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Parsing the associations between prenatal exposure to nicotine and offspring psychopathology in a non-referred sample

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Abstract

Purpose—Although several studies have suggested an association between maternal smoking during pregnancy and both attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) in their offspring. However, it is unclear whether one or both of the documented links are spurious given the considerable comorbidity between these disorders. The main aim of this study was to disentangle the association between maternal smoking during pregnancy with psychopathological outcomes, adjusting for possible confounders.

Methods—Two large, identically designed, longitudinal, case-control family studies of male and female probands with and without ADHD were combined. We used data from the non-referred siblings of the probands from both studies (n=536). All subjects were blindly assessed with structured diagnostic interviews. Logistic regression analysis was used to determine the adjusted effect of exposure to maternal smoking during pregnancy.

Results—Among all siblings, maternal smoking during pregnancy was significantly associated with ADHD, independent of CD and other covariates. In contrast, maternal smoking during pregnancy was a risk factor for CD only in siblings of Control probands, after adjusting for covariates.

Conclusions—These results support the hypothesis that maternal smoking during pregnancy is a risk factor for both ADHD and CD, independently of each other. However, the risk for CD appears to be conditional on family risk status.

INTRODUCTION

Several studies have documented associations between maternal smoking during pregnancy and both attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) in offspring [1–3]. For example, Milberger et al. found a 2.7-fold increased risk for ADHD associated with maternal smoking, and a 4.4-fold increased risk for ADHD in their high risk siblings [4,5]. Although Weissman et al. reported a 2-fold increased risk for ADHD associated with prenatal exposure to tobacco, these findings did not demonstrate statistical significance [6]. In a study of 280 ADHD cases and 242 non-ADHD controls, we found that ADHD cases

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were significantly more likely to have been exposed to cigarettes in utero than were controls, after adjustment for several risk factors [7].

Likewise, there is a growing literature finding an increased risk for CD in the offspring of mothers who smoked during pregnancy [8–12]. However, other studies have not replicated this finding. They instead suggested that the link between maternal smoking during pregnancy and CD is accounted for by the transmission of a latent maternal conduct problems factor [13] or the effect of confounding genetic and environmental factors [14].

However, this literature suffers from some methodological limitations. Although there is a strong overlap between ADHD and CD [15–19], not all studies have attended to this comorbidity, which raises questions as to whether the links between ADHD and CD with maternal smoking during pregnancy are spurious. Although some studies have addressed this question, the results have been inconsistent. In our study [7], the significant association between ADHD and maternal smoking during pregnancy was independent of CD. However, in our previous work examining high-risk siblings of ADHD probands, CD was not considered as a covariate. The study by Button et al [20] found that maternal smoking during pregnancy was independently associated with both ADHD and antisocial behavior. However, Nigg and Breslau [21] found that maternal smoking during pregnancy was associated with CD (mediated by the relationship with oppositional-defiant disorder), but not ADHD. Another study found that maternal smoking during pregnancy was associated with offspring aggression, but not hyperactivity-impulsivity. Also, this study showed that high levels of both aggression and hyperactivity-impulsivity were predicted by maternal smoking during pregnancy compared with either behavior problem alone [22]. Clearly, additional studies are needed to investigate these important questions.

Despite these uncertainties, the effects of nicotine on the developing fetus provide a plausible biological mechanism explaining the putative associations with ADHD and CD. Studies suggest that nicotine acts directly on the developing fetus, affecting serotonin and dopaminergic systems, brain cell growth, and DNA and RNA synthesis in the brain [11]. Roy et al [23] found increased incidence of apoptotic cells in the hindbrain, forebrain, and midbrain of rat embryos exposed to nicotine, and reported that damage to the developing neuroepithelium was evident at levels of prenatal exposure to nicotine that were insufficient to cause general dysmorphogenesis. Thus, levels of exposure to nicotine and alcohol that do not affect the viability of the fetus may result in disruption of normal brain development that could lead to behavioral and attentional problems in childhood and adolescence.

