tailed t-tests for continuous variables. Sex differences were tested with the Breslow-Day Test, which tests the null hypothesis that the association between exposure and outcome is the same across the sexes. To formally estimate effects of exposure on outcome, while adjusting for potential non-independence of outcomes among offspring from the same family, we used a generalized estimating equations (GEE) approach by means of the GENMOD procedure in SAS. All analyses were adjusted for familial risk for depression, offspring age at final interview, and sex (except in the sex-specific models). Further covariates were included as specified. Given the overall focus on externalizing disorders and prior findings showing differential effects in females and males, we made an a priori decision to test all findings in the full sample (primary) as well as in each gender separately.

To test whether birthweight (BW) mediated the associations between exposure, X, and diagnosis, Y, we first modeled the relationship between exposure and diagnosis without (model 1: $Y = \beta_1 X$) and with (model 2: $Y = \beta_1 X + \beta_2 BW$). To meet criteria for mediation, exposure had to be significantly associated with outcome (i.e., β_1 in model 1 significant), and this association attenuated by at least 10% following inclusion of birthweight into the model (i.e., $\beta_1\text{-model 2} / \beta_1\text{-model 1} < .90$). Because none of the models met these criteria (table 4), no further paths were tested.

3. Results

Mothers who smoked 10 cigarettes daily/nearly daily during pregnancy did not differ from those who did not on demographic or pregnancy-related characteristics (Table 1). Mothers who smoked were more likely to have consumed *any* alcohol in pregnancy, but there were no differences in chronic use, with only 3 mothers in each group reporting drinking more than

one glass every 2 weeks. Average offspring age at last follow-up was 44.7 ± 8.8 yrs, and 122 (51%) were female. Age, sex, and familial risk for depression did not vary by prenatal exposure (Table 1, bottom). If the mother smoked, she was more likely to have a lifetime history of nicotine dependence or other substance use, and her spouse more likely to have nicotine dependence or an anxiety disorder (Table 2).

3.1 Maternal prenatal smoking and offspring birthweight

Offspring of mothers who smoked during pregnancy had significantly lower birthweight than those who did not (*exposed*, mean lbs (std): 6.76 (1.31), *unexposed*, 7.46 (1.24); a 0.7 lb (9.4%) decrease, d.f.=236, $p=0.0002$). Twice as many exposed (16%) as compared to unexposed (7%) met formal criteria for low birthweight ($<2500\text{g}/5.5\text{lbs}$; $\chi^2=5.95$, d.f.=1, $p=0.015$). Exposure did not increase risk for premature birth however: 15% of exposed, and 13% of unexposed, were born >2 weeks prior to scheduled delivery date ($\chi^2=0.56$, d.f.=1, $p=0.46$).

Offspring birthweight was not predicted by maternal alcohol use, medication use, complications during pregnancy or delivery, by maternal lifetime smoking, or by any other maternal psychiatric diagnosis (e-Table 1). After accounting for maternal alcohol use during pregnancy, any psychiatric diagnosis in either parent, and gestational age, prenatal exposure to smoking remained the only significant predictor of offspring birthweight (-0.86 lbs, $t=4.61$, d.f.=236, $p<0.0001$).

3.2 Maternal prenatal smoking and offspring psychopathology

Exposed offspring had higher rates of disruptive behavior disorder (Table 3, left). Exploration by gender revealed the associations to be largely accounted for by conduct disorder in males. Associations for the former were concentrated among male offspring.

We next formally modeled the effect of prenatal exposure on each psychiatric diagnosis, adjusting for offspring age, sex (except in the sex-specific models), familial history for depression, and potential non-independence of outcomes among related individuals (Table 4, *Model A*, see caption for details). We then iteratively repeated the models further co-varying for lifetime nicotine dependence (*model B*), presence of the offspring psychiatric outcome (*Model C*), and any lifetime diagnosis (*Model D*) in either parent.

