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Original investigation

Maternal Smoking During Pregnancy and the Risk of Psychiatric Morbidity in Singleton Sibling Pairs

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Abstract

Introduction: Maternal smoking during pregnancy has been associated with an increased risk for psychiatric morbidity. We further studied this with Finnish siblings to control for genetic/familial factors.
Methods: From the Finnish Medical Birth Register, sibling pairs were selected as the first two children born 1987–1995 to the same mother (n = 150 168 pairs), along with information on maternal smoking (no smoking/smoking). Information on the children's psychiatric diagnoses related to outpatient care visits (1998–2013) and inpatient care (1987–2013), and the mothers' psychiatric morbidity (1969–2013) was derived from the Finnish Hospital Discharge Register. The first pair analysis compared siblings of mothers who only smoked in the first pregnancy (Quitters, 4.7%) and mothers who smoked in both pregnancies (Smokers, 9.6%); the second analysis included mothers who smoked only in the second pregnancy (Starters, 3.3%) and mothers who did not smoke in either pregnancy (Nonsmokers, 77.5%). Smoking information was missing for 5.0% of pairs. Psychiatric morbidity of the siblings and mother was included in the statistical analyses.
Results: The risk of psychiatric diagnoses was significantly lower for the second child of quitters (adjusted OR 0.77, 95% CI 0.72–0.83) compared to the risk among smokers. A higher risk for psychiatric diagnoses was found for the second child of starters (1.39, 1.30–1.49) compared to the risk among nonsmokers. The effect of smoking was more robust for externalizing diagnoses.
Conclusions: Maternal smoking was independently associated with a higher risk for psychiatric morbidity in children, even when controlling thoroughly for genetic and familial factors.
Implications: Maternal smoking during pregnancy has an independent effect on the risk of psychiatric morbidity in children, even after controlling for non-measurable genetic/familial factors by using a sibling pair design. The effect of maternal smoking was robust for externalizing diagnoses. Maternal smoking during pregnancy had an effect on diagnoses both in outpatient and inpatient care.

Introduction

Maternal smoking during pregnancy increases the risk for various pregnancy-related complications, such as miscarriage,[1] stillbirth,[2] and preterm birth.[3] Infants exposed to maternal smoking have been shown to have approximately 200 grams lower birth weight at birth compared to unexposed infants, and an even greater effect has been found in studies using cotinine verification of smoking exposure.[4–6] In addition, infants exposed to maternal smoking have been shown to have, on average, a 0.5 cm smaller head circumference at birth compared to unexposed infants, reflecting compromised fetal brain development.[7] Our previous study showed smaller frontal lobe and cerebellar volumes in very preterm infants exposed to maternal smoking compared to unexposed infants.[8] Neurobehavioral withdrawal symptoms after birth have also been seen in newborn infants exposed to maternal smoking.[9] Prenatal smoking exposure seems to alter brain function up to adolescence, causing a lack of coordination across a diverse set of brain regions.[10] These alterations in brain structure and function due to smoking exposure raise concerns about the long-term effects of maternal smoking during pregnancy on the mental health of the offspring.

Several studies have shown an association between maternal smoking during pregnancy and psychiatric problems and the strongest association has been seen with externalizing and attention problems.[11–14] A recent study by Niemelä et al.[15] showed that prenatal smoking exposure, verified by cotinine measurements, was associated with an increased risk for schizophrenia. In our previous population-based longitudinal register studies, we found that offspring exposed to maternal smoking had a 1.5 to 1.9-fold increased risk for having any psychiatric diagnoses in specialized hospital care and a 1.3 to 1.6-fold increased risk for psychotropic medication use compared to unexposed offspring.[11,12] A dose-response was observed even after adjusting for confounders including maternal psychiatric morbidity before the birth of the child.[11,12]

Since the publication of our register studies, other studies have shown that the magnitude of the effect of smoking on children's mental health is reduced or diminished when more comprehensive confounding factors were adjusted for.[16–19] Söderström et al.[19] found that maternal smoking during pregnancy had a lower, but still significant, 1.2-fold increased risk of offspring psychotropic drug use when studied in a sibling design analysis.

