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Maternal smoking and child psychological problems: Disentangling causal and non-causal effects

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Abstract

Objective—To explore associations of maternal prenatal smoking and child psychological problems and determine the role of causal intrauterine mechanisms.

Patients and Methods—Maternal smoking and child psychological problems were explored in 2 birth cohorts in Pelotas, Brazil (n=509; random sub-sample) and Avon Longitudinal Study of Parents and Children (ALSPAC), Britain (n=6,735). Four approaches for exploring causal mechanisms were applied: 1) cross-population comparisons between a high-income and a middle-income country, 2) multiple adjustment for socioeconomic and parental psychological factors, 3) maternal-paternal comparisons as a test of putative intrauterine effects; and 4) search for specific effects on different behavioural subscales.

Results—Socioeconomic patterning of maternal prenatal smoking was stronger in the ALSPAC compared with the Pelotas cohort. Despite this difference in a key confounder, consistency in observed associations was found between these cohorts. In both cohorts, unadjusted, maternal smoking was associated with greater offspring hyperactivity, conduct/externalizing problems, and peer problems, but not with emotional/internalizing problems. After adjusting for confounders and paternal prenatal smoking, only the association with conduct/externalizing problems persisted in both cohorts (conduct problems in the ALSPAC cohort, odds ratio OR: 1.24 [95% confidence interval (CI): 1.07–1.46], p=.005; externalizing problems in the Pelotas cohort, OR:1.82 [95% CI: 1.19–2.78], p=.005; ORs reflect ordinal ORs of maternal smokers having offspring with higher scores). Maternal smoking associations were stronger than paternal smoking associations, although statistical evidence for differences was weak in 1 cohort.

Conclusions—Evidence from 4 approaches suggests a possible intrauterine effect of maternal smoking on offspring conduct/externalizing problems.

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Keywords

ALSPAC; Pelotas; prenatal smoking; child; behavioral problems; developmental origins

Introduction

Many studies have reported associations between maternal smoking in pregnancy and increased psychological problems in offspring, including conduct disorders, antisocial behaviour, attention deficit hyperactivity disorder (ADHD) and externalizing problems¹⁻⁶. However, there is some evidence that these associations may be completely confounded by social and familial factors than have not been possible to fully take account of in studies to date⁷⁻⁹. Indeed, an inherent difficulty in epidemiological studies is the limited ability to control for all known confounders¹⁰. Thus, the implementation of various different approaches and alternative study designs are important in order to obtain converging evidence for causal inference¹¹.

We aimed to explore the association of maternal smoking in pregnancy on offspring psychological problems using four different approaches for exploring causality. Firstly, we compared the consistency of associations between two birth cohorts, one from a high-income country (the Avon Longitudinal Study of Parents and Children, ALSPAC, in Britain) and the second from a middle-income country (the Pelotas 1993 cohort, in Brazil), which would be likely to have different confounding structures for these associations. This has been found, for example, with respect to the confounding structure of breastfeeding¹². In high-income countries, breastfeeding is strongly associated with more favourable socioeconomic position, which is a known predictor of many beneficial health outcomes. This results in a high probability of observing associations between breastfeeding and improved health outcomes that are confounded by socioeconomic position (rather than reflecting causal effects of breastfeeding). However, as breastfeeding does not tend to be related to socioeconomic factors in low- and middle-income countries, if associations largely reported in high-income countries were due to residual confounding, we would anticipate that they would not be replicated in low- and middle-income countries. Conversely, causal relationships would be expected to replicate in both the high- and low- or middle-income countries despite the differing socioeconomic patterning.

Secondly, we used extensive adjustment for multiple socioeconomic and parental psychological factors. As stated above, the association between maternal smoking and offspring psychological problems may be completely confounded by socioeconomic and psychological factors. Previous studies have varied in the extent to which these factors have been adjusted for.

Thirdly, we aimed to compare the associations of maternal and paternal smoking during pregnancy with offspring outcomes as an approach for exploring intrauterine effects on fetal development¹³. Briefly, this method is based on the assumption that maternal exposures in pregnancy directly affecting fetal development will produce a much stronger association than paternal exposures at the same time, which would not generally be expected to affect fetal development or have minimal effects where second-hand smoke exposure is concerned. However, associations driven by shared familial, social, genetic and environmental factors will be likely to produce similar maternal-paternal associations. This approach is validated by markedly discordant associations of maternal and paternal smoking in pregnancy with offspring birth weight, which is known to be directly affected by maternal smoking in pregnancy¹³.