These models confirm that exposure to smoking remained associated with a more than two fold increased risk of disruptive behavior disorder, and more than two-fold decreased risk of any mood disorder, in males only (note trend for increased substance use disorders among exposed females) .

3.3 Maternal prenatal smoking, offspring birthweight, and offspring psychopathology

Finally, we tested whether birthweight accounted for associations between parental exposure and mood and disruptive behavior disorders, as found in Table 3. As shown in Table 5, birthweight did not explain this relationship, as evidenced by the lack of 10% reduction of significant exposure coefficients from birthweight-unadjusted to -adjusted models.

Birthweight was also not independently associated with any psychiatric outcomes except major depression and other mood disorders, where low birthweight appeared protective.

4. Discussion

Consistent with the literature on adverse effects of intrauterine exposure to tobacco, we find that offspring of mothers who smoke while pregnant have lower birthweight, as well as higher rates of externalizing psychopathology, notably disruptive behavior (trend for substance use in females). The findings are consistent with our earlier report (Weissman et al., 1999), and hold after accounting for lifetime nicotine dependence or other lifetime psychopathology in either parent. Importantly, birthweight did not mediate associations between exposure and any internalizing or externalizing psychopathology, indicating that the biological mechanisms through exposure increases risks for psychopathology are not operating through lower birthweight and consequently, that efforts aimed at improving birthweight would not reduce offspring risk. To our knowledge, this report represents the longest assessment period of any published study examining psychiatric outcomes of *in utero* exposures during pregnancy.

Nicotine, as well as other tobacco components, cross the placenta, and when the mother smokes chronically, can reach even higher levels in the fetus than in the mother (Lambers and Clark, 1996; Rogers, 2009). Cholinergic nicotinic receptors are located throughout the fetal brain, including on both serotonergic and dopaminergic neurons, and excessive stimulation of these receptors during gestation can change their sensitivity, leading to impaired neural growth and circuit formation (Ernst et al., 2001; Slotkin et al., 2006). Though some of the deficits may be seen in early life, others may not fully appear until childhood or adolescence, once brain circuits regulating behavioral control have matured (Baler et al., 2008; Wakschlag et al., 2002).

Our findings are consistent with other literature for externalizing, but inconsistent for internalizing disorders. Our finding of increased disruptive behavior disorders, which were accounted for by conduct disorder among males, is consistent with many previous studies (Baler et al., 2008; Lotfipour et al., 2014; Wakschlag and Hans, 2002; Wakschlag et al., 2002). In the present study, we further show that this risk is not a function of birthweight. We also previously reported higher rates of substance use disorders among exposed female offspring (Weissman et al., 1999), a finding also noted elsewhere (Brennan et al., 2002). In the present study we only observed a trend. This could be because in the earlier report, offspring were ~20 years younger, and the baseline rates of substance use (that is, the rates in the unexposed offspring) were lower, thereby allowing incremental risk conferred by exposure to be more clearly detectable. The higher rates baseline rates of substance use disorders in male offspring (43%, vs 25% in females) may have also contributed to a lack of detecting an exposure effect.

Finally, we found prenatal exposure appeared to protect against depression in males. Findings on the effects of prenatal exposure on internalizing disorders have been mixed, with some studies reporting increased associations with anxiety and depression, and others not [e.g., (Ashford et al., 2008; Carter et al., 2008; Hettema et al., 2005; Moylan et al., 2015;

Robinson et al., 2010)]. However, no study to our knowledge has reported a protective effect. Although we had not previously noted any overall associations in our earlier work either, stratifying the overall results in that work showed that the relative risk in males over 18 (as males under 18 would have lower risk for developing depression), though non-significant, was less than one, suggesting a potential protective effect.