Efforts at disentangling the associations between maternal smoking during pregnancy and psychopathological outcomes in the offspring are of high clinical, scientific, and public health importance. For example, if new research establishes that maternal smoking during pregnancy is only linked to ADHD, then hypotheses about maternal smoking during pregnancy causing CD through dopaminergic dysfunction would be abandoned and other neuropathological models would be considered. However, if the association between CD and maternal smoking during pregnancy were validated, additional research would be needed to develop novel interventions for CD. Findings documenting an association between maternal smoking during pregnancy with either ADHD or CD will further support public health efforts aimed at diminishing or eliminating this preventable risk.

The primary aim of the present study was to examine the impact of maternal smoking during pregnancy on psychopathological outcomes in the offspring, addressing issues of comorbidity between ADHD and CD, other forms of psychopathology, and referral bias. To this end we examined associations between maternal smoking during pregnancy with psychopathological outcomes in a large sample of referred and non-referred youth. Based on the literature, we

hypothesized that both ADHD and CD will exhibit independent associations with maternal smoking during pregnancy.

METHODS

Subjects

Subjects were siblings of both sexes derived from two identically designed, longitudinal case-control family studies conducted at the Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD at Massachusetts General Hospital (MGH). Detailed study methodology has been previously reported [24,25]. Briefly, these studies included male and female youth probands with and without ADHD and their first-degree relatives (hereafter referred to as the Boys and Girls ADHD study, respectively). For both studies, potential probands were excluded if they had been adopted, if their nuclear family was not available, if they had major sensorimotor handicaps (paralysis, deafness, blindness), if they had psychosis or autism, or if they were unable to participate in the assessments due to language barriers or an estimated IQ < 80. After a complete description of the study, parents provided written informed consent for their children, and children and adolescents provided written assent. The IRB at MGH approved this study.

We used a three-stage ascertainment procedure to select probands [26,27]. For ADHD subjects, the first stage was their referral, which resulted in a clinical diagnosis of ADHD. The second stage confirmed the diagnosis of ADHD through a telephone questionnaire administered to the mother. The third stage was a diagnostic assessment with a structured interview. Only patients who received a positive diagnosis at all three stages were included. Controls were similarly selected through a three-stage procedure. First, we ascertained them from consecutive referrals to medical clinics for routine physical examinations at both the psychiatric and pediatric sources. In stage two, the control mothers responded to the DSM-III-R ADHD telephone questionnaire about their daughters. Eligible controls meeting study entry criteria were recruited for the study and received the third stage, a diagnostic assessment with a structured interview. Only subjects classified as not having ADHD at all three stages were included in the control group.

To avoid the potential for bias resulting from studying referred samples, we utilized data from the non-referred sibling samples of both sexes from both studies (n=303 from the Boys study and n=274 from the Girls study). In the Boys study, the siblings were assessed at baseline and at four and ten-year follow-ups. In the Girls study, the siblings were assessed at baseline and at a five-year follow-up. The association between maternal smoking during pregnancy and ADHD was previously tested [5] using the baseline assessment of the sibling sample from the Boys study (n=303, 53% of our total sample). The present study is unique because: 1) we are examining other psychopathological outcomes, in addition to ADHD; 2) we are using both baseline and follow-up assessments of the Boys sibling sample; and 3) we have included additional subjects not examined previously. The age range of the sibling samples at baseline were 5 to 37 (mean 13.5) and 6 to 29 (mean 13.3) for the Boys and Girls studies, respectively.

Assessment Procedures

Psychiatric Assessment—Psychiatric assessments relied on the K-SADS-E (Epidemiologic Version) [28] for subjects less than 18 years of age and the Structured Clinical Interview for DSM-III-R (SCID) [29] (supplemented with modules from the K-SADS-E to assess childhood diagnoses) for subjects aged 18 and older. Diagnoses were based on direct interviews with the mothers and the offspring, except for children <12 years that were not interviewed directly. We combined data from direct and indirect interviews by considering a diagnosis positive if it was endorsed in either interview. All interviews conducted were blind

to the subject's referral source. Diagnoses were considered positive if DSM-III-R criteria were unequivocally met. A committee of board-certified child and adult psychiatrists, who were blind to the subject's ascertainment status and all other data, resolved diagnostic uncertainties. Diagnoses presented for review were considered positive only if a consensus was achieved that criteria were met to a degree that would be considered clinically meaningful.