In this study, our objective was thus to further investigate the effects of maternal smoking during pregnancy on psychiatric morbidity up to the year 2013 in Finnish sibling pairs born from 1987 through 1995, by using a population-based longitudinal register data. Our hypothesis was that maternal smoking during pregnancy has a significant, independent and robust effect on the risk of psychiatric morbidity in late adolescence and young adulthood even when non-measurable genetic/familial factors are controlled for.

Methods

Data Sources

The Medical Birth Register includes all live births and stillbirths of fetuses with a gestational age of 22 weeks or more or with a birth weight of 500 grams or more. The National Institute for Health and Welfare (THL, the current register keeper) collects the data from all delivery hospitals and, in the case of home births, from the assisting health care personnel. The register includes information on the mother's and the child's identification numbers; maternal background, health care, and interventions during pregnancy and delivery; and the newborn's outcome until 7 days of age. The Medical Birth Register is considered to be a complete record of all births and newborns in Finland after data linkage to the Central Population Register and the Cause-of-Death Register. Most of the register content corresponds well or satisfactorily with hospital record data according to two data quality studies.[20,21]

The Hospital Discharge Register includes information on all episodes of inpatient care (including all hospitalizations requiring an overnight stay) in public and private hospitals since 1969 and outpatient visits in public hospitals since 1998. The register contains information on the patient's background, hospitalization period, procedures, and the main diagnosis plus up to two other diagnoses by International Classification of Diseases (ICD) code (Eight Revision [ICD-8] in 1969–1986, Ninth Revision [ICD-9] in 1987–1995, and Tenth Revision [ICD-10] since 1996). A data quality study reported that 99% of hospitalizations relating to mental disorders were registered under the correct ICD chapter and 98% of the main diagnoses had been correctly reported at the three-digit ICD-code level.[22] In addition, a systematic review showed that the completeness and accuracy of the register range from satisfactory to very good.[23]

Data were complemented with information on all deaths and their causes for children from 1987 through 2013 from the Cause-of-Death Register (Statistics Finland). The register contains comprehensive information on all deaths of Finnish citizens and permanent residents who died in Finland and at least basic information on deaths of Finnish citizens that occurred abroad. The register includes data from death certificates written by the physician who took care of the patient or who performed the autopsy. All death certificates have been checked by a physician in the provincial government and by medical experts at Statistics Finland.

Participants and Background Information

The study population consisted of pairs of singleton siblings born from the same mother in Finland during the period from 1987 through 1995. Only children without major congenital anomalies and surviving the first year of life were included in the study. If these criteria were not fulfilled, the next child of the same mother was paired with the first child. The first child of the study was not necessarily the first child of the mother, but was the first child born during the study period. The children were linked to each other only with the mothers' identification numbers because the strict confidentially legislation in Finland prohibits collecting information on fathers. Therefore, some of the siblings might be half siblings who do share only maternal genetic factors. The final study population consisted of 300 336 children (150 168 sibling pairs).

Midwifes collected smoking information from the mothers during antenatal care, categorized between 1987 and 1990 as none/<10/>10 cigarettes per day, and since 1991 as smoking during the first trimester/smoking after the first trimester of pregnancy. For this study, smoking was dichotomized as smoking, if the mother had smoked at any time during pregnancy, or no smoking. Smoking information and other background factors (the child's sex, gestational age, birth weight, and 1-minute Apgar score; maternal age, parity, and marital status) were derived from the Finnish Medical Birth Register.

The sibling pairs were grouped into four groups according to smoking exposure: (1) Quitters: mother smoked in the first pregnancy, but not in the second pregnancy (n = 6986, 4.7%); (2) Smokers: mother smoked in both pregnancies (n = 14 394, 9.6%); (3) Starters: mother smoked in the second pregnancy, but did not

smoke in the first pregnancy (n = 4918, 3.3%), and (4) Nonsmokers: mother did not smoke in either pregnancy (n = 116 391, 77.5%). Sibling pairs with missing information on smoking for either of the pregnancies were excluded (n = 7479, 5.0%). The data on smoking during the pregnancies are presented in Table 1.