We acknowledge a number of limitations. The study was designed to evaluate cross-generational effects of psychopathology; rates of disorders, and associations between smoking and diagnoses, may not reflect those in the general population. Although exposure was assessed independently of, earlier to, and with a different informant than, offspring diagnoses, collection was still retrospective (average, 17 yrs after pregnancy), and is subject to recall and reporting biases. There could be misclassification, for example, if mothers of children with emotional or behavioral problems in adolescence reported their tobacco use differently from those without. Mothers were also not blind to the child's birthweight status, which could have influenced their report on prenatal tobacco exposure as well. Independent biological verification (e.g., cotinine) would have been useful, but were not part of the original design, and in any case, studies generally report high correlations between biological and self-reported measures in both pregnant and non-pregnant women (Klebanoff et al., 1998; Malcon et al., 2008; Pickett et al., 2009; Vartiainen et al., 2002). Birthweight could also be a proxy for other factors (e.g., maternal malnutrition, illness, stress) that may commonly predispose the mother to smoke and the offspring to have lower birthweight (Marceau et al., 2016). On the other hand, the parent sample was selected to be free of a lifetime history of schizophrenia, bipolar disorder, antisocial personality disorder (the adult presentation of conduct) and substance use disorders. This reduces the likelihood of the findings being driven by smoking in pregnancy being a proxy for these disorders in the parent generation.

Despite significant declines, 15% of US pregnant women continue to smoke (Tong, 2009), and smoking remains a leading cause of preventable illness among pregnant mothers and offspring (CDC, 2006). We show that exposure is associated with low birthweight and with externalizing psychopathology (particularly in male offspring), although these two pathways do not appear linked. But although birthweight cannot be directly manipulated, smoking is a modifiable risk factor. Thus, cessation efforts focused on pregnant women may not only improve maternal wellbeing, but also mitigate both proximal (e.g., birthweight) and long-term (psychopathology) outcomes in offspring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Relationship between offspring prenatal exposure and maternal demographic and pregnancy-related characteristics

	Maternal Prenatal Smoking		
	NO	YES	Group differences
	N = 164	N = 74	
Demography			
Socioeconomic Status ⁴			
Class I ⁵	5 (8)	12 (9)	$\chi^2 = 0.87^1$ $p = 0.93$
Class II	9 (15)	22 (17)	
Class III	14 (24)	25 (19)	
Class IV	25 (42)	62 (47)	
Class V	6 (10)	11 (8)	
Pregnancy and Delivery			
Mother's Age at Delivery (yrs, std)	26.6 (5.6)	26.4 (4.6)	$t = 0.18^2$, $p = 0.89$
Father's Age at Delivery (yrs, std)	29.5 (6.8)	28.6 (4.7)	$t = 1.01^2$, $p = 0.31$
Complications during pregnancy ⁶ , N (%)	42 (26)	13 (18)	$\chi^2 = 1.77$, $p = 0.18$
Complications during delivery ⁷ , N (%)	35 (21)	19 (26)	$\chi^2 = 0.60$, $p = 0.43$
No. of Prior Pregnancies (mean, std)	1.2 (0.6)	1.3 (0.6)	$t = 0.28$, $p = 0.78$
Medication Use ⁸ , N (%)	25 (16)	9 (13)	$\chi^2 = 0.33$, $p = 0.56$
Substance Use in pregnancy, N (%)			
Any Drug Use ⁹	0	1	–
Any Alcohol Use ⁹	21 (13)	23 (32)	$\chi^2 = 11.6$, $p = 0.0007$
Continuous Alcohol Use ¹⁰	3 (2)	3 (4)	0.38^{12}
Offspring			
Female, N (%)	84 (51)	38 (51)	$\chi^2 = 0.20$, $p = 0.84$
High Familial Risk, N (%)	107 (65)	53 (72)	$\chi^2 = 0.0004$, $p = 0.99$
Age at last follow-up (mean, std)	44.9 (8.4)	44.5 (9.8)	$t = 0.94^3$, $p = 0.33$

All tests have one degree of freedom except

¹(4 d.f.),

²(232 d.f.) and

³(236 d.f.).

