

Are Girls More Susceptible to the Effects of Prenatal Exposure to Tobacco Smoke on Asthma?

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Background: Prenatal exposure to tobacco smoke through mother's smoking increases the risk of developing asthma later in life. A recent study suggested that this effect is present only in girls. We explored potential differences in susceptibility between boys and girls.

Methods: We followed all 58,841 Finnish singleton babies born in 1987 through 5 nationwide registries for 7 years and identified all cases of doctor-diagnosed asthma (ICD-9 code 493). The birth registry provided categorical information on the mother's smoking during pregnancy: no smoking (reference), low exposure (<10 cigarettes per day), and high exposure (>10 cigarettes per day).

Results: In girls the cumulative incidence of asthma was 0.0245 in the reference group, 0.0310 in the low maternal smoking group (risk difference = 0.0065; 95% CI = 0.0053–0.0076), and 0.0360 in the high maternal smoking group (0.0115; 0.0096–0.0133). The corresponding cumulative incidences for boys were 0.0405, 0.0501 (0.0096; 0.0089–0.0103), and 0.0522 (0.0117; 0.0091–0.0142). In logistic regression analysis adjusting for confounding, the combined effect of male sex and high maternal smoking (compared with female sex and no smoking) was 112% excess risk. This corresponded closely to what would be expected from the additive independent effects of male sex (67% excess risk) and high maternal smoking (44% excess risk).

Conclusions: Effects of maternal smoking during pregnancy on the risk of developing asthma are similar in boys and girls, with no interaction on an additive scale.

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Early-life exposure to environmental tobacco smoke is an important determinant of the development of asthma later in life.¹ Recently, prenatal exposure to tobacco smoke (through mother's smoking during pregnancy) has also been linked to the risk of asthma in childhood and early-life wheezing.^{2–13} Some studies even suggest that prenatal exposure is more harmful than postnatal exposure.^{10,14} A recent

cohort study of 3915 Australian children reported that heavy maternal smoking was related to an increased risk of asthma in adolescence, although this effect was found only in girls.¹⁴ Other studies of the effects of prenatal exposure on asthma or wheezing have not provided information on sex differences.^{2–13}

We explored potential differences in the susceptibility of boys and girls to the effects of maternal smoking on asthma, using data from a cohort of Finnish children born in 1987.

METHODS

Data Sources and Study Population

The source population comprised all children born in Finland in 1987 (n = 60,254). We focused on all 58,841 singleton births and followed them through 5 national administrative health registries for 7 years.^{15,16}

Information on the child's birth weight, gestational age, and maternal smoking habits during pregnancy were obtained from the Finnish Medical Birth Registry established in 1987 and run by the National Research and Development Center for Welfare and Health.

Exposure Assessment

Information on smoking during pregnancy is routinely collected by the medical staff at the delivery hospital and registered in a standardized form. The individual forms are transferred to the Finnish Birth Registry in Helsinki, where the data are entered into electronic files. Information on maternal smoking is categorical: none, less than 10 cigarettes per day, and more than 10 cigarettes per day. (These are the categories as given on the questionnaire; exactly 10 cigarettes was not included.)

The validity of smoking information was assessed as part of the Finnish Prenatal Environment and Health Project by comparing the registry-based information on maternal smoking during pregnancy with 2 other sources of information: medical records that record maternal smoking routinely, and questionnaire information collected after the delivery.¹⁷ The agreement was excellent in both comparisons (daily smoking during pregnancy yes/no) with a κ coefficient of 0.84 [95% confidence interval (CI) = 0.81–0.87] against questionnaire information and 0.89 (0.86–0.91) against medical records. There was no information available on paternal smoking during pregnancy or postnatal exposure to tobacco smoke.

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Health Outcomes

The outcome of interest was asthma defined as at least 1 hospitalization due to asthma (ICD-9 code 493), at least 1 entitlement to free medication due to asthma, or at least 1 entitlement to special care support (which can be granted for families with a disabled child, or with a child who has a long-term illness needing continuous help or surveillance) due to asthma before the age of 7 years.