Psychiatric Morbidity

Information on psychiatric morbidity was obtained from the Finnish Hospital Discharge Register, and included all inpatient episodes in public and private hospitals from 1987 through 2013 and all outpatient visits to public hospitals from 1998 through 2013. Therefore, our data included all inpatient hospital care episodes from birth to the age of 18 to 26 years and all outpatient visits entered in the register. Because the outpatient visits were only recorded after 1998, the outpatient visits were included from the age of 3–11 years to the age of 18–26 years. For this study we included all episodes and visits with a psychiatric diagnosis (ICD-9 codes 290–319 in 1987–1995, and ICD-10 codes F00–F99 in 1996–2013) whether occurring as a primary or other diagnosis. The diagnoses included all psychiatric diagnostic groups according to ICD-10 classification: psychiatric disorders due to psychoactive substance use (ICD-10 codes: F10–F19), psychosis (ICD-10: F20–F29), mood disorders (ICD-10: F30–F39), behavioral syndromes, neurotic disorders, and stress-related disorders (ICD-10: F40–F59), disorders of adult personality and behavior (ICD-10: F60–F69), mental retardation (ICD-10: F70–F79), disorders of psychological development (ICD-10: F80–F89), and behavioral and emotional disorders occurring in childhood and adolescence (ICD-10: F90–F99). In addition, externalizing disorders were analyzed in a separate group including mental and behavioral disorders due to psychoactive substance use (ICD-10 codes F10–F19, ICD-9 codes 291–292, 303–305), disorders of adult personality and behavior (ICD-10 codes F60–F69, ICD-9 code 301), and hyperkinetic and conduct disorders (ICD-10 codes F90–F92, ICD-9 codes 3072A–D, 313–314).

Information on the mother's psychiatric morbidity leading to inpatient care since 1969, and outpatient care since 1998 was obtained from the Hospital Discharge Register. All treatment episodes were included for all psychiatric diagnoses (ICD-8 and ICD-9 codes 290–319, and ICD-10 codes F00–F99).

All register data were combined by using the mother's and child's unique personal identification numbers. The combined data included complete follow-up information until December 31, 2013, or the death of the child. Our data did not include information on children migrating out of Finland. Permission was sought and granted by the register-keeping organizations (THL and Statistics Finland) to use their confidential health register data in this study, as required by national data-protection legislation. The ethical evaluation was made by the statistical authorities. The data linkages were performed by the statistical authorities and only unidentifiable data were provided for the researchers.

Table 1. Smoking Exposure in First and Second Pregnancy During the Study Period

	First pregnancy		Second pregnancy	
Maternal smoking	*n*	%	*n*	%
No	124 197	82.7	126 728	84.4
Yes	21 891	14.6	19 877	13.3
No information	4080	2.7	3563	2.4
Total	150 168	100.0	150 168	100.0

Statistical Analyses

Sibling pair analyses were used to calculate the difference of the effect of smoking exposure on the risk for (1) any psychiatric diagnoses, (2) separately for externalizing diagnoses, and (3) further inpatient and outpatient care diagnoses of the second sibling in the sibling pair with a discordant smoking exposure status to the first sibling comparing the risk to the sibling pair with same the smoking exposure status. The aim was to evaluate the effect of the change in maternal smoking status on the child outcome. Therefore, two separate unconditional logistic regression sibling pair analyses were made (1) between quitters and smokers: mothers who smoked only during the first pregnancy were compared to those who smoked during both pregnancies, and (2) between starters and nonsmokers: mothers who smoked only during the second pregnancy were compared to those who did not smoke during either pregnancy. Siblings may have different risks for psychiatric morbidity regardless of maternal smoking status. Therefore, our study design controls for this increased risk in the second sibling when calculating the effects of the possible changes in maternal smoking status between the pregnancies.

The first sibling's follow-up was restricted to the age reached by the second sibling. Theoretically, the largest possible age difference was 8 years, if the first sibling was born in 1987 and the second in 1995. In case of this, the first sibling was followed up to the year 2005 when he/she reached the age of 18, which was the follow-up time of the second sibling. Statistical analyses were adjusted with the child's sex and birth year, first sibling's psychiatric morbidity (only for the second sibling), maternal age, parity, marital status, and psychiatric morbidity. We did not adjust for the child's perinatal health, gestational age, birth weight, or 1-minute Apgar score, since maternal smoking affects those negatively. Separate analyses showed that there was no difference in the risk of psychiatric morbidity in children if the mother's marital status changed between the pregnancies (married/cohabiting during the first pregnancy and single during the second pregnancy). The data included information on first two subsequent pregnancies of the same mother during the study period. The first child was not necessarily the first child of the mother, and therefore, separate analyses were made including only the actually first and second child of the mother.