The final approach was to search for specific effects of maternal smoking on different psychological outcomes, as specificity of effects provides evidence that associations are causal ¹⁴. If psychological problems involve different biological pathways, a physiological exposure would be expected to have specific effects on certain child psychological problems but not necessarily others.

Methods

Participants

ALSPAC—ALSPAC is a geographically-based prospective cohort study investigating the health and development of children ¹⁵. Pregnant women residing in three health districts in the South West of England with an expected date of delivery between 1st April 1991 and 31st December 1992 were eligible to enrol. 14,541 pregnant women were recruited and 13,678 had a live-born, singleton child. For this study we excluded parents and children of multiple births. Data on both maternal and paternal smoking is available in 12,366 mother-partner pairs. Data on psychological problems are available in 9,314 children, with 8,816 of these children also having complete data on parental smoking. Analyses were carried out on 6,735 children with complete data on socioeconomic confounders and mediators. Further analyses were also carried out in 4,394 children with multiple measures of parental psychopathology. Ethical approval of the study was obtained from the ALSPAC Law and Ethics Committee (IRB00003312) and three Local Research Ethics Committees.

Pelotas—The 1993 Pelotas cohort consists of 5,249 live newborns delivered in 1993 in Pelotas, Brazil. This cohort is described in detail elsewhere ¹⁶. Briefly, during 1993 interviewers paid daily visits to all five maternity hospitals in the city. Pelotas is situated in the extreme south of Brazil, near the Uruguayan border and has a population of approximately 320,000 urban inhabitants. At 4 years postnatal, a sub-sample consisting of all low birth weight children plus a systematic sample of 20% of the remaining cohort were followed up. A random 50% sub-sample of the 1,363 children located on that occasion were invited to take part in an assessment comprising detailed psychological measures ¹⁷. Of these children (n=634) the present analysis was carried out in 509 singleton children with complete data on maternal smoking, paternal smoking, psychological problems, confounders and mediators.

Measures

Parental smoking—In ALSPAC, maternal smoking in each trimester is available from questionnaires sent to mothers at 18- and 32-weeks gestation. Partner smoking in pregnancy was assessed from a questionnaire for partners given at 18-weeks. In Pelotas, information on maternal smoking in each trimester, as well as partner smoking, was collected at the perinatal visit.

Psychological measures—In ALSPAC, child psychological problems were assessed at 4 years by maternal report using the Strengths and Difficulties Questionnaire (SDQ), a brief behavioral screening questionnaire for children aged 4 to 16 ¹⁸. The SDQ comprises 25 questions which generate scores for Inattention-Hyperactivity, Emotional Symptoms (anxious and depressive symptoms), Peer Problems and Conduct Problems (aggressive and rule-breaking behaviour). In Pelotas, child psychological problems were assessed using the child behaviour checklist (CBCL) ¹⁹ administered at the 4-year follow-up by a psychologist ¹⁷. The CBCL consists of 118 items completed by parental reporting which generate scores for scales on Withdrawn, Somatic Complaints, Anxious / Depressed, Social Problems, Thought Problems, Attention Problems, Aggressive Behavior and Rule-Breaking

Behavior. Validity of the CBCL has been demonstrated in a population of Brazilian children ²⁰.

Previous comparisons between the SDQ and CBCL suggest equivalent validity between the instruments, with scores from the SDQ and CBCL being both highly correlated and equally able to identify psychiatric cases ²¹. Furthermore, when judged against a semi-structured interview, the SDQ was as good as the CBCL at detecting inattention and hyperactivity, internalizing problems and externalizing problems. The psychological groups compared between ALSPAC and Pelotas are based on those previously compared by Goodman [ie SDQ scales of Inattention-Hyperactivity, Peer Problems, Emotional Symptoms and Conduct Problems compared with the CBCL scales of Attention Problems, Social Problems, Internalizing (Anxious/Depressed, Somatic Complaints, Thought Problems) and Externalizing (Aggressive Behavior, Rule-Breaking Behavior), respectively]. ²¹

Confounders and mediators

Associations were adjusted for socioeconomic position (maternal and paternal education, social class, family income), parental psychopathology (ALPSAC: maternal prenatal and postnatal depression, maternal prenatal anxiety, paternal prenatal and postnatal depression, paternal prenatal anxiety, maternal prenatal alcohol, paternal prenatal alcohol intake; Pelotas: maternal psychiatric problems; measures of parental aggression/antisocial behaviour were not available in either cohort) and (in later models) for mediators (birthweight, gestational age and breastfeeding). Detailed information on these measures are provided as supplementary information (see journal website).

