



## Original Contribution

# Maternal and Paternal Smoking During Pregnancy and Risk of ADHD Symptoms in Offspring: Testing for Intrauterine Effects

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Maternal smoking during pregnancy is associated with attention deficit hyperactivity disorder (ADHD) in offspring. It is assumed by many that this association is causal. Others suggest that observed associations are due to unmeasured genetic factors or other confounding factors. The authors compared risks of maternal smoking during pregnancy with those of paternal smoking during pregnancy. With a causal intrauterine effect, no independent association should be observed between paternal smoking and offspring ADHD. If the association is due to confounding factors, risks of offspring ADHD should be of similar magnitudes regardless of which parent smokes. This hypothesis was tested in 8,324 children from a well-characterized United Kingdom prospective cohort study, the Avon Longitudinal Study of Parents and Children (data from 1991–2000). Associations between offspring ADHD and maternal and paternal smoking during pregnancy were compared using regression analyses. Offspring ADHD symptoms were associated with exposure to both maternal and paternal smoking during pregnancy (mothers:  $\beta = 0.25$ , 95% confidence interval: 0.18, 0.32; fathers:  $\beta = 0.21$ , 95% confidence interval: 0.15, 0.27). When paternal smoking was examined in the absence of maternal smoking, associations remained and did not appear to be due to passive smoking exposure in utero. These findings suggest that associations between maternal smoking during pregnancy and child ADHD may be due to genetic or household-level confounding rather than to causal intrauterine effects.

attention deficit disorder with hyperactivity; causality; confounding factors (epidemiology); maternal exposure; paternal exposure; pregnancy; prenatal exposure delayed effects; smoking

Abbreviations: ADHD, attention deficit hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; CI, confidence interval; DAWBA, Development and Well-Being Assessment; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; OR, odds ratio; SD, standard deviation.

Exposure to maternal smoking during pregnancy has been observed to be associated with symptoms and diagnoses of childhood attention deficit hyperactivity disorder (ADHD) (1–3). Although findings are not unequivocal, associations have been demonstrated across case-control and epidemiologic samples controlling for potentially confounding effects, with support for a dose-dependent relation whereby risk increases with the quantity of cigarettes smoked (4). Biologically plausible pathways through which smoking could affect the fetus have been proposed (2, 5) and fit with suggestions that biologic programming in utero

results in ADHD in later life (6). Thus, until recently, maternal smoking during pregnancy has mainly been viewed as a causal risk factor for ADHD.

However, smoking during pregnancy is not evenly distributed across the population. Mothers who smoke during pregnancy probably differ from those who do not (7), and it might be other factors which lead to ADHD rather than exposure to tobacco smoke. Although studies have statistically controlled for a myriad of potentially confounding factors, if risk factors are not known, have not been directly measured, have been measured with error, or are due to

inherited factors, their influence will not have been accounted for. Therefore, methods which specifically distinguish possible risk factors are needed to robustly demonstrate a causal association.

In a few studies utilizing genetically sensitive samples, researchers have attempted this (7–11). Most have suggested that the association may arise from previously unmeasured familial and inherited confounding factors, leading some epidemiologists to question the assumed causal association between maternal smoking during pregnancy and ADHD (12). Others still continue to regard it as a likely causal risk factor, which has an influence on governmental policy (13).

A report by the British Academy of Medical Sciences (14) highlighted the need to question and explicitly test assumptions that observed associations are causal, before findings can be used to inform prevention and intervention strategies. In this report, the Academy notes that the most robust causal associations have been demonstrated across study designs, while there are numerous examples where initial causal assumptions have proven to be false following specific tests of these assumptions. Therefore, we aimed to further test the causal hypothesis regarding the association between maternal smoking during pregnancy and offspring ADHD by comparing the risk incurred when exposed to maternal smoking during pregnancy with that incurred with paternal smoking during pregnancy.