⁴Data were missing for 47 households. (Note, marital status and race/ethnicity were not tested as, due to the study design, all mothers were married, and all were of Caucasian ancestry)

⁵Class I indicates the highest, and V, the lowest class

⁶Reported complications included severe nausea and vomiting, vaginal bleeding, toxemia, or anemia

⁷Reported complications included unusual presentation at delivery/breech, use of forceps, tight or knotted cord, blueness at birth, lack of breath for 1–3 mins or requirement of oxygen for 1 min, cry weak or abnormal, fetal distress (meconium fluid or fetal heart rate under 100).

⁸Includes antibiotics, nausea pills, blood pressure medication, thyroid, tranquilizers, sedatives, pain killers.

⁹Any use during pregnancy

¹⁰Defined as 2 drinks per day, at least every two weeks in pregnancy

¹¹Fisher's Exact Test

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Table 2

Relationship between offspring prenatal exposure and maternal and paternal clinical history

	Maternal Prenatal Smoking		
	NO	YES	Group differences
	N = 164	N = 74	
<i>Parental Lifetime Psychiatric History, N(%)</i>			
<i>Mother</i>			
Major Depression	84 (51)	44 (61)	$\chi^2 = 1.97$ $p= 0.16$
Any Mood Disorder ¹	87 (53)	47 (65)	$\chi^2 = 3.04$, $p= 0.081$
Any Anxiety Disorder ²	120 (73)	50 (70)	$\chi^2 = 0.35$, $p= 0.56$
Any Substance Use Disorder ³	10 (6)	13 (16)	$\chi^2 = 6.62$, $p= 0.010$
Nicotine Dependence	14 (8)	13 (18)	$\chi^2 = 4.48$, $p= 0.034$
<i>Father</i>			
Major Depression	59 (36)	20 (29)	$\chi^2 = 1.04$, $p= 0.31$
Any Mood Disorder ¹	64 (39)	25 (38)	$\chi^2 = 0.032$, $p= 0.86$
Any Anxiety Disorder ²	57 (35)	34 (50)	$\chi^2 = 4.39$, $p= 0.036$
Any Substance Use Disorder ³	41 (25)	21 (30)	$\chi^2 = 0.76$, $p= 0.38$
Nicotine Dependence	13 (8)	19 (29)	$\chi^2 = 15.86$, $p < 0.0001$

(All tests have one degree of freedom).

¹Includes major or minor depressive disorder, or dysthymia.²Includes generalized anxiety disorder, obsessive compulsive disorder, panic disorder, separation anxiety disorder, social anxiety disorder, or specific (simple) phobia (anxiety disorders were not examined individually due to low Ns).³Includes drug or alcohol abuse or dependence (excludes nicotine dependence).

TABLE 3

Rates of Diagnoses by Prenatal Exposure to maternal smoking

	-----Full Sample-----				-----Female-----				-----Male-----				Exposure x Sex	
	<i>In Utero Exposure</i>				<i>In Utero Exposure</i>				<i>In Utero Exposure</i>					
	NO N = 164	YES N = 74	Chi-Square (χ^2), p		NO N = 84	YES N = 38	Chi-Square (χ^2), p		NO N = 80	YES N = 36	Chi-Square (χ^2), p		p	
	N (%)	N (%)			N (%)	N (%)			N (%)	N (%)				
<i>Diagnoses¹</i>														
Major Depression	77 (45)	40 (54)	$\chi^2=0.029$, p=0.31		46 (52)	22 (57)	$\chi^2=0.10$, p=0.75		31 (38)	18 (50)	$\chi^2=1.28$, p=0.25		0.55	
Any Mood Disorder	114 (70)	48 (65)	$\chi^2=0.51$, p=0.48		59 (70)	29 (76)	$\chi^2=0.48$, p=0.49		55 (68)	19 (52)	$\chi^2=2.74$, p=0.097		0.10	
Any Anxiety Disorder	81 (51)	31 (42)	$\chi^2=1.77$, p=0.18		54 (64)	19 (60)	$\chi^2=2.22$, p=0.14		30 (37)	12 (33)	$\chi^2=0.19$, p=0.66		0.48	
Any Disruptive Behavior ³	46 (28)	33 (45)	$\chi^2=6.29$, p=0.012		18 (21)	12 (32)	$\chi^2=1.45$, p=0.23		28 (35)	21 (58)	$\chi^2=5.54$, p=0.018		0.47	
(ADHD)	13 (7)	9 (12)	$\chi^2=1.09$, p=0.29		2 (2)	3 (8)	p = 0.17 ¹		11 (13)	6 (16)	$\chi^2=0.16$, p=0.68		0.33	
(Conduct Disorder)	40 (24)	26 (35)	$\chi^2=2.93$, p=0.086		17 (20)	8 (21)	$\chi^2=0.010$, p=0.91		23 (28)	18 (50)	$\chi^2=4.91$, p=0.026		0.18	
Any Substance Use Disorder	56 (34)	30 (41)	$\chi^2=0.90$, p=0.34		21 (25)	16 (42)	$\chi^2=3.6$, p=0.057		35 (43)	14 (39)	$\chi^2=0.24$, p=0.62		0.091	
Nicotine Dependence	25 (15)	11 (15)	$\chi^2=0.0057$, p=0.94		12 (14)	9 (23)	$\chi^2=1.62$, p=0.21		13 (16)	2 (6)	p = 0.14 ²		–	