Covariates

The basic adjustment was made using the following core covariates: sex, birth order, maternal age, marital status, and index of socioeconomic status.

Statistical Methods

We compared the risks (cumulative incidence in 7 years) of asthma according to fetal exposure to tobacco smoke due to maternal smoking separately among boys and girls. Risk difference was used as the measure of absolute effect; risk ratio (RR) and odds ratio (OR) were measures of relative effect. We used logistic regression analysis to estimate adjusted odds ratios for the relations of interest. The adjustment was made using the covariates listed above.

Next, we calculated independent and joint effects of sex and fetal exposure tobacco smoke products on an additive scale.^{18,19} We compared the risk of asthma in 6 exposure categories: 1) female sex and no smoking exposure (R_{00} , reference category); 2) male sex and no smoking exposure (R_{10}); 3) female sex and low smoking exposure (R_{01}); 4) female sex and high smoking exposure (R_{02}); 5) male sex and low smoking exposure (R_{11}); and 6) male sex and high smoking exposure (R_{12}). On an additive scale, the interaction or joint effect of maternal smoking and sex was quantified by calculating the risk that is more than expected based on the independent effects of these factors. The interaction (IA) for heavy smoking and sex was:

$$IA = (R_{12} - R_{00}) - (R_{10} - R_{00}) - (R_{02} - R_{00}).$$

We also assessed how sex alone predicts the risk of developing asthma. To assess the joint effect of sex and exposure to tobacco smoke products, we calculated odds ratios contrasting each of the 5 exposure categories to the reference category. Estimates for the independent effects of sex and maternal smoking during pregnancy and their joint effect were derived from the same logistic regression model adjusting for covariates.

RESULTS

Study Population

The follow-up rate was 99.9%. The prevalence of smoking during pregnancy was 15.5%, which was similar among the mothers of boys and girls. Smoking during pregnancy was related to young age, not being married, and low education.

Effect of Fetal Tobacco Smoke Product Exposure in Boys and Girls

Table 1 presents the risk of developing asthma and the relations between maternal smoking during pregnancy separately in boys and girls. In boys the risk of asthma was 0.0405 among unexposed, 0.0501 when the mother smoked less than 10 cigarettes per day during pregnancy, and 0.0522 with over 10 cigarettes per day. The corresponding effect estimates expressed in risk differences were 0.0096 (95% CI = 0.0089–0.0103) and 0.0117 (0.0091–0.0142) and in odds ratios 1.25 (1.05–1.49) and 1.30 (1.04–1.64). The adjusted odds ratios were similar to the crude odds ratios. The cumulative incidence of asthma was lower in girls than in boys, with a risk of 0.0245 among unexposed girls, 0.0310 with prenatal exposure less than 10 cigarettes per day, and 0.0360 with more than 10 cigarettes per day. The effect estimates in risk differences were 0.0065 (0.0053–0.0076) and 0.0115 (0.0096–0.0133), slightly smaller than those among boys, but expressed in crude odds ratios slightly greater, 1.26

TABLE 1. Maternal Smoking During Pregnancy and Asthma (ICD-9 Code 493) at the Age of 7, The Finnish 1987 Birth Cohort

Sex	No. Cigarettes/d	No. Cases	No. Children	Risk	Crude RR (95% CI)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Total	0†	1565	47,845	0.0327	1.00	1.00	1.00
	<10	234	5729	0.0408	1.25 (1.09–1.43)	1.26 (1.09–1.45)	1.23 (1.07–1.42)
	>10	136	3055	0.0445	1.36 (1.15–1.62)	1.38 (1.15–1.65)	1.35 (1.13–1.62)
Girls	0†	574	23,403	0.0245	1.00	1.00	1.00
	<10	86	2776	0.0310	1.26 (1.01–1.58)	1.26 (1.01–1.60)	1.22 (0.97–1.54)
	>10	52	1445	0.0360	1.47 (1.11–1.94)	1.49 (1.11–1.98)	1.43 (1.07–1.92)
Boys	0†	991	24,442	0.0405	1.00	1.00	1.00
	<10	148	2983	0.0501	1.24 (1.04–1.46)	1.25 (1.05–1.49)	1.24 (1.03–1.48)
	>10	84	1610	0.0522	1.29 (1.04–1.60)	1.30 (1.04–1.64)	1.30 (1.03–1.64)

*Logistic regression analysis: adjusted for birth order, maternal age, marital status, and index of socioeconomic status.