All interviewers had undergraduate degrees in psychology and were trained to high levels of inter-rater reliability. First, they underwent several weeks of classroom style training, learning interview mechanics, diagnostic criteria, and coding algorithms. Then, they observed interviews by experienced raters and clinicians. They subsequently conducted at least six practice (non-study) interviews and at least two study interviews while being observed by senior interviewers. The principal investigator (JB) supervised the interviewers throughout the study. We computed kappa coefficients of agreement by having child and adult psychiatrists and clinical psychologists diagnose subjects from audio taped interviews. Based on 500 assessments from interviews of children and adults, kappa coefficients for ADHD and CD were 0.88 and 1.0, respectively.

We considered a diagnosis of major depression only if the depressive episode was associated with severe impairment, in order to avoid false positive diagnoses [30,31]. Since there are many anxiety disorders, we aggregated them into a binary measure coded positive only if two or more anxiety disorders were endorsed. We previously found this summary variable to measure a meaningful anxiety syndrome [32]. Socio-economic status (SES) was measured with the 5-point Hollingshead scale [33], using the occupational and educational status of the parents.

Measurement of prenatal exposure to maternal substance use—As we have done in previous studies [7], we used two measures of maternal substance use during pregnancy to improve the reliability and precision of our estimates. In the first measure, mothers were directly questioned regarding the pregnancy, delivery, and infancy complications they experienced with each child during the structured diagnostic interview they completed pertaining to the child's psychiatric history. This interview included direct questions regarding prenatal use of cigarettes, alcohol, or drugs. The second measure of exposure was derived from the mother's self-reported structured diagnostic interview regarding her own psychiatric history, which included a lifetime self-report of alcohol, illicit drug and cigarette use. We defined a lifetime history of smoking as positive if the mother met full or subthreshold criteria for nicotine dependence. Subthreshold cases were defined as the endorsement of smoking any amount of cigarettes four to six days per week. We included subthreshold cases to capture regular smoking habits that, while not as serious as dependence, still represent a potential risk to the fetus. Utilizing the reported onsets and offsets of the substance diagnoses in mothers, in combination with the date-of-birth of the offspring, we determined exposure status to nicotine, alcohol, and illicit drugs during fetal development. We combined these measures for each substance by considering an offspring exposed in utero if either source of information indicated maternal use during pregnancy. For the purposes of our analyses, we created an aggregate measure of maternal substance use during pregnancy by combining the alcohol and illicit drug variables, which were coded positive if either measure was positive. All studies included both sources of information across each of the three substance categories, with the exception of the Boys ADHD study, which did not assess smoking in the mothers' structured interview. For the offspring in this study, the measure of maternal smoking during pregnancy was based only on the direct questioning regarding the pregnancy.

Statistical Analysis—First, we examined demographic characteristics, stratified by exposure status, using Chi Square tests and one-way analysis of variance for categorical and dimensional variables, respectively.

Our hypothesis examined the relationship between ADHD and maternal smoking during pregnancy, independent of CD, and also CD and maternal smoking during pregnancy, independent of ADHD. However, our sample was comprised of siblings of both ADHD probands and controls, and it is possible that the relative risk of maternal smoking during pregnancy on these outcomes may differ according to the referral status of the proband from which the sibling is ascertained. That is, high-risk siblings (i.e., siblings of ADHD probands) may have a different genetic and post-natal environmental risk profile relative to siblings of controls, which could influence the effect of maternal smoking during pregnancy on subsequent psychopathology (e.g., ADHD and CD). To test this, we estimated lifetime ADHD status as a function of offspring CD, maternal smoking during pregnancy, proband referral status (i.e., the ADHD or control status of the proband from which the sibling was ascertained), and the maternal smoking -by-proband referral status interaction, using logistic regression. A significant interaction term would indicate that the association between maternal smoking during pregnancy and sibling ADHD status differed according to their referral source. If the interaction term was significant, we estimated the effect of maternal smoking during pregnancy on ADHD within strata of referral status. If the interaction term was not significant, we collapsed across referral status and estimated the effect of maternal smoking during pregnancy on ADHD, including referral status as a covariate. The same procedure was used to test the association between maternal smoking during pregnancy and a lifetime history of CD, except that offspring ADHD was used as a covariate. To adjust for potential confounding, all the models described above were also adjusted for maternal age at offspring birth, social class, offspring age at baseline, offspring sex, parental lifetime history of ADHD, parental lifetime history of CD, prenatal exposure to maternal alcohol or illicit drugs, study of origin (Boys ADHD, Girls ADHD) and number of assessments.