Statistical analysis

Socioeconomic patterning of maternal / paternal smoking was assessed using quintiles/ groups of family income and chi-square tests for linear trend, with cross-cohort differences explored using indices of inequality ²² and the Q-statistic for heterogeneity. Statistical evidence of heterogeneity provide support for the hypothesis that systematic differences between the cohorts exist with respect to the socioeconomic patterning (and thus the confounding structure) of maternal smoking. Psychological problem subscales were analysed in original score units, grouped where appropriate to facilitate ordinal logistic regression (for ordered categorical outcomes). Results reflect the ordinal odds ratios of maternal smokers having offspring with higher problems scores ie a single odds ratio for maternal smoking and higher offspring problem scores, combined over increasing categories of offspring problem scores. Associations of maternal / paternal smoking in pregnancy with offspring psychological problems were explored using the following models: 1) unadjusted, 2) adjusted for socioeconomic confounders, 3) additionally adjusted for mediators, and 4) adjusted for parental psychological factors. Analyses are explored firstly for maternal and paternal smoking individually, followed by mutually-adjusted models of maternal and paternal smoking adjusted for one another. Differences between maternal and paternal associations were assessed using the Wald statistic. Sensitivity analyses exploring effects of varying putative levels of non-paternity on maternal and paternal associations were carried out using simulations (see supplementary information). All Pelotas analyses were weighted to correct for the over-sampling of low birth weight babies. Analyses were repeated using dichotomous outcomes clinical psychological problems. All analyses were performed using STATA 10.

Results

The prevalence of any maternal smoking in pregnancy in the Pelotas subsample (similar to that of the whole cohort ²³) was almost twice as high as that in ALSPAC (29.4% vs. 15.9%,

respectively). In addition, the proportion of mothers who smoked at high doses (20 or more cigarettes per day in the 3rd trimester) was greater in Pelotas than in ALSPAC (see Table 1).

Maternal and paternal smoking in pregnancy were both associated with lower socioeconomic position in both ALSPAC and Pelotas, with associations appearing steeper in ALSPAC than Pelotas (Table 2). Indices of inequality between the highest and lowest income level with respect to maternal smoking were 3.7 times greater in ALSPAC (OR=0.14, 95% CI: 0.11-0.18, $p<0.001$, for maternal smoking in the highest level compared with lowest) than in Pelotas (OR=0.52, 95% CI: 0.25-1.06, $p=0.07$, for maternal smoking in the highest level compared with lowest). There was modest evidence of statistical heterogeneity between ALSPAC and Pelotas ($p=0.07$). Indices of inequality for paternal smoking were also greater in ALSPAC (OR=0.19, 95% CI: 0.16-0.23, $p<0.001$) compared with Pelotas (OR=0.32, 95% CI: 0.17-0.63, $p=0.001$), although with weak evidence of ALSPAC-Pelotas heterogeneity ($p=0.3$). Thus, although the statistical evidence for ALSPAC-Pelotas differences were modest to weak, differences in point estimates suggest a stronger influence of socioeconomic position on parental smoking during pregnancy in the British cohort compared with the Brazilian cohort. This is further supported by the confounder associations below.

Associations with confounding factors are explored in Tables 3 and 4. In ALSPAC, child psychological problems were associated with lower socioeconomic position and maternal and paternal anxiety/depression. In Pelotas, child psychological problems were unassociated with socioeconomic position, but strongly associated with maternal psychiatric problems. Maternal and paternal smoking were associated with socioeconomic position and maternal prenatal alcohol in ALSPAC. In Pelotas, maternal smoking was associated with maternal and paternal lower education, but was unassociated with other indicators of socioeconomic position and maternal psychiatric problems. Paternal smoking in Pelotas was associated with all indicators of lower socioeconomic position and maternal psychiatric problems.