The data analysis was performed using commercially available software (SAS, version 9.3; SAS Institute Inc, Cary, NC). Differences in the results were evaluated by using 95% confidence intervals. Nonoverlapping confidence intervals were considered to be significant.

Results

The smoking exposure and subsequent psychiatric diagnoses of the children by sibling status and background factors are shown in Table 2. The background information of the sibling pairs according to smoking exposure is shown in the Supplementary Tables 1 and 2.

Quitters: Stopping Smoking After the First Pregnancy

The risk of psychiatric morbidity was significantly lower in the second child of the quitters compared to the risk among the smokers (adjusted OR 0.77, 95% CI 0.72–0.83, Table 3). The results were similar when diagnoses were divided according to inpatient and outpatient care (adjusted OR 0.82, 0.74–0.91 and adjusted OR 0.77, 0.71–0.82, respectively). Similarly, the second child of the quitters had a smaller risk for externalizing diagnoses (adjusted OR 0.74, 0.66–0.82), and externalizing diagnoses in outpatient care (adjusted

Table 2. Background Information of the Study Population

	First sibling			Second sibling			
	n	Maternal smoking exposure[a], %	Child's psychiatric diagnosis, %	*n*	Maternal smoking exposure[a], %	Child's psychiatric diagnosis, %	Total, *n*
All children	150 168	15.0	18.7	150 168	13.6	18.7	300 336
Maternal age							
<20	7256	38.1	27.7	1149	41.9	33.8	8405
20–34	135 999	13.9	17.8	130 190	13.8	18.6	266 189
35 or more	6913	11.8	19.3	18 829	10.3	18.7	25 742
Marital status, single							
No	138 948	13.1	14.4	142 499	12.4	18.3	281 447
Yes	11 220	29.4	19.7	7669	29.3	25.0	18 889
Parity							
0	110 669	14.6	18.0	0	0.0	0.0	110 684
1	23 657	15.2	19.0	111 281	12.8	18.3	134 938
2–3	11 457	17.3	20.3	33 582	16.3	20.1	45 039
4 or more	2467	7.0	18.2	5017	12.4	18.9	7484
Unknown	1918	15.9	18.4	288	29.2	23.8	2191
Mother's psychiatric diagnosis							
No	140 247	15.3	17.3	140 247	12.5	17.7	280 494
Yes	9921	30.1	33.5	9921	29.2	33.2	19 842
Sibling's psychiatric diagnosis							
No	122 112	17.3	17.3	127 884	13.87	12.0	249 996
Yes	28 056	27.6	31.2	22 284	20.7	24.8	50 340
Sex							
Male	76 433	15.0	17.6	76 221	13.5	18.6	152 654
Female	73 735	15.0	19.1	73 947	13.6	18.9	147 682
Birth weight							
<1500	376	25.5	34.6	368	25.6	43.5	744
1500–2499	3219	15.5	22.1	2052	27.3	26.9	5271
2500–3999	118 925	15.7	18.4	110 226	14.9	18.9	229 151
4000 or more	26 388	10.4	17.4	36 793	8.5	17.5	63 181
Unknown	1260	5.9	18.9	729	16.7	22.2	1989
Gestational age, wk							
23–27	102	15.6	43.1	130	26.6	51.5	232
28–31	369	20.6	30.6	390	23.4	34.4	759
32–36	5325	17.2	19.8	4147	18.4	21.4	9472
37 or more	142 743	14.9	18.3	144 467	13.4	18.6	287 210
Unknown	1629	20.5	19.4	1034	16.0	22.4	2663
1-min Apgar score							
0–3	1097	16.1	22.6	653	18.0	26.2	1750
4–6	4111	15.1	19.2	2584	15.2	20.6	6695
7–10	143 605	15.0	18.3	146 017	13.5	18.6	289 622
Unknown	1355	20.0	19.0	914	22.5	22.9	2269

[a]excluding unknown smoking.

OR 0.74, 0.66–0.82) compared to the risk among the smokers, but no statistically significant difference was found in externalizing diagnoses in inpatient care (adjusted OR 0.79, 0.57–1.09).