All tests have one degree of freedom.

¹ See Table 2 for classification of diagnoses² Fisher's Exact Test³ We explored individual disruptive behavior disorders including ADHD and conduct (rates of oppositional defiant disorder were too low to permit analyses). Because the rates of ADHD were much lower, we only use conduct disorder and the omnibus disruptive behavior categories hereon.

Table 4

Adjusted associations between prenatal exposure and offspring psychopathology

	ALL OFFSPRINGN = 238	FEMALE ONLYN = 122	MALE ONLYN = 116
	AOR ^I (95% CI)	AOR ^I (95% CI)	AOR ^I (95% CI)
<i>Major Depressive Disorder</i>			
A: Exposure only	1.34 (0.77, 2.31)	1.14 (0.52, 2.46)	1.58 (0.72, 3.49)
B: Exposure + parental diagnosis of nicotine dependence	1.26 (0.70, 2.25)	1.24 (0.54, 2.85)	1.29 (0.55, 2.99)
C: Exposure + parental diagnosis of major depression	1.15 (0.62, 2.09)	1.21 (0.50, 2.93)	1.12 (0.46, 2.69)
D: Exposure + parental diagnosis of any disorder	1.30 (0.73, 2.31)	1.22 (0.54, 2.75)	1.42 (0.61, 3.39)
<i>Any Mood Disorder</i>			
A: Exposure only	0.81 (0.45, 1.45)	1.36 (0.56, 3.23)	0.44 (0.18, 0.99)*
B: Exposure + parental diagnosis of nicotine dependence	0.68 (0.37, 1.25)	1.24 (0.47, 3.21)	0.42 (0.17, 0.99)*
C: Exposure + parental diagnosis of any mood disorder	0.61 (0.33, 1.15)	1.41 (0.53, 3.75)	0.33 (0.13, 0.81)*
D: Exposure + parental diagnosis of any disorder	0.73 (0.40, 1.34)	1.46 (0.57, 3.71)	0.42 (0.17, 0.98)*
<i>Any Anxiety Disorder</i>			
A: Exposure only	0.69 (0.39, 1.20)	0.56 (0.25, 1.20)	0.83 (0.36, 1.91)
B: Exposure + parental diagnosis of nicotine dependence	0.49 (0.27, 0.90)	0.37 (0.15, 0.91)	0.61 (0.25, 1.47)
C: Exposure + parental diagnosis of any anxiety disorder	0.51 (0.27, 0.93)	0.45 (0.19, 1.08)	0.59 (0.23, 1.48)
D: Exposure + parental diagnosis of any disorder	0.58 (0.32, 1.03)	0.53 (0.23, 1.20)	0.58 (0.23, 1.41)
<i>Any Disruptive Disorder</i>			
A: Exposure	2.07 (1.17, 3.66)*	1.69 (0.72, 4.00)	2.60 (1.16, 5.83)*
B: Exposure + parental diagnosis of nicotine dependence	2.05 (1.14, 3.68)*	1.85 (0.76, 4.47)	2.54 (1.50, 6.12)*
C: n.a. ²	—	—	—
D: Exposure + parental diagnosis of any disorder	2.12 (1.18, 3.80)*	1.75 (0.72, 4.22)	2.66 (1.15, 6.16)*
<i>Conduct Disorder</i>			