In unadjusted models, maternal smoking in pregnancy was associated with inattention/hyperactivity, conduct/externalizing and peer/social problems, but not with emotional/internalizing problems (Table 5). In models adjusted for socioeconomic factors and maternal-paternal smoking mutually adjusted for one another, maternal smoking associations persisted for conduct/externalizing problems in both cohorts. Adjustment for potential mediators (birth weight, gestational age, breastfeeding duration) did not change the associations (data not shown). After adjusting for parental psychopathology, socioeconomic factors and maternal-paternal smoking mutually adjusted (Table 6), the associations with conduct/externalizing problems persisted in both cohorts, with weaker or null associations observed with hyperactivity, emotional/internalizing, peer/social problems. Associations (fully adjusted, mutual model) did not differ systematically between ALSPAC and Pelotas (P values for heterogeneity: attention/hyperactivity $p=0.2$, emotional/internalizing $p=0.6$, conduct/externalizing $p=0.1$, peer/social $p=0.5$).

Statistical evidence for differences between the maternal and paternal smoking associations with child psychological problems were explored. In fully-adjusted models there were differences between point estimates of maternal and paternal smoking associations with child conduct/externalizing problems, although with weak evidence of statistical difference in ALSPAC [$p(\text{difference})=0.3$ and 0.03 ALSPAC and Pelotas respectively]. There was no strong evidence of maternal-paternal differences in associations with the remaining types of child psychological problems, fully adjusted [attention problems $p(\text{difference})=0.9$ and 0.3 ; emotional/internalizing problems $p(\text{difference})=0.9$ and 0.3 ; peer problems $p(\text{difference})=0.1$ and 0.3 ; ALSPAC and Pelotas respectively, for all]

Sensitivity analyses were explored modelling effects of non-paternity on the fully adjusted associations of maternal and paternal smoking on child conduct problems using simulated data sets (see Supplementary Table 1). These simulations suggested that the ALSPAC data exhibited some sensitivity to non-paternity with the paternal smoking association increasing by 10% and maternal association reducing by 2% for a 10% non-paternity rate. In contrast the Pelotas data were relatively insensitive to non-paternity. This may reflect the small/null paternal smoking effect on conduct problems. These results indicate that any difference in parental effects in the ALSPAC study was weakened further noting that even without any non-paternity there was little statistical evidence for differences in parental effects (p for difference=0.3), despite maternal-paternal point estimates being in the ratio of 2:1. In contrast, for the Pelotas data, the greater maternal effect reported for the observed data is likely to be resilient to non-paternity.

When psychological problems were analysed as dichotomous outcomes for clinical psychological problems (in ALSPAC only, Pelotas analyses were underpowered), similar results were observed to those using ordered categories of psychological problem scores (see supplementary Table 2).

Discussion

There was some evidence that maternal smoking in pregnancy is associated with greater conduct/externalizing problems in offspring at age 4 via a causal intrauterine mechanism. Consistent results were observed between the British and Brazilian cohorts despite different strengths in the confounding patterning of maternal smoking by socioeconomic position. In both cohorts associations of maternal smoking in pregnancy persisted following adjustment for socioeconomic position, parental psychopathology and paternal smoking, with consistent results in both cohorts regarding the specificity of the maternal smoking association with conduct/externalizing problems. Stronger maternal, versus paternal, smoking associations were observed in both cohorts (although not statistically different in ALSPAC) with paternal smoking not being strongly associated with offspring conduct/externalizing in either cohort.

Discordant maternal-paternal smoking associations suggest that maternal prenatal smoking may have specific intrauterine effects on components of offspring development. Any direct effects of maternal smoking in pregnancy on fetal development would be expected to be substantially greater than effects of partners smoking during this period (including effects of exposures to second hand smoke). However, maternal smoking may be more strongly associated with child problems than paternal smoking, mediated by, for example, maternal psychological problems exerting a stronger influence on child behaviour than paternal problems. Indeed, mothers who smoke during pregnancy have higher rates of interpersonal and behaviour problems, notably aggressive and antisocial behaviours²⁴. Although maternal antisocial behaviour has been found to be an important component of the association between maternal smoking and child conduct problems⁸, this could not be explored in the present study as data on maternal aggressive or antisocial behaviour were not available.

