Maternal Smoking and Child Psychological Problems: Disentangling Causal and Noncausal Effects

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KEY WORDS

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

ABBREVIATIONS

ALSPAC—Avon Longitudinal Study of Parents and Children
SDQ—Strengths and Difficulties Questionnaire
CBCL—Child Behavior Checklist
OR—odds ratio
CI—confidence interval

Dr Brion conducted the analyses, wrote the first draft, and coordinated subsequent versions; Drs Victora, Horta, Matijasevich, Smith, and Lawlor provided guidance on the analyses; all the authors commented on the first and subsequent drafts; Dr Anselmi is the psychologist for the Pelotas cohort and coordinated the collection of the psychological data; and Mr Steer conducted the statistical simulations for the nonpaternity sensitivity analyses.

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WHAT'S KNOWN ON THIS SUBJECT: Maternal prenatal smoking is strongly associated with various child psychological problems. It is not clear if this association reflects biological intrauterine effects of smoking or confounding by broader social, environmental, and genetic factors.

WHAT THIS STUDY ADDS: Using multiple approaches for exploring causality we found evidence that whilst other psychological problems are unlikely to be causally related to maternal smoking, there is evidence that maternal smoking is causally related via intrauterine effects to child conduct/externalizing problems.

abstract

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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 subsample), and the Avon Longitudinal Study of Parents and Children (ALSPAC) in Britain (n = 6735). 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) searching for specific effects on different behavioral 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 odds ratios of maternal smokers having offspring with higher scores). Maternal smoking associations were stronger than paternal smoking associations, although statistical evidence that these associations differed was weak in 1 cohort.

CONCLUSION: Evidence from 4 approaches suggests a possible intrauterine effect of maternal smoking on offspring conduct/externalizing problems. *Pediatrics* 2010;126:e57–e65

Associations between maternal smoking in pregnancy and increased psychological problems in offspring, including conduct disorders, antisocial behavior, attention-deficit/hyperactivity disorder, and externalizing problems, have been reported in many studies.[1–6] However, there is some evidence that these associations may be completely confounded by social and familial factors that have not been possible to fully take account of in studies to date.[7–9] Indeed, an inherent difficulty in epidemiologic studies is the limited ability to control for all known confounders.[10] Thus, in order to obtain reliable evidence of causal effects, it is important to use various different analytic approaches and alternative study designs.[11]

We aimed to explore the association of maternal smoking in pregnancy on offspring psychological problems by using 4 different approaches for exploring causality. First, we compared the consistency of associations between 2 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. Such differences have been found, for example, with respect to the confounding structure of breastfeeding.[12] In high-income countries, breastfeeding is strongly associated with more favorable socioeconomic position, which is a known predictor of many beneficial health outcomes. This association between breastfeeding and favorable socioeconomic position results in a high probability of observing relationships between breastfeeding and improved health outcomes that are confounded by socioeconomic position (rather than reflecting causal effects of breastfeeding). However, because 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 a result of residual confounding, we would anticipate that they would not be replicated in low- and middle-income countries. Conversely, causal relationships would be expected to be replicated in both the high- and low- or middle-income countries despite the differing socioeconomic patterning.

Second, 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.

Third, 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 development.[13] Briefly, this method was based on the assumption that maternal exposures in pregnancy that directly affect 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 secondhand 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 was 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 pregnancy.[13]

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

METHODS

Participants

The ALSPAC Cohort

The ALSPAC cohort is a geographically based prospective cohort study that is investigating the health and development of children.[15] Pregnant women who resided in 3 health districts in the southwest of England with an expected date of delivery between April 1, 1991, and December 31, 1992, were eligible to enroll. In total, 14 541 pregnant women were recruited, 13 678 of whom delivered a live-born singleton child. For this study we excluded parents and children of multiple births. Data on both maternal and paternal smoking were available for 12 366 mother-partner pairs. Data on psychological problems were available for 9314 children, and complete data on parental smoking were available for 8816 of these children. Analyses were conducted on 6735 children with complete data on socioeconomic confounders and mediators. Further analyses were also conducted on 4394 children with multiple measures of parental psychopathology. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee (IRB00003312) and 3 local research ethics committees.