A: Exposure only	1.68 (0.93, 3.05) ⁺	1.05 (0.41, 2.70)	2.48 (1.10, 5.59)*
B: Exposure + parental diagnosis of nicotine dependence	1.67 (0.91, 3.08) ⁺	0.53 (0.15, 1.87)	2.19 (0.95, 5.06) ⁺
C: n.a. ²	—	—	—
D: Exposure + parental diagnosis of any disorder	1.75 (0.94, 3.23) ⁺	1.08 (0.41, 2.82)	2.63 (1.05, 6.49)*
<i>Any Substance Use Disorder</i>			
A: Exposure only	1.32 (0.75, 2.31)	2.18 (0.97, 4.91) ⁺	0.82 (0.37, 1.83)
B: Exposure + parental diagnosis of nicotine dependence	1.18 (0.66, 2.11)	1.95 (0.84, 4.55)	0.79 (0.34, 1.87)
C: Exposure + parental diagnosis of substance use disorder	1.13 (0.62, 2.06)	1.62 (0.65, 3.96)	0.82 (0.35, 1.91)
D: Exposure + parental diagnosis of any disorder	1.28 (0.72, 2.28)	2.23 (0.98, 5.09) ⁺	0.80 (0.35, 1.84)
<i>Nicotine Dependence</i>			
A: Exposure only	0.97 (0.45, 2.09)	1.86 (0.71, 4.89)	0.27 (0.057, 1.28)
B: Exposure + parental diagnosis of nicotine dependence	0.91 (0.41, 1.98)	1.89 (0.70, 5.12)	0.29 (0.060, 1.44)
C: n.a., same as above ³	—	—	—
D: Exposure + parental diagnosis of any disorder	0.88 (0.41, 1.93)	1.87 (0.70, 4.94)	0.21 (0.042, 1.03)

	ALL OFFSPRINGN = 238	FEMALE ONLYN = 122	MALE ONLYN = 116
	AOR ^I (95% CI)	AOR ^I (95% CI)	AOR ^I (95% CI)

*
p<0.05;

+
p< 0.07

AOR = Adjusted Odds Ratio.

¹ All models adjust for offspring age at last interview, risk status, sex (except the sex-specific models), and within family correlations. *Model A* tests the effect of prenatal exposure on the respective psychiatric outcome after adjusting for the aforementioned variables. *Model B* retests *A* with the further inclusion of the presence of a lifetime diagnosis of nicotine dependence in either parent as a covariate; *model C* retests *Model A* with the inclusion of the presence of the child outcome of interest in either parent; finally *model D* tests the effects of prenatal exposure on child outcome after adjusting for any maternal or paternal diagnosis (including nicotine dependence).

² Model C is not applicable as no mother or father had a disruptive behavior diagnosis

³ Model C is the same as Model B for nicotine dependence, as that was the outcome being tested

Table 5

Association between prenatal exposure to maternal smoking and offspring psychopathology before and after inclusion of birthweight