The potential role of genetic factors has been discussed previously^{8,25-27}. There is evidence from studies utilising different study designs (such as children of twins³, discordant siblings²⁸ and prenatal cross-fostering⁹), that genetic factors may play an important role in moderating the association between maternal prenatal smoking and child behavioural problems. In addition, maternal smoking associations may also be partly confounded by genetic factors. Indeed, a recent twin study found that genetic effects may account for around half of the observed association between maternal smoking and child conduct problems⁸. This could occur if, for example, mothers with behavioural problems / antisocial behaviour are more likely to smoke and, via genetic transmission, also have greater risk of

children with behavioural problems³. One might anticipate that such pathways would result in associations of both mother's and father's smoking with offspring behaviours as genetic variants would be inherited from both parents. A stronger maternal association would be consistent with a parent of origin effect of inheritance but to our knowledge such effects have not been found or suggested for inheritance patterns of smoking behaviours. In the present study there was no association between paternal smoking and offspring psychological problems, which would suggest that confounding by inheritance of genetic factors in this way may not be driving the associations observed here. Paternal associations may be diluted by non-paternity, however, while the ALSPAC results were sensitive to increasing levels of non-paternity, this was not the case for the Pelotas associations.

The specificity of the maternal smoking association with child conduct/externalizing problems, lends further support to the possibility that this association is mediated via adverse effects of intrauterine exposure to tobacco on neurodevelopmental pathways. There is evidence to support a developmental neurobiological basis of antisocial and aggressive behaviour, and in particular in relation to fetal exposure to nicotine²⁹. In animals, fetal nicotine exposure results in altered physiology at neuronal sites controlling arousal and more excitable offspring³⁰. Nicotine-induced inhibition of the monoamine oxidase (MAO) system during fetal development has also been implicated in the relationship between maternal smoking and offspring aggression and conduct disorders²⁹.

Whilst in ALSPAC maternal smoking was strongly associated with all indicators of socioeconomic position (a key confounder), in Pelotas, maternal smoking was not consistently associated with these factors. Furthermore, indices of inequality (based on income) for maternal smoking were approximately four times lower in Pelotas than ALSPAC. Thus, due to this weaker socioeconomic patterning of maternal smoking observed in Pelotas, if maternal smoking associations were driven by confounding by socioeconomic position, one would expect smaller associations in Pelotas compared with ALSPAC. However, we observed consistent patterns of association in both cohorts. This suggests that residual confounding by socioeconomic factors is not likely to be completely driving the association of maternal smoking with offspring conduct/externalizing problems.

Limitations

Several potentially important confounders were not available in the present; these include maternal antisocial behaviour and, in Pelotas, data on paternal psychological factors and maternal/paternal prenatal alcohol. Secondly, whilst we aimed to compare the same psychological measures across cohorts, different instruments were used to assess child behaviour (SDQ vs CBCL). However, as discussed in the methods, these instruments have been found to have equivalent validity and comparable subscales. Finally, assessment of parental smoking in both cohorts was based on self-report. A meta-analysis of comparisons with biochemical measures found self-reported smoking measures to be accurate³¹. However, a recent retrospective cross-sectional study suggests that there may be substantial underestimation of smoking behaviour by women who are pregnant³². If any such misclassification occurred in our cohorts and was non-systematic with respect to our outcome measures (which is likely since we obtained smoking data prospectively at the time of pregnancy or birth and mothers could not have known what their children's behaviour would be like at that time) the statistical expectation would be that associations would be biased towards the null. Thus, the true association between maternal smoking and child conduct/externalizing problems may be stronger.

Conclusion

Based on several different approaches, we find some evidence of a causal relationship between maternal smoking and offspring conduct/externalizing problems. This was not found for offspring ADHD or emotional/internalizing problems. If the present findings are confirmed in future studies, this implies that interventions to reduce maternal smoking in pregnancy might have beneficial effects on future offspring conduct/externalizing problems. Using multiple approaches (as we have done here) for assessing causality in observational studies, particularly those exploring developmental origins of health and disease, could improve aetiological epidemiology studies in general.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
ASEBA	Achenbach System of Empirically Based Assessment
CBCL	Child Behavior Checklist
CI	Confidence interval
MAO	Monoamine oxidase
OR	Odds ratio
SDQ	Strengths and Difficulties Questionnaire