The Pelotas Cohort

The 1993 Pelotas cohort consists of 5249 live-born newborns delivered in 1993 in Pelotas, Brazil. This cohort has been described in detail elsewhere.[16] Briefly, during 1993 interviewers paid daily visits to all 5 maternity hospitals

in the city. Pelotas is situated in the extreme south of Brazil near the Uruguayan border and has a population of ~320 000 urban inhabitants. Four years after birth, a subsample that consisted of all low birth weight children plus a systematic sample of 20% of the remaining cohort were followed up. A random 50% subsample of the 1363 children located on that occasion were invited to take part in an assessment comprising detailed psychological measures.[17] Of these children (n = 634), our analysis was conducted on 509 singleton children with complete data on maternal smoking, paternal smoking, psychological problems, confounders, and mediators.

Measures

Parental Smoking

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

Psychological Measures

For the ALSPAC cohort, 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 years.[18] The SDQ comprises 25 questions that generate scores for inattention/hyperactivity, emotional symptoms (anxious and depressive symptoms), peer problems, and conduct problems (aggressive and rule-breaking behavior). For the Pelotas cohort, child psychological problems were assessed by using the Child Behavior Checklist (CBCL)[19] administered at the 4-year follow-up by a psychologist.[17] The CBCL consists of 118 items completed by parents and generates 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 have suggested 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 semistructured interview, the SDQ was as good as the CBCL at detecting inattention and hyperactivity, internalizing problems, and externalizing problems. The psychological groups compared between the ALSPAC and Pelotas cohorts were based on those previously compared by Goodman and Scott[21] (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).

Confounders and Mediators

Associations were adjusted for socioeconomic position (maternal and paternal education, social class, family income), parental psychopathology (ALSPAC cohort: maternal prenatal and postnatal depression, maternal prenatal anxiety, paternal prenatal and postnatal depression, paternal prenatal anxiety, maternal prenatal alcohol intake, and paternal prenatal alcohol intake; Pelotas cohort: maternal psychiatric problems; measures of parental aggression/antisocial behavior were not available for either cohort), and (in later models) for mediators (birth weight, gestational age, and breastfeeding). Detailed information on these measures is provided in the Supplemental Text.

Statistical Analysis

Socioeconomic patterning of maternal/paternal smoking was assessed by using quintiles/groups of family income and χ^2 tests for linear trend, and cross-cohort differences were explored by using indices of inequality[22] and the Q statistic for heterogeneity. Statistical evidence of heterogeneity provides 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 analyzed in original score units, grouped where appropriate to facilitate ordinal logistic regression (for ordered categorical outcomes). Results reflect the ordinal odds ratios (ORs) of maternal smokers having offspring with higher problem scores, that is, a single OR 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 by using models that were (1) unadjusted, (2) adjusted for socioeconomic confounders, (3) additionally adjusted for mediators, and (4) adjusted for parental psychological factors. Analyses were explored first 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 by using the Wald statistic. Sensitivity analyses were conducted to explore the effects of varying putative levels of nonpaternity on maternal and pater-

TABLE 1 Maternal and Paternal Smoking in Pregnancy in the ALSPAC and Pelotas Cohorts

Parental Smoking in Pregnancy	ALSPAC, %	Pelotas, %[a]
Maternal smoking		
Any smoking in pregnancy[b]	15.9	29.4
First trimester		
Smoked in the first trimester[b]	18.3	27.3
Smoked ≥20 cigarettes per d[c]	11.6	21.5
Second trimester		
Smoking in the second trimester[b]	14.1	27.1
Smoked ≥20 cigarettes per d[c]	11.8	21.6
Third trimester		
Smoking in the third trimester[b]	15.4	26.0
Smoked ≥20 cigarettes per d[c]	13.2	24.3
Paternal smoking		
Any smoking in pregnancy[b]	31.9	49.6

[a] The Pelotas prevalence was weighted (because of the oversampling of low birth weight infants).
[b] Proportion as a percentage of the whole sample.
[c] Proportion as a percentage of the smokers for that particular trimester.