In analyses including only mother's first and second child, the risk of psychiatric morbidity was significantly lower in the second child of the quitters compared to the risk among the smokers (adjusted OR 0.77, 95% CI 0.71–0.83). The analyses did not change the results for other outcomes either.

Starters: Smoking Only in the Second Pregnancy

A higher risk for psychiatric morbidity was found in second child of the starters compared to the risk among the nonsmokers (adjusted OR 1.39, 95% CI 1.30–1.49, Table 4). The results were similar when diagnoses were divided according to inpatient and outpatient care (adjusted OR 1.40, 1.27–1.55 and adjusted OR 1.38, 1.29–1.48, respectively). An even more robust effect of smoking exposure was found in the risk for externalizing diagnoses in the second child in starters (adjusted OR 1.68, 1.51–1.87) compared to the risk among the nonsmokers. Similar results were found for inpatient and outpatient care diagnoses (adjusted OR 1.66, 1.49–1.86 and adjusted OR 1.66, 1.23–2.24, respectively).

Including only mother's first and second child, the results were similar. A higher risk for psychiatric morbidity was found for the second child among the starters compared to the risk among the nonsmokers (adjusted OR 1.39, 95% CI 1.28–1.51).

Discussion

In this study we used a sibling pair design to investigate the effects of antenatal smoking exposure on a child's psychiatric morbidity. This

Table 3. Comparison Between Smokers' and Quitters' Sibling Pair Groups

	First sibling			Second sibling			
	n	%	per 1000	*n*	%	per 1000	total
Any psychiatric diagnosis							
Quitters	1455	20.8	10.5	1546	22.1	11.3	6986
Smokers	3546	24.6	12.6	4107	28.5	15.0	14 394
				The second sibling in smokers	The second sibling in quitters		
Crude OR (95% CI)				1	0.81	0.75–0.86	
Adjusted OR (95% CI)				1	0.77	0.72–0.83	
Any psychiatric diagnosis in inpatient care							
Quitters	494	7.1	3.4	568	8.1	4.0	6986
Smokers	1358	9.4	4.6	1553	10.8	5.3	14 394
				The second sibling in smokers	The second sibling in quitters		
Crude OR (95% CI)				1	0.73	0.66–0.81	
Adjusted OR (95% CI)				1	0.82	0.74–0.91	
Any psychiatric diagnosis in outpatient care							
Quitters	1143	16.4	8.1	1450	20.8	10.5	6986
Smokers	2758	19.2	9.6	3889	27.0	14.0	14 394
				The second sibling in smokers	The second sibling in quitters		
Crude OR (95% CI)				1	0.83	0.77–0.89	
Adjusted OR (95% CI)				1	0.77	0.71–0.82	
Externalizing psychiatric diagnosis							
Quitters	483	6.9	3.3	526	7.5	3.6	6986
Smokers	1400	9.7	4.6	1611	11.2	5.3	14 394
				The second sibling in smokers	The second sibling in quitters		
Crude OR (95% CI)				1	0.69	0.62–0.77	
Adjusted OR (95% CI)				1	0.74	0.66–0.82	
Externalizing psychiatric diagnosis in inpatient care							
Quitters	64	0.9	0.4	51	0.7	0.3	6986
Smokers	220	1.5	0.7	156	1.1	0.5	14 394
				The second sibling in smokers	The second sibling in quitters		
Crude OR (95% CI)				1	0.60	0.45–0.79	
Adjusted OR (95% CI)				1	0.79	0.57–1.09	
Externalizing psychiatric diagnosis in outpatient care							
Quitters	419	6.0	2.9	475	6.8	3.2	6986
Smokers	1180	8.2	3.9	1455	10.1	4.8	14 394
				The second sibling in smokers	The second sibling in quitters		
Crude OR (95% CI)				1	0.71	0.64–0.80	
Adjusted OR (95% CI)				1	0.74	0.66–0.82	

CI = confidence interval; OR = odds ratio. Smoking in both pregnancies referred as smokers and smoking only in the first pregnancy as quitters.

design enabled us to study how different smoking habits of the same mother during two pregnancies affect the risks for the children. As the control was siblings born to the same mother, but not necessarily to the same father, genetic and other familial factors were widely controlled for. Our study showed that if the mother stopped smoking between the pregnancies, the second sibling was protected from an increased risk of psychiatric problems. Correspondingly, if the mother had started smoking between the pregnancies, a significantly higher risk was observed for psychiatric problems in the second sibling. The association between smoking exposure and the risk of psychiatric problems seems to be more robust in externalizing problems in our study, as was also found in previous studies.[13,14]