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Table 1

Maternal and paternal smoking in pregnancy in ALSPAC and Pelotas

Parental smoking in pregnancy	ALSPAC %	Pelotas [*] %
Maternal smoking		
Any smoking in pregnancy ¹	15.9%	29.4%
<u>1st trimester</u>		
Smoked in the 1 st trimester ¹	18.3%	27.3%
Smoked 20 or more cigarettes/day ²	11.6%	21.5%
<u>2nd trimester</u>		
Smoking in the 2 nd trimester ¹	14.1%	27.1%
Smoked 20 or more cigarettes/day ²	11.8%	21.6%
<u>3rd trimester</u>		
Smoking in the 3 rd trimester ¹	15.4%	26.0%
Smoked 20 or more cigarettes/day ²	13.2%	24.3%
Paternal smoking		
Any smoking in pregnancy ¹	31.9%	49.6%

¹ Proportion as percentage of the whole sample² Proportion as percentage of the smokers for that particular trimester^{*} Pelotas prevalence weighted (due to low birth weight oversampling)

Table 2

Prevalence of maternal and paternal smoking in pregnancy by family income

<u>Prevalence of parental smoking in pregnancy (%)</u>						
Cohort	Lowest Income Group	2	3	4	Highest Income Group	P trend
Maternal smoking						
ALSPAC	45.5	31.6	20.2	15.1	11.1	<0.001
Pelotas	38.1	25.0	35.1	30.4	20.5	0.05
Paternal smoking						
ALSPAC	60.6	48.8	33.2	27.1	22.3	<0.001
Pelotas	69.0	42.2	54.2	57.5	31.4	<0.001

ALSPAC groups: <£100, £100-£199, £200-£299, £300-£399, >£400 weekly take-home income

Pelotas groups: based on quintiles of income assessed in multiples of the Brazilian minimum wage.

Table 3

Associations of child psychological problems with confounders

Confounder	Ordinal odds for higher child psychological problem score											
	Inattention-Hyperactivity			Emotional Problems			Conduct Problems			Peer Problems		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
ALSPAC (N=4394)												
Maternal Education (non-degree vs degree)	1.97	1.71, 2.27	<0.001	0.86	0.75, 1.00	0.04	1.23	1.07, 1.42	0.003	1.50	1.30, 1.73	<0.001
Paternal Education (non-degree vs degree)	1.83	1.61, 2.06	<0.001	0.95	0.84, 1.08	0.4	1.08	0.95, 1.22	0.2	1.35	1.19, 1.53	<0.001
Income (lowest quarter vs rest)	1.61	1.40, 1.87	<0.001	1.17	1.01, 1.36	0.03	1.55	1.34, 1.80	<0.001	1.66	1.43, 1.92	<0.001
Occupation (manual vs nonmanual)	1.51	1.29, 1.77	<0.001	0.95	0.81, 1.12	0.6	1.40	1.19, 1.64	<0.001	1.37	1.17, 1.61	<0.001
Maternal anxiety/depression ^I (highest quarter vs rest)	1.60	1.41, 1.81	<0.001	1.73	1.52, 1.97	<0.001	1.76	1.55, 2.01	<0.001	1.75	1.54, 2.00	<0.001
Paternal anxiety/depression ^I (highest quarter vs rest)	1.13	1.00, 1.28	0.05	1.14	1.01, 1.30	0.04	1.32	1.17, 1.50	<0.001	1.11	0.98, 1.26	0.1
Maternal prenatal alcohol (1 glass/wk vs less)	1.08	0.93, 1.25	0.3	0.99	0.85, 1.15	0.9	1.25	1.08, 1.45	0.003	1.23	1.06, 1.42	0.007
Paternal prenatal alcohol (1 glass/day vs less)	0.86	0.75, 0.98	0.03	0.99	0.86, 1.14	0.9	1.12	0.98, 1.29	0.1	0.92	0.80, 1.06	0.2
	Attention Problems			Internalizing Problems			Externalizing Problems			Social Problems		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Pelotas 1993 (N=523)												
Maternal education (<10 years vs higher)	1.06	0.70, 1.61	0.8	1.13	0.74, 1.72	0.6	0.80	0.55, 1.17	0.3	0.98	0.63, 1.54	0.9
Paternal education (10 years vs higher)	1.97	1.22, 3.17	0.003	1.30	0.83, 2.02	0.3	1.05	0.67, 1.65	0.8	1.07	0.66, 1.72	0.8
Income (lowest quarter vs rest)	0.95	0.66, 1.37	0.8	1.36	0.93, 1.99	0.1	0.83	0.56, 1.22	0.3	1.03	0.68, 1.58	0.9
Occupation (proletariat vs bourgeois)	0.88	0.58, 1.32	0.5	1.05	0.69, 1.58	0.8	0.71	0.48, 1.07	0.1	1.00	0.67, 1.48	0.99
Maternal psychiatric problems (yes vs no)	3.31	2.21, 4.95	<0.001	5.03	3.34, 7.59	<0.001	3.06	2.07, 4.50	<0.001	2.26	1.51, 3.38	<0.001