As an exploratory analysis, we estimated additional models with the following disorders as the dependent variables: major depression with severe impairment, bipolar disorder, multiple anxiety disorder, full or subthreshold cigarette smoking, and substance use disorder (alcohol or drug abuse or dependence). Because our sample is not entirely through the period of risk for these disorders, we used Cox proportional hazard survival models, which accommodate these subjects through censoring. Cases were defined as a positive response at any assessment. These models utilize all available data for each subject, including those only assessed at baseline; thus, all eligible subjects are included, using as many waves of follow-up data as are available. We used the earliest age of onset as the survival time for cases and the age at most recent interview as the time of censoring for non-cases. Across all models, we used robust estimates of variance to account for the non-independence of the sample resulting from the correlation between family members. All tests were two-tailed, and our alpha level was set at 0.05 for a priori hypotheses and 0.10 for exploratory analyses.

RESULTS

Demographic characteristics

Among the 577 siblings available for study, 34 (6%) were discarded because of missing maternal smoking during pregnancy data. Another seven subjects were discarded because of missing data on other covariates. Thus, the final sibling sample used for this study was 536. Twenty-one percent (n=115) of the sample was exposed to maternal smoking during pregnancy. The demographic characteristics of this sample, stratified by maternal smoking during pregnancy exposure, are presented in Table 1. As shown, there were no statistically significant differences between subjects with and without exposure to maternal smoking during pregnancy on sex, study of origin, or age at baseline. However, the exposed group was significantly more likely to be high-risk (i.e., belong to a family ascertained by an ADHD proband), and had significantly higher rates of prenatal exposure to alcohol/drugs, parental

history of ADHD, and parental history of CD. Also, the mothers of the exposed group were, on average, significantly younger than the mothers of the unexposed group, and the social class of the exposed group was significantly higher (indicating less affluence relative to the unexposed group). Finally, the unexposed group returned for follow-up assessments significantly more times than the exposed group.

The proportions of subjects with ADHD in the unexposed and exposed groups were 14% and 28%, respectively. The proportions of subjects with CD in the unexposed and exposed groups were 10% and 20%, respectively. Also, the proportions of subjects with both ADHD and CD in the unexposed and exposed groups were 3% and 13%, respectively.

Effect of maternal smoking during pregnancy on ADHD, adjusting for CD

The coefficient examining the interaction between referral status and maternal smoking during pregnancy on the risk for ADHD, adjusting for other covariates, was not significant ($z=1.87$, $p=0.061$). Thus, we removed the interaction term and estimated the risk for ADHD as a function of maternal smoking during pregnancy, CD, and the covariates listed above. We detected a significant effect of maternal smoking during pregnancy on ADHD risk ($z=3.04$, $p=0.002$). Siblings with exposure to maternal smoking during pregnancy were 2.5 times (95% confidence interval: 1.39, 4.51) more likely to have ADHD compared to unexposed siblings, independently of CD and the other covariates. This effect was similar to the unadjusted, univariate association between maternal smoking during pregnancy and ADHD risk (odds ratio (95% confidence interval): 2.46 (1.47, 4.12); $z=3.43$, $p=0.001$).

Effect of maternal smoking during pregnancy on CD, adjusting for ADHD

The coefficient examining the interaction between referral status and maternal smoking during pregnancy on the risk for ADHD, adjusting for other covariates, was statistically significant ($z=-2.48$, $p=0.013$). Thus, we estimated the risk for CD as a function of maternal smoking during pregnancy, ADHD, and the covariates listed above, within strata of referral status. Among high-risk siblings from ADHD families ($n=291$), we did not detect a significant effect of maternal smoking during pregnancy on CD risk ($z=-1.26$, $p=0.209$). This effect remained non-significant when estimated without covariates ($z=0.66$, $p=0.510$).

However, among siblings from control families ($n=245$), we found a significant effect of maternal smoking during pregnancy on CD risk ($z=2.37$, $p=0.018$). Siblings from control families with exposure to maternal smoking during pregnancy were 3.3 times (95% confidence interval: 1.23, 8.88) more likely to have CD compared to unexposed siblings, independently of ADHD and the other covariates. This effect was somewhat attenuated relative to the unadjusted association between maternal smoking during pregnancy and CD (odds ratio (95% confidence interval): 4.69 (1.70, 12.89); $z=2.99$, $p=0.003$).