Diagnoses ²	Model	ALL N = 238	FEMALE ONLY N = 122	MALE ONLY N = 116
		beta ¹ (s.e.), p value	beta ¹ (s.e.), p value	beta ¹ (s.e.), p value
<i>Major Depression</i>				
Model 1 (birthweight unadjusted)	<i>Exposure</i>	0.28 (0.28), p = 0.31	0.13 (0.40), p = 0.75	0.46 (0.40), p = 0.26
Model 2 (birthweight adjusted)	<i>Exposure</i>	0.18 (0.30), p = 0.55	-0.095 (0.42), p = 0.82	0.52 (0.43), p = 0.23
	<i>Birthweight</i>	-0.28 (0.11), p = 0.009	-0.23 (0.16), p = 0.133	-0.30 (0.15), p = 0.048
<i>Any Mood Disorder</i>				
Model 1 (birthweight unadjusted)	<i>Exposure</i>	-0.21 (0.30), p = 0.48	0.31 (0.45), p = 0.49	-0.68 (0.41), p = 0.10
Model 2 (birthweight adjusted)	<i>Exposure</i>	-0.38 (0.32), p = 0.23	0.13 (0.48), p = 0.79	-0.80 (0.45), p = 0.076
	<i>Birthweight</i>	-0.33 (0.12), p = 0.0053	-0.20 (0.17), p = 0.26	-0.40 (0.17), p = 0.018
<i>Any Anxiety Disorder</i>				
Model 1 (birthweight unadjusted)	<i>Exposure</i>	-0.38 (0.28), p = 0.18	-0.59 (0.40), p = 0.14	-0.18 (0.42), p = 0.67
Model 2 (birthweight adjusted)	<i>Exposure</i>	-0.38 (0.30), p = 0.20	-0.80 (0.43), p = 0.064	-0.010 (0.43), p = 0.98
	<i>Birthweight</i>	-0.13 (0.10), p = 0.21	-0.21 (0.16), p = 0.18	0.012 (0.15), p = 0.93
<i>Any Disruptive Behavior Disorder</i>				
Model 1 (birthweight unadjusted)	<i>Exposure</i>	0.73 (0.29), p = 0.013	0.53 (0.44), p = 0.23	0.96 (0.41), p = 0.020
Model 2 (birthweight adjusted)	<i>Exposure</i>	0.78 (0.31), p = 0.011	0.54 (0.47), p = 0.25	1.025 (0.43), p = 0.017
	<i>Birthweight</i>	0.060 (0.11), p = 0.59	0.018 (0.17), p = 0.92	-0.015 (0.15), p = 0.92
<i>Conduct Disorder</i>				
Model 1 (birthweight unadjusted)	<i>Exposure</i>	0.52 (0.30), p = 0.088	0.050 (0.48), p = 0.92	0.91 (0.41), p = 0.028
Model 2 (birthweight adjusted)	<i>Exposure</i>	0.56 (0.32), p = 0.080	0.06 (0.51), p = 0.91	0.95 (0.43), p = 0.028
	<i>Birthweight</i>	0.062 (0.11), p = 0.59	0.011 (0.18), p = 0.95	-0.0093 (0.15), p = 0.95
<i>Substance Use Disorder</i>				
Model 1 (birthweight unadjusted)	<i>Exposure</i>	0.27 (0.29), p = 0.34	0.78 (0.41), p = 0.06	-0.20 (0.41), p = 0.62
Model 2 (birthweight adjusted)	<i>Exposure</i>	0.25 (0.30), p = 0.40	0.60 (0.44), p = 0.18	-0.18 (0.43), p = 0.67
	<i>Birthweight</i>	-0.036 (0.10), p = 0.73	-0.21 (0.17), p = 0.23	0.062 (0.14), p = 0.66
<i>Nicotine Dependence</i>				
Model 1 (birthweight unadjusted)	<i>Exposure</i>	-0.030 (0.39), p = 0.94	0.62 (0.49), p = 0.21	-n.e. ³
Model 2 (birthweight adjusted)	<i>Exposure</i>	-0.25 (0.43), p = 0.55	0.50 (0.53), p = 0.34	
	<i>Birthweight</i>	-0.046 (0.14), p = 0.75	-0.12 (0.20), p = 0.54	

s.e. = standard error

¹All models adjust for offspring age at last interview, risk status, sex (except the sex-specific models), and within family correlations.

²Diagnoses classified as summarized in Table 1;

³Model could not be estimated due to low Ns.