Our previous study showed that children exposed to maternal smoking had a higher risk for psychiatric morbidity in a large group of diagnoses. In addition, a dose–response relationship was strong even after controlling for maternal psychiatric hospital care.[11] However, the previous study design did not allow us to control for non-measurable maternal and family factors, which may be a common underlying cause for both maternal smoking and morbidity. In this current large-scale epidemiological study, we were able to show an independent association between smoking during pregnancy and the risk of psychiatric morbidity within families. Genetic and familial factors are known to have a significant role in the etiology of psychiatric problems. The role of heritability has been suggested to be around 80% for attention deficit and hyperkinetic disorders (ADHD) and 30% for anxiety disorders.[24,25] It is likely that maternal smoking is associated with differences in the emotional growth environment for the child, in the type of mother–child attachment, and in socioeconomic status. Maternal attachment to the fetus has been shown to be weaker in heavily smoking pregnant women compared to the others.[26] This study, with a sibling pair design, largely controls for these kinds of non-measurable and even unknown maternal and family background factors,[27] which do not often change between the pregnancies. In addition, it is likely that there are fewer differences in the parental use of alcohol and drugs, which have been associated with an increased risk for a broad range of externalizing problems in the offspring,[28] and in the smoking status of the partner within the same family compared to other families. Our results were consistent regarding diagnoses in outpatient care and in inpatient care. This suggests that the effects of smoking exposure cover both milder and more severe psychiatric problems.

Table 4. Comparison Between Nonsmokers' and Starters' Sibling Pair Groups

	First sibling			Second sibling			
	n	%	per 1000	*n*	%	per 1000	total
Any psychiatric diagnosis							
Starters	1051	21.4	10.7	1224	24.9	12.5	4918
Nonsmokers	18 139	15.6	7.7	19 807	17.0	8.5	116 391
				The second sibling in nonsmokers	The second sibling in starters		
Crude OR (95% CI)				1	1.47	1.37–1.58	
Adjusted OR (95% CI)				1	1.39	1.30–1.49	
Any psychiatric diagnosis in inpatient care							
Starters	379	7.7	3.7	470	9.6	4.6	4918
Nonsmokers	5683	4.9	2.3	6745	5.8	2.8	116 391
				The second sibling in nonsmokers	The second sibling in starters		
Crude OR (95% CI)				1	1.63	1.46–1.81	
Adjusted OR (95% CI)				1	1.40	1.27–1.55	
Any psychiatric diagnosis in outpatient care							
Starters	846	17.2	8.5	1 157	23.5	11.9	4918
Nonsmokers	14 117	12.1	5.9	18 697	16.1	7.9	116 391
				The second sibling in nonsmokers	The second sibling in starters		
Crude OR (95% CI)				1	1.51	1.40–1.62	
Adjusted OR (95% CI)				1	1.38	1.29–1.48	
Externalizing psychiatric diagnosis							
Starters	394	8.0	3.8	448	9.1	4.3	4918
Nonsmokers	4650	4.0	1.9	5127	4.4	2.1	116 391
				The second sibling in nonsmokers	The second sibling in starters		
Crude OR (95% CI)				1	2.09	1.88–2.33	
Adjusted OR (95% CI)				1	1.68	1.51–1.87	
Externalizing psychiatric diagnosis in inpatient care							
Starters	61	1.2	0.6	51	1.0	0.5	4918
Nonsmokers	631	0.5	0.3	570	0.5	0.2	116 391
				The second sibling in nonsmokers	The second sibling in starters		
Crude OR (95% CI)				1	2.30	1.77–3.00	
Adjusted OR (95% CI)				1	1.66	1.23–2.24	
Externalizing psychiatric diagnosis in outpatient care							
Starters	333	6.8	3.2	397	8.1	3.8	4918
Nonsmokers	4019	3.5	1.6	4557	3.9	1.8	116 391
				The second sibling in nonsmokers	The second sibling in starters		
Crude OR (95% CI)				1	2.03	1.81–2.28	
Adjusted OR (95% CI)				1	1.66	1.49–1.86	

CI = confidence interval; OR = odds ratio. "Smoking in neither pregnancy" referred as nonsmokers and "Smoking only in the second pregnancy" as starters.