Comparisons of risk between maternal and paternal smoking during pregnancy allow researchers to strengthen inferences regarding potentially causal intrauterine effects, particularly the effects of household-level confounders (15). If the influence of prenatal smoking on offspring ADHD is truly causal, maternal smoking during pregnancy should confer greater risk to the child than paternal smoking, as only the mother provides the intrauterine environment; indeed, paternal smoking should only be related to ADHD to the extent predicted by smoking-related assortative mating. If, however, observed effects are due to an association between smoking during pregnancy and other confounding factors, paternal smoking during pregnancy might also confer increased risk through both genetic and social environmental confounders.

In a longitudinal, prospective cohort study of United Kingdom children, we examined the associations of both maternal and paternal smoking with risk of offspring ADHD to further understand the putative causal basis of the former association.

## MATERIALS AND METHODS

Participants were part of the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective longitudinal study of children followed from gestation to (currently) late adolescence. The study methods have been detailed elsewhere (16). Briefly, pregnant women in the Avon, United Kingdom, area with due dates between April 1, 1991, and December 31, 1992, were invited to participate. Mothers, their partners, and subsequently the children themselves regularly completed assessments regarding their environment, experiences, and physical and psychological well-

being. At least 1 questionnaire or assessment was obtained for 13,988 children who were alive at age 1 year with mothers recruited during pregnancy. The ALSPAC Law and Ethics Committee and local research ethics committees provided ethical approval for the study. Parents provided written consent for participation, and their children provided assent (when possible) at each assessment.

## Measurement of variables

**Smoking during pregnancy.** At 18 and 32 weeks' gestation, mothers were questioned regarding their cigarette smoking. In line with previous analyses of this data set (17), the questions "Have you smoked regularly during your pregnancy?" and "Have you smoked during the past 2 weeks?" and an additional question on the quantity of cigarettes smoked were collapsed into a single variable denoting the presence or absence of smoking during pregnancy. For quantity of cigarettes smoked, we utilized the highest reported number of cigarettes smoked per day (categories: 0, 1–9, 10–19, and  $\geq 20$  cigarettes/day).

Paternal smoking during pregnancy was ascertained by asking similar questions at 18 weeks' gestation. Additionally, mothers reported whether their partners currently smoked, and variables for presence/absence and quantity were derived. To ensure that we included only biologic fathers, at 18 weeks' gestation, partners were asked whether they were the biologic father of the child. Those who replied no or were unsure ( $n = 68$ ; 0.7%) were excluded from the analyses. Maternal and paternal smoking when the child was 97 months (8 years) of age (the closest to our ADHD measures) was assessed using the question "Have you smoked regularly in the past 2 weeks?" (yes/no).

**Passive smoking.** At 18 weeks' gestation, mothers reported their exposure to passive smoking. In line with previous analyses (18), those living with a smoker (yes/no) or who worked "mostly" or "always" in a smoky environment were considered exposed to passive smoking.

**Childhood ADHD.** When children were aged 91 months (7.6 years), parents completed the Development and Well-Being Assessment (DAWBA) (19), which assesses the presence of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* (20), symptoms of psychiatric disorders, including ADHD. Because evidence suggests that ADHD behaviors lie on a continuum (21, 22), parent-rated ADHD symptom scores were utilized as the primary outcome variable. Teachers also completed the DAWBA when participants were in school year 3 (ages 7–8 years; US grade 2). Parent ratings were primarily used because of missing teacher data. Additionally, diagnoses of DSM-IV ADHD were generated using parent and teacher data.

**Potential covariates.** On the basis of previous reports, the following factors were considered: child's sex (51% male), ethnicity, multiple births (twins), maternal alcohol use during pregnancy, and social class. Mothers reported the quantity of alcohol (if any) that they had consumed per week 1) during the first 3 months of pregnancy and 2) since they had first felt the baby move in the womb. Mothers who reported consuming 1 or more alcoholic

drinks per week were considered to have used alcohol during pregnancy (23, 24). Mothers' highest level of education (dichotomized at O-level or above (age 16 examinations)) and parental occupation provided measures of social class (23). Mothers reported on their own occupation and their partner's occupation at 32 weeks' gestation. The higher social class of both parents, derived from the 1991 Standard Occupational Classification (25), was used. Because lower birth weight and premature birth are thought to be causally associated with maternal smoking during pregnancy, in accordance with previous evidence that co-varying such factors might lead to confounding (26), we did not control for these variables.