TABLE 2 Prevalence of Maternal and Paternal Smoking in Pregnancy According to Family Income

Cohort	Prevalence of Parental Smoking in Pregnancy, %					*P*, Trend
	Group 1 (Lowest Income)	Group 2	Group 3	Group 4	Group 5 (Highest Income)	
Maternal smoking						
ALSPAC	45.5	31.6	20.2	15.1	11.1	<.001
Pelotas	38.1	25.0	35.1	30.4	20.5	.05
Paternal smoking						
ALSPAC	60.6	48.8	33.2	27.1	22.3	<.001
Pelotas	69.0	42.2	54.2	57.5	31.4	<.001

ALSPAC groups: less than £100, £100 to £199, £200 to £299, £300 to £399, and £400 or more weekly take-home income; Pelotas groups: based on quintiles of income assessed in multiples of the Brazilian minimum wage.

nal associations by using simulations (see Supplemental Text). All Pelotas-cohort analyses were weighted to correct for the oversampling of low birth weight infants. Analyses were repeated by using dichotomous outcomes for clinical psychological problems. All analyses were performed by using Stata 10 (Stata Corp, College Station, TX).

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 the ALSPAC sample (29.4% vs 15.9%, respectively). In addition, the proportion of mothers who smoked at high doses (≥20 cigarettes per day in the third trimester) was greater in the Pelotas cohort than in the ALSPAC cohort (see Table 1).

Maternal and paternal smoking in pregnancy were both associated with lower socioeconomic position in both the ALSPAC and Pelotas cohorts but the associations seemed steeper in the ALSPAC cohort (Table 2). Indices of inequality between the highest and lowest income levels with respect to maternal smoking were 3.7 times greater in the ALSPAC cohort (OR: 0.14 [95% confidence interval (CI): 0.11–0.18]; $P < .001$, for maternal smoking in the highest compared with lowest level) than in the Pelotas cohort (OR: 0.52 [95% CI: 0.25–1.06]; $P = .07$, for maternal smoking in the highest compared with lowest level). There was modest evidence of statistical heterogeneity between the ALSPAC and Pelotas cohorts ($P = .07$). Indices of inequality for paternal smoking were also greater in the ALSPAC cohort (OR: 0.19 [95% CI: 0.16–0.23]; $P < .001$) compared with those in the Pelotas cohort (OR: 0.32 [95% CI: 0.17–0.63]; $P = .001$), although there was weak evidence of ALSPAC-Pelotas heterogeneity ($P = .3$). 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 that in the Brazilian cohort, which is further supported by the confounder associations discussed below.

Associations with confounding factors are listed in Tables 3 and 4. In the ALSPAC cohort, child psychological problems were associated with lower socioeconomic position and maternal and paternal anxiety/depression. In the Pelotas cohort, 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 intake in the ALSPAC cohort. In the Pelotas cohort, maternal smoking was associated with maternal and paternal lower education but unassociated with other indicators of socioeconomic position and maternal psychiatric problems. Paternal smoking in the Pelotas cohort 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 for socioeconomic factors and maternal-paternal smoking that were 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 mutually adjusting for parental psychopathology, socioeconomic factors, and maternal-paternal smoking (Table 6), the associations