Obel et al.[29] used Danish register data to study the association between maternal smoking and diagnosis of hyperkinetic disorder and/or ADHD medication in almost one million children aged 4–20 years. After sibling analyses, no association was found. The study also included young children, aged 4–10 years of age, who had substantially fewer diagnoses or medication (1%) compared to the rest of the study population (2.4%), which underestimates the true effect of smoking. In addition, Lavigne et al.[17] found no difference between smoking exposure and externalizing and internalizing problems at the age of 4 years after controlling for a wide range of background factors, including maternal stress and depression and mother–child attachment. However, these studies lacked a long follow-up, which is important because most psychiatric problems emerge in adolescence or later. Especially girls have an increase in diagnoses from 14 years of age onwards, including behavioral syndromes and both neurotic and stress-related disorders with later manifestation.[11]

Our study showed, interestingly, that the second sibling had a higher prevalence for psychiatric morbidity regardless of smoking status. Our study design controls for this increased risk in the second sibling when calculating the effects of the possible changes in maternal smoking status between the pregnancies. The results of previous studies have been controversial about the influence of birth order on the risk of psychiatric morbidity.[30,31] It has been reported that being the first child in the family increases the risk for developing emotional disorders and attention problems and being the middle child protects against the development of attention problems.[30,31] However, birth order had no effect on developing conduct disorders.[30] To our knowledge, the finding of an increased risk of psychiatric problems in a latter sibling is new. The risk of psychiatric problems seemed to increase even more in families where the mother smoked during both pregnancies.

The strengths of this study include the use of a large national study population covering all sibling pairs born from 1987 to 1995. The data were composed from national registers covering information from the whole of Finland. These registers have been shown to be reliable for research purposes.[20–23] An important strength of our study was a long and complete follow-up to 18–26 years of age. A long follow-up is important because the prevalence of psychiatric problems

increases from adolescence. We also had complete data on the mothers' psychiatric diagnoses given in specialized hospital care, for use in adjustments. For this study, we controlled maternal psychiatric morbidity even during the childhood of the study population; in our previous study the maternal follow-up ended at the birth of the child.[11]

The major concern of this study is in the accuracy of the smoking data. Smoking information was based on mothers' self-reporting, gathered by a midwife during antenatal care. Self-reporting of smoking underestimates the true extent of smoking,[32] which in turn underestimates the true effect of smoking. However, it is not possible to use objective measurements for detecting smoking, for example, cotinine verification, in this kind of large epidemiological study. The data on maternal smoking from the Medical Birth Register have been shown to be in excellent agreement with questionnaire information in Finland.[33] In addition, we could not categorize smoking women by the amount of smoking because the categorization changed during the study period. It is possible that some of the pregnant women only smoked in early pregnancy. However, only 1 out of 10 women stopped smoking during pregnancy during the time period when the study population was born.[34]

The siblings were only matched by the mother because of the strict confidentially legislation in Finland that prohibits collecting information on fathers. Therefore, some of the siblings might be half siblings who do not share a similar genetic background. We adjusted the analyses with maternal parity because the first child included in the study was not necessarily the first child of the mother. Therefore, separate analyses with mother's actual first and second child were made with similar results than for the whole data. Our study also lacks information on partners' smoking habits, maternal alcohol and illicit drug use, and socioeconomic status because this information is not available in the Medical Birth Register. Pregnant women who continue to smoke might use more often alcohol and illicit drugs during pregnancy and this might affect the association.[35–36] It is possible that differences in the mothers who continued smoking compared to the mothers who succeeded in quitting smoking explain part of the difference in the risk between the sibling pairs. Similarly, it is possible that there are non-measurable differences between mothers who do not smoke compared to those who start smoking. These differences are not adjusted for in a sibling pair comparison.

We conclude that these results suggest that maternal smoking during pregnancy has an independent effect on the risk of psychiatric morbidity in children even when genetic and other familial factors are controlled for by using a sibling pair design.

Supplementary Material

Supplementary data are available at *Nicotine & Tobacco Research* online.

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Declaration of Interests

None declared.

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