### Statistical methods

Skewed data were transformed to approximate normality. First, we used separate linear regression analyses to test for associations between maternal and paternal smoking during pregnancy and child ADHD symptoms. We then reanalyzed maternal and paternal associations simultaneously. *F* statistics were used to compare associations between mothers and fathers. Associations present for maternal smoking but not paternal smoking support the hypothesis that smoking during pregnancy poses a causal intrauterine risk for ADHD. If paternal smoking is also associated, this supports the hypothesis that the observed association for maternal smoking during pregnancy is not causal but the result of confounding factors. Measured, previously identified confounding factors were included in the model.

Because people are more likely to smoke if their partner smokes, we repeated paternal analyses after removing families in which the mothers smoked during pregnancy.

To account for the possibility that paternal smoking during pregnancy has a direct intrauterine effect through passive smoking, we analyzed associations between maternal exposure to passive smoking and childhood ADHD after restricting the data to families in which neither parent smoked during pregnancy.

As with any longitudinal data set, there were missing data. It has been demonstrated in this sample that, despite some selective dropout's affecting the overall prevalence of disorder, this does not alter associations between the DAWBA child behavior measures and pregnancy data (27). To ascertain the effect of missing data, as was done previously in this data set (28), we employed multivariate multiple imputation using chained equations, utilizing a published procedure for STATA (29) to impute missing ADHD and covariate data, repeating the analyses on imputed data sets ( $n = 8,324$ ). We used 20 cycles of regression switching and generated 20 imputed data sets.

All analyses were undertaken using STATA, version 10 (30).

### RESULTS

Pregnancy data were available for 8,324 families and parent-reported ADHD data at 7.5 years for 5,719. Because of a positive skew, ADHD parent data were transformed using the natural log +1. The mean number of parent-rated

ADHD symptoms for all children was 4.79 (standard deviation (SD), 6.71). DSM-IV ADHD was diagnosed in 119 children (2.1%). Smoking during pregnancy was reported by 18% of mothers and 32% of fathers, similar to contemporary United Kingdom estimates (31). The correlation between maternal and paternal smoking ( $r$ ) was 0.39. Offspring with no exposure to parental smoking had the fewest ADHD symptoms (mean = 4.31 (SD, 6.29)); similar mean numbers of symptoms were present when either parent smoked (mothers: mean = 5.19 (SD, 7.02); fathers: mean = 5.20 (SD, 7.06)); and numbers of symptoms were highest when both parents smoked (mean = 6.37 (SD, 7.70)).

### Associations of maternal and paternal smoking during pregnancy with ADHD symptoms

The mean number of ADHD symptoms in children whose mother or father had smoked during pregnancy was greater than that for unexposed children (mothers: mean = 5.99 (SD, 7.5) in the exposed vs. mean = 4.52 (SD, 6.5) in the unexposed; fathers: mean = 5.64 (SD, 7.3) vs. mean = 4.38 (SD, 6.3)). Maternal smoking during pregnancy was associated with offspring ADHD symptoms ( $\beta = 0.25$ , 95% confidence interval (CI): 0.18, 0.32), as was paternal smoking ( $\beta = 0.21$ , 95% CI: 0.15, 0.27; Table 1).

When maternal and paternal smoking were analyzed together, both continued to predict offspring ADHD symptoms, with moderately attenuated effect sizes (mothers:  $\beta = 0.18$ , 95% CI: 0.10, 0.26; fathers:  $\beta = 0.15$ , 95% CI: 0.09, 0.22 (Table 1)). There was no statistically robust difference between the strengths of the maternal and paternal associations ( $F = 0.21$ ,  $P = 0.65$ ).