TABLE 3 Associations of Child Psychological Problems With Confounders

Confounder	Ordinal Odds for Higher Child Psychological Problem Score											
	Inattention/Hyperactivity (ALSPAC) or Attention Problems (Pelotas)			Emotional (ALSPAC) or Internalizing (Pelotas) Problems			Conduct (ALSPAC) or Externalizing (Pelotas) Problems			Peer (ALSPAC) or Social (Pelotas) Problems		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
ALSPAC ($N = 4394$)												
Maternal education (nondegree vs degree)	1.97	1.71–2.27	<.001	0.86	0.75–1.00	.04	1.23	1.07–1.42	.003	1.50	1.30–1.73	<.001
Paternal education (nondegree vs degree)	1.83	1.61–2.06	<.001	0.95	0.84–1.08	.4	1.08	0.95–1.22	.2	1.35	1.19–1.53	<.001
Income (lowest quarter vs rest)	1.61	1.40–1.87	<.001	1.17	1.01–1.36	.03	1.55	1.34–1.80	<.001	1.66	1.43–1.92	<.001
Occupation (manual vs nonmanual)	1.51	1.29–1.77	<.001	0.95	0.81–1.12	.6	1.40	1.19–1.64	<.001	1.37	1.17–1.61	<.001
Maternal anxiety/depression (highest quarter vs rest)[a]	1.60	1.41–1.81	<.001	1.73	1.52–1.97	<.001	1.76	1.55–2.01	<.001	1.75	1.54–2.00	<.001
Paternal anxiety/depression (highest quarter vs rest)[a]	1.13	1.00–1.28	.05	o1.14	1.01–1.30	.04	1.32	1.17–1.50	<.001	1.11	0.98–1.26	.1
Maternal prenatal alcohol intake (≥1 vs <1 glass per wk)	1.08	0.93–1.25	.3	0.99	0.85–1.15	.9	1.25	1.08–1.45	.003	1.23	1.06–1.42	.007
Paternal prenatal alcohol intake (≥1 vs <1 glass per d)	0.86	0.75–0.98	.03	0.99	0.86–1.14	.9	1.12	0.98–1.29	.1	0.92	0.80–1.06	.2
Pelotas 1993 ($N = 523$)												
Maternal education (≤10 vs >10 y)[b]	1.06	0.70–1.61	.8	1.13	0.74–1.72	.6	0.80	0.55–1.17	.3	0.98	0.63–1.54	.9
Paternal education (≤10 vs >10 y)[b]	1.97	1.22–3.17	.003	1.30	0.83–2.02	.3	1.05	0.67–1.65	.8	1.07	0.66–1.72	.8
Income (lowest quarter vs rest)	0.95	0.66–1.37	.8	1.36	0.93–1.99	.1	0.83	0.56–1.22	.3	1.03	0.68–1.58	.9
Occupation (proletariat vs bourgeois)	0.88	0.58–1.32	.5	1.05	0.69–1.58	.8	0.71	0.48–1.07	.1	1.00	0.67–1.48	.99
Maternal psychiatric problems (yes vs no)	3.31	2.21–4.95	<.001	5.03	3.34–7.59	<.001	3.06	2.07–4.50	<.001	2.26	1.51–3.38	<.001

[a] Maternal and paternal anxiety/depression scores represent combined scores on prenatal and postnatal depression and prenatal anxiety.
[b] Total number of years of schooling.