^I Maternal and paternal anxiety/depression scores represent combined scores on prenatal and postnatal depression and prenatal anxiety

Table 4

Associations between maternal and paternal smoking and confounders

Confounder	Odds of Maternal and Paternal Smoking During Pregnancy					
	Maternal smoking			Paternal smoking		
	OR	95% CI	P	OR	95% CI	P
ALSPAC (N=4604)						
Maternal Education (non-degree vs degree)	3.61	2.66, 4.88	<0.001	2.94	2.37, 3.65	<0.001
Paternal Education (non-degree vs degree)	3.23	2.52, 4.13	<0.001	2.81	2.34, 3.38	<0.001
Income (lowest quarter vs rest)	2.69	2.23, 3.24	<0.001	3.02	2.55, 3.57	<0.001
Occupation (manual vs nonmanual)	2.68	2.20, 3.28	<0.001	2.53	2.11, 3.03	<0.001
Maternal anxiety/depression ^I (highest quarter vs rest)	1.70	1.43, 2.03	<0.001	1.46	1.25, 1.70	<0.001
Paternal anxiety/depression ^I (highest quarter vs rest)	1.31	1.10, 1.57	0.003	1.44	1.24, 1.68	<0.001
Maternal prenatal alcohol (1 glass/wk vs less)	1.81	1.49, 2.21	<0.001	1.33	1.11, 1.58	0.002
Paternal prenatal alcohol (1 glass/day vs less)	1.01	0.83, 1.24	0.9	1.58	1.34, 1.95	<0.001
Pelotas 1993 (N=523)						
Maternal education (10 years vs higher)	2.11	1.17, 3.82	0.01	1.94	1.18, 3.17	0.009
Paternal education (10 years vs higher)	3.84	1.90, 7.77	<0.001	2.09	1.25, 3.49	0.005
Income (lowest quarter vs rest)	1.40	0.89, 2.21	0.1	2.08	1.34, 3.24	0.001
Occupation (proletariat vs bourgeois)	1.26	0.77, 2.08	0.4	1.47	0.93, 2.30	0.1
Maternal psychiatric problems (yes vs no)	1.36	0.87, 2.14	0.2	1.64	1.06, 2.53	0.03

^I Maternal and paternal anxiety/depression scores represent combined scores on prenatal and postnatal depression and prenatal anxiety

Table 5

Associations of maternal and paternal smoking in pregnancy with offspring psychological problem subtypes