Effect of maternal smoking during pregnancy on the comorbidity between CD and ADHD

We estimated the risk for the comorbidity between ADHD and CD (i.e., subjects with both ADHD and CD versus all other subjects) as a function of maternal smoking during pregnancy and the covariates listed above. We detected a trend towards statistical significance ($z=1.92$, $p=0.054$). Siblings with exposure to maternal smoking during pregnancy were 2.6 times (95% confidence interval: 0.98, 7.36) more likely to have both ADHD and CD compared to unexposed siblings, independently of the other covariates.

Effect of maternal smoking during pregnancy on other psychopathological outcomes

The prevalence of major depression, multiple anxiety disorder, bipolar disorder, alcohol dependence, drug dependence, and smoking dependence in the exposed and unexposed groups

are presented in table 2. As shown, the prevalence of each disorder was higher in the exposed group relative to the unexposed group. However, bipolar disorder was the only outcome found by the survival models to be significantly associated with maternal smoking during pregnancy. Exposed offspring were 3.3 times more likely to meet criteria for bipolar disorder compared to offspring not exposed, independent of maternal age at offspring birth, social class, offspring age at baseline, offspring sex, parental lifetime history of bipolar disorder, prenatal exposure to maternal alcohol or illicit drugs, study of origin, number of assessments, and proband referral status. Additional adjustment for offspring CD and offspring ADHD did not appreciably alter the results (hazard ratio (95% confidence interval) = 2.99 (1.56, 5.72), $z=3.31$, $p=0.001$).

We also estimated each subjects' number of comorbid disorders (including ADHD, CD, major depression, multiple anxiety disorder, bipolar disorder, alcohol dependence, drug dependence, and smoking dependence) as a function of maternal smoking during pregnancy in a poisson regression model, adjusting for the covariates listed above. There was a positive relationship between exposure and the number of comorbid disorders (relative risk (95% confidence interval) 1.30 (0.99, 1.71), but this association did not reach statistical significance ($z=1.86$, $p=0.062$).

DISCUSSION

In a large, non-referred sample of siblings of ADHD and non-ADHD probands of both sexes, we found that maternal smoking during pregnancy was associated with a significantly increased risk for ADHD independently of CD. These results confirm and extend previous findings [1–3]. These findings also extend our previous work [5] by expanding the sample to include non-referred siblings of probands with and without ADHD and by incorporating more stringent statistical control for potential confounders, particularly CD. The present results also complement another of our previous studies in probands with and without ADHD [7] by extending the results to a non-referred sample.

The association between maternal smoking during pregnancy and CD in our sample was confined to the siblings of non-ADHD probands, consistent with some studies in the literature linking maternal smoking during pregnancy and CD in non-referred samples [8–11]. However, our results are discordant with other studies that did not find a relationship between CD and maternal smoking during pregnancy [13,14]. Additional research is clearly needed to help reconcile these discrepant findings.

Although the reasons why there was no association detected in our study between maternal smoking during pregnancy and CD in siblings of ADHD probands, several possibilities are plausible. Given our previous findings demonstrating that ADHD and antisocial disorders (CD and antisocial personality disorder) are a familial subtype of ADHD in these data [34,35], it may be that the risk for CD is elevated in all siblings of ADHD probands as a result of familial factors, regardless of maternal smoking during pregnancy. Alternatively, the siblings of control probands may not have an underlying familial vulnerability for CD, allowing the risk mediated through maternal smoking during pregnancy to be detected. More work is needed to address these issues.

Our exploratory results also showed that maternal smoking during pregnancy was associated with bipolar disorder, independently of ADHD and CD, but not with other psychopathological outcomes. To our knowledge, this is the first study to suggest this association. If confirmed, this finding would suggest that the effect of maternal smoking during pregnancy may be circumscribed to ADHD, CD and bipolar disorder, and not generalized to other psychopathological conditions. However, because this was a post-hoc analysis, the association

between maternal smoking during pregnancy and bipolar disorder should be interpreted with caution until replicated in other samples.