TABLE 4 Associations Between Maternal and Paternal Smoking and Confounders

Confounder	Odds of Maternal and Paternal Smoking in Pregnancy					
	Maternal Smoking			Paternal Smoking		
	OR	95% CI	*P*	OR	95% CI	*P*
ALSPAC ($N = 4604$)						
Maternal education (nondegree vs degree)	3.61	2.66–4.88	<.001	2.94	2.37–3.65	<.001
Paternal education (nondegree vs degree)	3.23	2.52–4.13	<.001	2.81	2.34–3.38	<.001
Income (lowest quarter vs rest)	2.69	2.23–3.24	<.001	3.02	2.55–3.57	<.001
Occupation (manual vs nonmanual)	2.68	2.20–3.28	<.001	2.53	2.11–3.03	<.001
Maternal anxiety/depression (highest quarter vs rest)[a]	1.70	1.43–2.03	<.001	1.46	1.25–1.70	<.001
Paternal anxiety/depression (highest quarter vs rest)[a]	1.31	1.10–1.57	.003	1.44	1.24–1.68	<.001
Maternal prenatal alcohol intake (≥1 vs <1 glass per wk)	1.81	1.49–2.21	<.001	1.33	1.11–1.58	.002
Paternal prenatal alcohol intake (≥1 vs <1 glass per d)	1.01	0.83–1.24	.9	1.58	1.34–1.95	<.001
Pelotas 1993 ($N = 523$)						
Maternal education (≤10 vs >10 y)[b]	2.11	1.17–3.82	.01	1.94	1.18–3.17	.009
Paternal education (≤10 vs >10 y)[b]	3.84	1.90–7.77	<.001	2.09	1.25–3.49	.005
Income (lowest quarter vs rest)	1.40	0.89–2.21	.1	2.08	1.34–3.24	.001
Occupation (proletariat vs bourgeois)	1.26	0.77–2.08	.4	1.47	0.93–2.30	.1
Maternal psychiatric problems (yes vs no)	1.36	0.87–2.14	.2	1.64	1.06–2.53	.03

[a] Maternal and paternal anxiety/depression scores represent combined scores on prenatal and postnatal depression and prenatal anxiety.
[b] Total number of years of schooling.

with conduct/externalizing problems persisted in both cohorts, and weaker or null associations were observed with hyperactivity, emotional/internalizing, and peer/social problems. Associations (fully adjusted, mutual model) did not differ systematically between the ALSPAC and Pelotas cohorts (*P* values for heterogeneity: attention/hyperactivity, $P = .2$; emotional/internalizing, $P = .6$; conduct/externalizing, $P = .1$; peer/social, $P = .5$).

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 the ALSPAC cohort (*P*[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 when fully adjusted (*P*[difference] = 0.9 and 0.3 [attention problems], 0.9 and 0.3 [emotional/internalizing problems], and 0.1 and 0.3 [peer problems], ALSPAC and Pelotas, respectively).

Sensitivity analyses were explored by modeling effects of nonpaternity on the fully adjusted associations of ma-

TABLE 5 Associations of Maternal and Paternal Smoking in Pregnancy With Offspring Psychological Problems

Parental Smoke	Offspring Psychological Problems, Score											
	Individual Maternal-Paternal Models						Mutually Adjusted Maternal-Paternal Models					
	Model 1[a]			Model 2[b]			Model 1[a]			Model 2[b]		
	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	<.001	1.17	1.05–1.31	.004	1.37	1.22–1.53	<.001	1.17	1.04–1.31	.009
Paternal smoking	1.28	1.17–1.40	<.001	1.06	0.96–1.16	.3	1.17	1.07–1.29	.001	1.02	0.92–1.12	.7
Pelotas												
Maternal smoking	1.56	1.08–2.25	.02	1.38	0.94–2.03	.1	1.48	0.99–2.19	.05	1.35	0.90–2.01	.1
Paternal smoking	1.31	0.94–1.82	.1	1.17	0.82–1.68	.4	1.18	0.82–1.69	.4	1.10	0.76–1.60	.6
Emotional/internalizing problems												
ALSPAC												
Maternal smoking	1.05	0.94–1.17	.4	1.00	0.89–1.12	.96	1.05	0.94–1.18	.4	1.01	0.90–1.14	.8
Paternal smoking	1.01	0.92–1.11	.8	0.97	0.88–1.07	.5	0.99	0.90–1.10	.9	0.97	0.87–1.07	.5
Pelotas												
Maternal smoking	0.98	0.68–1.41	.9	0.95	0.65–1.39	.9	0.99	0.67–1.46	.9	0.97	0.65–1.45	.9
Paternal smoking	0.98	0.69–1.38	.9	0.92	0.65–1.32	.7	0.98	0.68–1.42	.9	0.93	0.64–1.36	.7
Conduct/externalizing problems												
ALSPAC												
Maternal smoking	1.65	1.48–1.84	<.001	1.46	1.30–1.63	<.001	1.52	1.36–1.71	<.001	1.40	1.24–1.58	<.001
Paternal smoking	1.36	1.24–1.49	<.001	1.22	1.11–1.34	<.001	1.20	1.09–1.33	<.001	1.12	1.02–1.24	.02
Pelotas												
Maternal smoking	1.67	1.17–2.39	.005	1.72	1.18–2.51	.005	1.68	1.13–2.50	.01	1.72	1.14–2.58	.009
Paternal smoking	1.15	0.82–1.60	.4	1.16	0.82–1.63	.4	0.98	0.68–1.42	.9	0.96	0.66–1.39	.8
Peer/social problems												
ALSPAC												
Maternal smoking	1.46	1.31–1.63	<.001	1.23	1.09–1.37	<.001	1.42	1.27–1.56	<.001	1.24	1.10–1.40	<.001
Paternal smoking	1.19	1.09–1.31	<.001	1.02	0.92–1.12	.7	1.07	0.97–1.18	.2	0.96	0.92–1.03	.4
Pelotas												
Maternal smoking	1.45	1.00–2.11	.05	1.45	0.98–2.14	.06	1.43	0.98–2.11	.09	1.44	0.97–2.15	.07
Paternal smoking	1.15	0.80–1.63	.5	1.10	0.76–1.60	.6	1.05	0.73–1.51	.7	1.02	0.70–1.50	.9