Mothers were 4 times more likely and fathers 2.5 times more likely to smoke if their partner smoked. To ensure that associations for paternal smoking during pregnancy were not due to co-occurring maternal smoking, we analyzed families in which the mother did not smoke ( $n = 6,478$ ). An association between paternal smoking during pregnancy and offspring ADHD symptoms continued to be observed (Table 1).

### Passive smoking

We investigated the possibility that paternal smoking could have an intrauterine effect on the fetus through passive smoking.

For families in which neither parent smoked ( $n = 4,757$ ), 2.5% of mothers ( $n = 119$ ) reported living with other household members who smoked, and 4.7% of mothers ( $n = 224$ ) reported being exposed to a smoky working atmosphere. Analysis revealed that neither exposure to passive smoking was robustly associated with offspring ADHD symptoms (Table 1). When these measures were combined, 6.0% of mothers reported exposure to passive smoking. Again, no robust association was observed ( $\beta = 0.09$ , 95% CI: -0.07, 0.26).

Within our sample, child's sex, mother's education, family social class, and maternal alcohol consumption during pregnancy were associated with offspring ADHD symptoms (Appendix Table 1). Results from models that

**Table 1.** Association Between Parental Smoking During Pregnancy and Number of ADHD Symptoms in Offspring at Age 91 Months (7.6 Years), Avon Longitudinal Study of Parents and Children, 1991–2000<sup>a</sup>

	Unadjusted $\beta^b$	95% CI	Adjusted $\beta^b$ (Including Covariates)	95% CI
Parents entered in separate analyses				
Mother	0.25**	0.18, 0.32	0.19**	0.12, 0.27
Father	0.21**	0.15, 0.27	0.17**	0.11, 0.23
Both parents included in the same model				
Mother	0.18**	0.10, 0.26	0.14*	0.06, 0.22
Father	0.15**	0.09, 0.22	0.14**	0.07, 0.20
Paternal smoking, where mother is a nonsmoker ( $n=6,478$ )	0.15**	0.08, 0.22	0.12**	0.04, 0.20
Passive smoking, where neither parent smokes ( $n=4,757$ )				
Another smoker in household	0.11	-0.15, 0.36	0.13	-0.13, 0.39
Exposure to smoke at work	0.07	-0.13, 0.26	0.04	-0.16, 0.25

Abbreviations: ADHD, attention deficit hyperactivity disorder; CI, confidence interval.

\*  $P < 0.01$ ; \*\*  $P < 0.001$ .

<sup>a</sup> Results from linear regression analysis.

<sup>b</sup> Change in number of ADHD symptoms.

included all covariates showed the same pattern (Table 1), while maternal and paternal associations showed no meaningful difference ( $F=0.03$ ,  $P=0.86$ ). Finally, findings obtained using imputed data remained the same.

Teacher reports of ADHD also demonstrated an association between smoking by both parents during pregnancy and offspring ADHD (mothers:  $\beta=1.68$ , 95% CI: 1.27, 2.09; fathers:  $\beta=1.00$ , 95% CI: 0.65, 1.34 (note: nontransformed scores)). Comparisons between maternal and paternal associations did not yield robust evidence of difference ( $F=2.02$ ,  $P=0.16$ ). Findings obtained using combined parent and teacher ratings of ADHD were consistent.

Because ADHD behaviors are more prevalent in males (32) and there may be differential influences of smoking during pregnancy by sex (33), analyses were stratified by sex. Associations were observed between offspring ADHD and maternal and paternal smoking for both males and females, with no robust differences between maternal and paternal associations (see Appendix Table 2).

Because some investigators have suggested an influence of postnatal exposure to cigarette smoke, we tested for associations with current parental smoking. Neither maternal smoking nor paternal smoking was robustly associated with

offspring ADHD symptoms (adjusted analyses—mothers:  $\beta=0.09$ , 95% CI: -0.08, 0.27; fathers:  $\beta=0.13$ , 95% CI: -0.04, 0.31).