It is important to consider the methodological limitations of our study. Because our sampling consisted largely of Caucasian subjects, our results may not generalize to other racial or ethnic groups. Our measure of maternal smoking during pregnancy was based on retrospective reports from the mothers, and may be subject to recall bias. We attempted to deal with this bias by including information from both direct questioning regarding substance use during pregnancy as well as a separate interview of the mother in which it was not known (to the subject or interviewer) that we would later use information collected regarding her history of smoking to recalculate in utero exposure to her children. Also, our measure was binary, and we were unable to test the effect of varying magnitudes of exposure on offspring outcomes. Finally, although we used stringent statistical controls, we still cannot definitively conclude that maternal smoking during pregnancy exerts a causal effect on offspring CD or ADHD, or rule out interactive effects with other factors, such as genetic factors [36].

Despite these limitations, our results document the independent effect of maternal smoking during pregnancy on both ADHD and CD in a non-referred sample with strict statistical control of confounding factors. Also, our study provides preliminary evidence of an association between maternal smoking during pregnancy and bipolar disorder. These data can contribute to our understanding of the pathophysiology of these disorders and potentially lead to novel treatment approaches.

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Table 1

Demographic characteristics of offspring (n=536) stratified by exposure to maternal smoking during pregnancy

Demographic Characteristic	Unexposed n=421	Exposed n=115	Test Statistic, p value
	n (%)	n (%)	
Sex (male)	230 (55)	64 (56)	$\chi^2_{(1)}=0.04$, p=0.85
Study of origin			$\chi^2_{(1)}=0.49$, p=0.49
Boys ADHD study	235 (56)	60 (52)	
Girls ADHD study	186 (44)	55 (48)	
Proband ascertainment status ¹	210 (50)	81 (70)	$\chi^2_{(1)}=15.38$, p<0.01
Prenatal exposure to alcohol/drugs	19 (5)	17 (15)	$\chi^2_{(1)}=15.20$, p<0.01
Parental history of ADHD	93 (22)	36 (31)	$\chi^2_{(1)}=4.20$, p=0.04
Parental history of CD	42 (10)	35 (30)	$\chi^2_{(1)}=30.73$, p<0.01
	mean±SD	mean±SD	
Age of mother at offspring birth	29.0±4.4	26.4±4.7	$t_{(534)}=5.53$, p<0.01
Offspring age at baseline	13.1±5.1	13.3±5.5	$t_{(534)}=-0.49$, p=0.63
Parental social class ¹	1.6±0.8	2.4±1.0	$t_{(534)}=-8.1$, p<0.01
Number of assessments	2.9±1.0	2.7±1.0	$t_{(534)}=2.04$, p=0.04

¹ ADHD² Social class measurement ranges from 1 through 5; 1 indicates most affluent social class, 5 indicates least affluent

Table 2

Exploratory analysis of the association between exposure to maternal smoking during pregnancy and mood, anxiety and substance use disorders in the offspring (n=536)

Psychiatric Diagnosis ¹	Unexposed n=421 n (%)	Exposed n=115 n (%)	Adjusted Hazard Ratio	95 % CI	Test Statistic, p value
Major depression	60 (14)	21 (19)	0.90	0.49, 1.64	$z=-0.35$, $p=0.724$
Multiple (≥ 2) anxiety disorder	81 (19)	29 (26)	1.20	0.73, 1.97	$z=0.72$, $p=0.471$
Bipolar disorder *	21 (5)	19 (17)	3.28	1.60, 6.71	$z=3.25$, $p=0.001$
Alcohol dependence	41 (10)	16 (15)	1.12	0.63, 2.01	$z=0.39$, $p=0.695$
Illicit drug dependence	26 (6)	12 (11)	1.03	0.47, 2.27	$z=0.08$, $p=0.935$
Smoking dependence ²	74 (18)	36 (34)	1.49	0.94, 2.36	$z=1.73$, $p=0.084$

¹ Each model adjusted for maternal age at offspring birth, study of origin, proband ascertainment status, offspring age, sex, social class, maternal use of alcohol or drugs during pregnancy, number of assessments and parental lifetime history of the disorder estimated as the dependent variable; reported rates are lifetime

² Parental smoking history was not recorded in the Boys study, so parental lifetime history of smoking not included as a covariate

* still significant after additional adjustment for CD and ADHD