Ordinal logistic regression; ORs of having offspring in higher scores for psychological problems in maternal smokers versus non-smokers. ALSPAC: $N = 6735$; Pelotas: $N = 509$.

[a] Model 1: unadjusted.

[b] Model 2: adjusted for maternal education, paternal education, income, social class.

ternal and paternal smoking on child conduct problems by using simulated data sets (see Supplemental Table 7). The results of these simulations suggest that the ALSPAC data exhibited some sensitivity to nonpaternity, with the paternal smoking association increasing by 10% and maternal association decreasing by 2% for a 10% nonpaternity rate. In contrast, the Pelotas data were relatively insensitive to nonpaternity, which 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; even without any nonpaternity there was little statistical evidence for differences in parental effects (*P*[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 nonpaternity.

When psychological problems were analyzed as dichotomous outcomes for clinical psychological problems (in the ALSPAC cohort only; the Pelotas analyses were underpowered), results similar to those found when using ordered categories of psychological problem scores were observed (see Supplemental Table 8).

DISCUSSION

There was some evidence that maternal smoking in pregnancy is associated with greater conduct/externalizing problems in offspring at the age of 4 years 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 according to socioeconomic position. In both cohorts associations of maternal smoking in pregnancy persisted after adjustment for socioeconomic position, parental psychopathology, and paternal smoking, and there were consistent results for 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 the ALSPAC

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	.9
Paternal smoking	1.03	0.91–1.17	.6
Pelotas			
Maternal smoking	1.44	0.94–2.19	.09
Paternal smoking	1.04	0.71–1.50	.8
Emotional/internalizing problems			
ALSPAC			
Maternal smoking	0.95	0.81–1.11	.5
Paternal smoking	0.93	0.82–1.06	.3
Pelotas			
Maternal smoking	0.99	0.66–1.50	.98
Paternal smoking	0.85	0.58–1.24	.4
Conduct/externalizing			
ALSPAC			
Maternal smoking	1.24	1.07–1.46	.005
Paternal smoking	1.11	0.98–1.26	.1
Pelotas			
Maternal smoking	1.82	1.19–2.78	.005
Paternal smoking	0.96	0.66–1.41	.9
Peer/social problems			
ALSPAC			
Maternal smoking	1.20	1.03–1.40	.02
Paternal smoking	1.01	0.89–1.15	.9
Pelotas			
Maternal smoking	1.46	0.97–2.19	.1
Paternal smoking	0.98	0.67–1.45	.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 were adjusted for each other. All models were adjusted for socioeconomic position (maternal education, paternal education, income, social class) plus maternal psychopathology (prenatal and postnatal depression, prenatal anxiety), paternal psychopathology (prenatal and postnatal depression, prenatal anxiety) maternal prenatal alcohol intake, and paternal prenatal alcohol intake (ALSPAC) or maternal psychiatric problems (Pelotas).