We investigated the possibility of a dose-dependent association whereby quantity of cigarettes smoked was related to ADHD symptoms. Maternal and paternal smoking during pregnancy in quantity categories (1–9, 10–19, or  $\geq 20$  cigarettes/day) was associated with ADHD symptom scores (adjusted analyses—mothers:  $\beta=0.07$ , 95% CI: 0.03, 0.12; fathers:  $\beta=0.06$ , 95% CI: 0.03, 0.09).

#### Diagnosis of ADHD and parental smoking during pregnancy

As previously described (27), the prevalence of ADHD in this sample was relatively low (2.1%). In unadjusted analyses, maternal smoking during pregnancy was associated with ADHD diagnosis (odds ratio (OR) = 1.68, 95% CI: 1.11, 2.53), while paternal smoking during pregnancy showed a similar but weaker association (OR = 1.43, 95% CI: 0.99, 2.07), with no meaningful difference between the two ( $\chi^2=0.31$  (1 df),  $P=0.58$ ). This pattern continued when potential covariates were included (Table 2).

**Table 2.** Association Between Maternal and Paternal Smoking During Pregnancy and Offspring Diagnosis of ADHD, Avon Longitudinal Study of Parents and Children, 1991–2000

	ADHD Cases						Unadjusted Analyses			Adjusted Analyses (Including Covariates)		
	No Smoke Exposure			Smoke Exposure			Wald Test Value	OR	95% CI	Wald Test Value	OR	95% CI
	No.	Total	%	No.	Total	%						
Mother	89	4,623	1.9	32	1,014	3.1	6.08	1.68*	1.11, 2.53	6.54	1.72	1.14, 2.61
Father	71	3,827	1.8	48	1,810	2.6	3.57	1.43	0.99, 2.07	3.52	1.43	0.98, 2.07

Abbreviations: ADHD, attention deficit hyperactivity disorder; CI, confidence interval; OR, odds ratio.

\*  $P < 0.05$ .



Smoking was not associated with ADHD diagnosis for either parent using imputed data. Because of the low frequency of ADHD diagnosis, we repeated these analyses for a broader category of parent-rated symptom scores above the 95th percentile. Both maternal and paternal smoking were associated with high ADHD scores (mothers: OR = 1.43, 95% CI: 1.06, 1.93; fathers: OR = 1.42, 95% CI: 1.10, 1.84), while paternal smoking in families where mothers did not smoke was also associated (OR = 1.42, 95% CI: 1.04, 1.93).

### Parental smoking and birth weight

To demonstrate the utility of our design in identifying causal intrauterine effects, we compared the relations of maternal and paternal smoking during pregnancy with offspring birth weight. Maternal smoking but not paternal smoking was robustly associated with offspring birth weight, with a clear difference between the two (mothers:  $\beta = -152.66$ , 95% CI:  $-183.99$ ,  $-121.33$ ; fathers:  $\beta = -21.15$ , 95% CI:  $-48.20$ ,  $5.89$  ( $F = 28.23$ ,  $P < 0.001$ )). Paternal smoking in families where the mother did not smoke was not associated with offspring birth weight.

## DISCUSSION

In line with previous studies (1, 2, 34), we found an association between maternal smoking during pregnancy and offspring ADHD symptoms. To investigate whether this association was due to causal intrauterine effects, as previously proposed (2, 5), or to social environmental or genetic confounding factors, we examined the influence of paternal smoking during pregnancy. Because fathers do not provide the intrauterine environment but share genes and other environmental factors with their offspring, any association observed would support the latter hypothesis.

Paternal smoking during pregnancy was also associated with offspring ADHD symptoms, supporting our second hypothesis. This association continued to be observed in families where the mother did not smoke and in analyses considering potential covariates. Furthermore, we examined exposure from other smokers in the household and from working in a smoky environment. The lack of association between passive smoking and offspring ADHD supports our conclusions. However, the passive smoking analysis necessarily utilized a subsample of families. Because the direction of effects for passive smoking was the same as that for parental smoking, we cannot rule out the possibility that our lack of findings was due to reduced statistical power.