Offspring Psychological Problems, Score												
Parental Smoke	Individual Maternal-Paternal Models						Mutually Adjusted Maternal-Paternal Models					
	Model I *			Model II **			Model I *			Model II **		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Hyperactivity /Attention problems												
ALSPAC												
Maternal smoking	1.46	1.31, 1.62	<0.001	1.17	1.05, 1.31	0.004	1.37	1.22, 1.53	<0.001	1.17	1.04, 1.31	0.009
Paternal smoking	1.28	1.17, 1.40	<0.001	1.06	0.96, 1.16	0.3	1.17	1.07, 1.29	0.001	1.02	0.92, 1.12	0.7
Pelotas												
Maternal smoking	1.56	1.08, 2.25	0.02	1.38	0.94, 2.03	0.1	1.48	0.99, 2.19	0.05	1.35	0.90, 2.01	0.1
Paternal smoking	1.31	0.94, 1.82	0.1	1.17	0.82, 1.68	0.4	1.18	0.82, 1.69	0.4	1.10	0.76, 1.60	0.6
Emotional/Internalizing problems												
ALSPAC												
Maternal smoking	1.05	0.94, 1.17	0.4	1.00	0.89, 1.12	0.96	1.05	0.94, 1.18	0.4	1.01	0.90, 1.14	0.8
Paternal smoking	1.01	0.92, 1.11	0.8	0.97	0.88, 1.07	0.5	0.99	0.90, 1.10	0.9	0.97	0.87, 1.07	0.5
Pelotas												
Maternal smoking	0.98	0.68, 1.41	0.9	0.95	0.65, 1.39	0.9	0.99	0.67, 1.46	0.9	0.97	0.65, 1.45	0.9
Paternal smoking	0.98	0.69, 1.38	0.9	0.92	0.65, 1.32	0.7	0.98	0.68, 1.42	0.9	0.93	0.64, 1.36	0.7
Conduct/Externalizing problems												
ALSPAC												
Maternal smoking	1.65	1.48, 1.84	<0.001	1.46	1.30, 1.63	<0.001	1.52	1.36, 1.71	<0.001	1.40	1.24, 1.58	<0.001
Paternal smoking	1.36	1.24, 1.49	<0.001	1.22	1.11, 1.34	<0.001	1.20	1.09, 1.33	<0.001	1.12	1.02, 1.24	0.02
Pelotas												
Maternal smoking	1.67	1.17, 2.39	0.005	1.72	1.18, 2.51	0.005	1.68	1.13, 2.50	0.01	1.72	1.14, 2.58	0.009
Paternal smoking	1.15	0.82, 1.60	0.4	1.16	0.82, 1.63	0.4	0.98	0.68, 1.42	0.9	0.96	0.66, 1.39	0.8
Peer/Social problems												
ALSPAC												
Maternal smoking	1.46	1.31, 1.63	<0.001	1.23	1.09, 1.37	<0.001	1.42	1.27, 1.56	<0.001	1.24	1.10, 1.40	<0.001
Paternal smoking	1.19	1.09, 1.31	<0.001	1.02	0.92, 1.12	0.7	1.07	0.97, 1.18	0.2	0.96	0.92, 1.03	0.4
Pelotas												
Maternal smoking	1.45	1.00, 2.11	0.05	1.45	0.98, 2.14	0.06	1.43	0.98, 2.11	0.09	1.44	0.97, 2.15	0.07
Paternal smoking	1.15	0.80, 1.63	0.5	1.10	0.76, 1.60	0.6	1.05	0.73, 1.51	0.7	1.02	0.70, 1.50	0.9

Ordinal logistic regression; Odds ratios of having offspring in higher scores for psychological problems in maternal smokers vs non-smokers

ALSPAC n=6735; Pelotas n=509

* Model I: unadjusted

** Model II: adjusted for maternal education, paternal education, income, social class

Table 6

Associations of maternal and paternal smoking in pregnancy with offspring psychological problems adjusted for socioeconomic and parental psychopathology factors

Parental Smoke	Offspring Psychological Problems, Score		
	OR	95% CI	P
Hyperactivity / Attention problems			
ALSPAC			
Maternal smoking	1.01	0.87, 1.18	0.9
Paternal smoking	1.03	0.91, 1.17	0.6
Pelotas			
Maternal smoking	1.44	0.94, 2.19	0.09
Paternal smoking	1.04	0.71, 1.50	0.8
Emotional / Internalizing Problems			
ALSPAC			
Maternal smoking	0.95	0.81, 1.11	0.5
Paternal smoking	0.93	0.82, 1.06	0.3
Pelotas			
Maternal smoking	0.99	0.66, 1.50	0.98
Paternal smoking	0.85	0.58, 1.24	0.4
Conduct / Externalizing			
ALSPAC			
Maternal smoking	1.24	1.07, 1.46	0.005
Paternal smoking	1.11	0.98, 1.26	0.1
Pelotas			
Maternal smoking	1.82	1.19, 2.78	0.005
Paternal smoking	0.96	0.66, 1.41	0.9
Peer / Social problems			
ALSPAC			
Maternal smoking	1.20	1.03, 1.40	0.02
Paternal smoking	1.01	0.89, 1.15	0.9
Pelotas			
Maternal smoking	1.46	0.97, 2.19	0.1
Paternal smoking	0.98	0.67, 1.45	0.99

Ordinal logistic regression; Odds of having offspring with higher problem scores in maternal smokers versus nonsmokers

ALSPAC N=4394; Pelotas N=509; Maternal and paternal smoking adjusted for each other

All models adjusted for socioeconomic position (maternal education, paternal education, income, social class) plus:

* ALSPAC additionally adjusted for: maternal psychopathology (prenatal and postnatal depression, prenatal anxiety), paternal psychopathology (prenatal and postnatal depression, prenatal anxiety) maternal prenatal alcohol, paternal prenatal alcohol intake

* Pelotas additionally adjusted for: maternal psychiatric problems