cohort), and paternal smoking was not 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 the effects of exposures to secondhand 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 behavior than paternal problems. Indeed, mothers who smoke during pregnancy have higher rates of interpersonal and behavior problems and notably aggressive and antisocial behaviors.[24] Although maternal antisocial behavior has been found to be an important component of the association between maternal smoking and child conduct problems,[8] it could not be explored in our study because data on maternal aggressive or antisocial behavior were not available.

The potential role of genetic factors has been discussed previously.[8,25–27] There is evidence from studies that used different study designs (such as studying children of twins,[3] discordant siblings,[28] and prenatal cross-fostering[9]) that genetic factors may play an important role in moderating the association between maternal prenatal smoking and child behavioral problems. In addition, maternal smoking associations may also be partly confounded by genetic factors. Indeed, a recent twin study revealed that genetic effects may account for approximately half of the observed association between maternal smoking and child conduct problems.[8] This could occur if, for example, mothers with behavioral problems/antisocial behavior are more likely to smoke and, via genetic transmission, also have greater risk of having children with behavioral problems.[3] One might anticipate that such pathways would result in associations of both mother's and father's smoking with offspring behaviors, 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 behaviors. In our 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 nonpaternity; however, although the ALSPAC results were sensitive to increasing levels of nonpaternity, such 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 behavior and, in particular, in relation to fetal exposure to nicotine.[29] In animals, fetal nicotine exposure results in altered physiology at neuronal sites that control arousal and more excitable offspring.[30] Nicotine-induced inhibition of the monoamine oxidase system during fetal development has also been implicated in the relationship between maternal smoking and offspring aggression and conduct disorders.[29]

Although in the ALSPAC cohort maternal smoking was strongly associated with all indicators of socioeconomic position (a key confounder), in the Pelotas cohort maternal smoking was not consistently associated with these factors. Furthermore, indices of inequality (based on income) for maternal smoking were ~4 times lower in

the Pelotas than in the ALSPAC cohort. Thus, as a result of this weaker socioeconomic patterning of maternal smoking observed in the Pelotas cohort, if maternal smoking associations were driven by confounding by socioeconomic position, one would expect smaller associations in the Pelotas cohort compared with the ALSPAC cohort. However, we observed consistent patterns of association in both cohorts, which 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 this study, including maternal antisocial behavior and, in the Pelotas cohort, data on paternal psychological factors and maternal/paternal prenatal alcohol intake. Second, although we aimed to compare the same psychological measures across cohorts, different instruments were used to assess child behavior (SDQ versus CBCL). However, as discussed in "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 revealed self-reported smoking measures to be accurate.[31] However, results of a recent retrospective cross-sectional study suggest that there may be substantial underestimation of smoking behavior by women who are pregnant.[32] If any such misclassification occurred in our cohorts and was nonsystematic with respect to our outcome measures (which is likely, because we obtained smoking data prospectively at the time of pregnancy or birth, and mothers could not have known what their children's behavior would be like at that time), the statistical expectation would be that associations would be biased toward the null. Thus, the true association between maternal smoking and child conduct/externalizing problems may be stronger.

CONCLUSIONS

On the basis of several different approaches, we found some evidence of a causal relationship between maternal smoking and offspring conduct/externalizing problems, but this association was not found for offspring attention-deficit/hyperactivity disorder or emotional/internalizing problems. If our findings are confirmed in future studies, they imply that interventions to reduce maternal smoking in pregnancy might have beneficial effects on future offspring conduct/externalizing problems. By using multiple approaches (as we have done here) for assessing causality in observational studies, particularly those that explore developmental origins of health and disease, etiologic epidemiology studies in general could be improved.

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