There was no evidence of any difference between the strength of association of maternal and paternal smoking during pregnancy and offspring ADHD diagnosis, but the low number of ADHD diagnoses in this sample ( $n = 119$ ) (27) meant that statistical power to detect any difference was low. Analysis of offspring with high numbers of ADHD symptoms also suggested no difference in the strength of the association between maternal and paternal prenatal tobacco exposure.

In line with previous studies (10, 17, 35), our primary analyses utilized a presence/absence measure of smoking. As with previous studies, we found evidence of a dose-dependent association between smoking during pregnancy and offspring ADHD (4). This suggests that the confounders that account for the association between maternal smoking in pregnancy and offspring ADHD also contribute to the quantities of cigarettes smoked. However, caution is warranted, since reported measures of quantity smoked may be prone to measurement error.

There is likely to be an effect of smoking-related assortative mating; mothers are more likely to smoke if their partner does, increasing the possibility of associations between paternal smoking during pregnancy and offspring ADHD symptoms. The household-level factors which may account for this association may also be increased in families where both parents smoke. Because we also analyzed children from families where only fathers smoked, our findings are not likely to have been solely the result of assortative mating. Families in which only fathers smoke may also differ with regard to household-level factors, although it is unclear what influence this might have.

### Strengths and weaknesses

The large sample size was a strength of this study, even when only families in which neither parent smoked were analyzed. As would be expected in a large, prospective longitudinal study of this kind, there were some missing data. Reanalysis following data imputation indicated that our results were robust.

The prospective study design was advantageous. Parents reported their smoking during pregnancy, eliminating issues of retrospective recall, though not of deliberate underreporting.

Using teacher ratings of ADHD symptoms, we again found no robust differences in the strength of associations between maternal and paternal smoking during pregnancy and offspring ADHD ( $F = 2.02$ ,  $P = 0.16$ ). However, there was a larger difference between the  $\beta$  values than for parent-rated ADHD scores ( $\beta = 1.68$  for maternal associations using teacher reports and  $\beta = 1.00$  for paternal associations), although there were more missing data for teacher reports. It is possible that although findings were not significantly different, there was a difference in the degree of association between exposure to maternal and paternal smoking during pregnancy and teacher-rated ADHD symptoms. That is, we cannot completely rule out intrauterine risk effects of maternal smoking on teacher-reported symptoms. Because parents rated both their own smoking and their child's ADHD behaviors, there may have been rater effects whereby parents who smoked rated their children's behavior differently from those who did not. However, evidence from clinical and cognitive studies (36, 37) indicates that parent- and teacher-rated ADHD are not necessarily the same constructs. Ideally, future studies that are larger, that use multiple-informant assessments of ADHD, and that assess reported smoking more objectively (e.g., using cotinine levels) will help to resolve this issue.

This investigation showed findings similar to those of previous studies for diagnoses of ADHD (21, 22, 38). The low rate of diagnosis can be considered a weakness of the analysis. For offspring with high ADHD scores, the pattern of results remained the same, although caution is warranted when extrapolating findings to diagnoses. It is important to replicate and investigate effects across ADHD subtypes.

We studied exposure to any smoking during pregnancy, while it might be interesting to investigate exposure during different trimesters. Self-reports of smoking might be prone to measurement error; an objective measure of smoking, such as serum cotinine samples, would be preferable.

It is possible that postnatal environmental smoke exposure also influences ADHD symptoms (39, 40). Current parental smoking was not associated with offspring ADHD symptoms. While not accounting for exposure to tobacco smoke from nonparental sources, this suggests that later exposure in this sample was not a confounder.

We also examined birth weight, which has been widely demonstrated to be lowered because of direct causal intrauterine influences of maternal smoking (41). As with similar analyses in this sample (15), maternal smoking was associated with offspring birth weight but paternal smoking was not, demonstrating the ability of the study design to identify causal intrauterine effects and supporting our conclusions in relation to ADHD. It also suggests accuracy in the self-reports of smoking.

Another approach to this issue would be the use of Mendelian randomization (42), utilizing identified genetic variants related to smoking behavior (43–46). The genetic variants will not be related to confounding factors (47). If maternal smoking-related variants are associated with offspring outcomes, conditional on offspring genotype, but paternal variants are not, this would suggest intrauterine effects of smoking. If neither maternal nor paternal smoking-related variants were related to offspring outcomes, this would suggest no causal association, while if both parental smoking-related variants were associated with offspring ADHD, this would suggest genetic confounding or an influence that was not mediated through an intrauterine effect.

These findings support a small body of evidence using genetically sensitive designs (7, 9, 10, 48) suggesting that the association reflects inherited and household-level confounders rather than direct intrauterine effects. However, in one study using a similar design, Nomura et al. (11) found an association between ADHD symptoms and maternal, but not paternal, exposure to smoking during pregnancy. Such work demonstrates the need to question previous assumptions regarding a causal effect (14). In this study, we used a much larger sample and examined passive smoking.

## Conclusions

These findings support the hypothesis that associations between maternal smoking during pregnancy and offspring ADHD symptoms (and possibly diagnoses) are due to unmeasured familial confounding factors, rather than to a direct intrauterine effect.

This should not alter advice to pregnant women regarding smoking; although there may not be a direct influence on risk of offspring ADHD, there are many negative consequences of smoking during pregnancy (41, 49, 50). Instead, in this study we aimed to demonstrate the pitfalls of assuming that smoking during pregnancy (or any other factor) has a direct, causal risk effect on all offspring outcomes, including ADHD, and to remind researchers to consider alternative risk factors. The study also highlights the need to test such assumptions using different designs.

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**Appendix Table 1.** Associations Between Potential Covariates and Number of ADHD Symptoms in Offspring, Avon Longitudinal Study of Parents and Children, 1991–2000

	$\beta^a$	95% Confidence Interval
Child's sex	-0.33**	-0.40, -0.29
Multiple births	0.17	-0.03, 0.39
Mother's education	-0.15**	-0.22, -0.08
Family social class	0.07**	0.04, 0.10
Ethnicity	0.06	-0.12, 0.23
Mother's alcohol use during pregnancy	0.13*	0.06, 0.20

Abbreviation: ADHD, attention deficit hyperactivity disorder.

\*  $P < 0.05$ ; \*\*  $P < 0.001$ .

<sup>a</sup> Change in number of ADHD symptoms.

**Appendix Table 2.** Associations Between Parental Smoking During Pregnancy and Number of ADHD Symptoms in Offspring, by Parental Sex, Avon Longitudinal Study of Parents and Children, 1991–2000

	Fathers ( $n = 2,921$ )		Mothers ( $n = 2,798$ )	
	$\beta^a$	95% CI	$\beta^a$	95% CI
Parents entered in separate analyses				
Mother	0.18**	0.07, 0.28	0.32***	0.22, 0.42
Father	0.19***	0.10, 0.28	0.23***	0.15, 0.31
Both parents included in the same model				
Mother	0.11*	-0.00, 0.22	0.26***	0.15, 0.36
Father	0.16**	0.06, 0.25	0.15***	0.07, 0.24
Paternal smoking, where mother is a nonsmoker ( $n = 6,478$ )	0.16**	0.05, 0.26	0.14**	0.04, 0.23
Passive smoking, where neither parent smokes ( $n = 4,757$ )				
Another smoker in household	0.008	-0.39, 0.41	0.24	-0.07, 0.54
Exposure to smoke at work	-0.14	-0.43, 0.15	0.28*	0.03, 0.54

Abbreviations: ADHD, attention deficit hyperactivity disorder; CI, confidence interval.

\*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$ .

<sup>a</sup> Change in number of ADHD symptoms.