†Reference category.

Excluding 2209 children (with 2 cases) without information on maternal smoking (boys: 0/1141, girls 2/1068) + 4 cases of children with undetermined sex (for which one had no information on maternal smoking).

(1.00–1.60) and 1.49 (1.11–1.98). Again the adjusted odds ratios did not differ from the corresponding crude odds ratios.

The independent effect of male sex on asthma risk was 0.0160 expressed in risk difference and 1.67 (1.51–1.85) expressed in adjusted odds ratio, which is approximately a 67% excess risk (Table 2). The independent effect of tobacco smoke exposure among girls was 0.0065 and 0.0115 expressed in risk differences and 1.22 (0.97–1.54) and 1.44 (1.08–1.92) expressed in adjusted odds ratios and representing an excess risk of approximately 22% and 44%. The difference between the joint effect of male sex and heavy maternal smoking and the sum of their separate effects was 0.0002 (0.027–0.0160–0.0115), ie, with no evidence of interaction.

DISCUSSION

In our large cohort study comprising approximately 409,500 person-years of follow-up, we addressed the question of whether girls through age 7 years are more susceptible to the effects of maternal smoking during pregnancy on the development of asthma. As has been shown before, boys had a higher risk of asthma than girls, and maternal smoking during pregnancy increased the risk. The magnitude of absolute effect with mothers' smoking was similar among boys and girls. The combined effect of male sex and maternal smoking corresponded to what was expected from the additive independent effects of male sex and maternal smoking, with no evidence for interaction.

Validity of Results

The source population included all children registered at birth in Finland in 1987. The coverage of the Finnish Birth Registry is close to 100%.¹⁵ For the purposes of the study we focused on all singleton births. The registry-based follow-up of asthma was expected to identify almost all the diagnosed cases.⁸

The outcome was doctor-diagnosed asthma, based on the registries. This information is likely to be both complete and of high quality for the following reasons. The registry-based follow-up of asthma was expected to identify almost all the diagnosed cases of asthma through the use of registries recording subsidized drug and other treatment. The National Social Insurance Institute covers all residents of Finland and provides 75% reimbursement of asthma medications for those whose asthma fulfilled strict and explicit diagnostic criteria. This reimbursement was granted for a lifetime until the early mid-1990s, when the system changed to require new cases to use medications for half a year before granted a right to reimbursement, and then for only a limited time period. The reimbursement right for asthma is indicated by a number in the Social Insurance Card. Registry information on special support and hospital discharge registration served as complementary information on cases not receiving drug treatment. Thus, the financial incentive to undergo clinical examination and asthma diagnostics is substantial, and the National Social Insurance Institute controls the quality of the diagnostic procedures.

The lack of information on smoking during pregnancy was a potential source of selection bias. The magnitude of bias even in the worst scenario would be small, because this information was missing for less than 4% of mothers. The possibility of information bias was minimized because information on smoking during pregnancy and other relevant information were collected before the onset of the outcome.

We were able to control for several potential confounders. However, the birth registry data did not include information on exposure to environmental tobacco smoke (ETS) during pregnancy, and the registry-based follow-up data included no information on family smoking habits after birth. Maternal smoking during pregnancy and postnatal exposure to ETS from maternal smoking are strongly correlated.

TABLE 2. Independent and Joint Effects of Sex and Maternal Smoking on the Risk of Asthma (ICD-9 Code 493), The Finnish 1987 Birth Cohort

Sex	No. Cigarettes/d	Exposure Category	No. Cases	No. Children	Risk	Risk Difference*	Interaction	Crude RR (95% CI)	Crude OR† (95% CI)	Adjusted OR† (95% CI)
Girl	0	(R ₀₀)	23,403	574	0.0245			1.00	1.00	1.00
	<10	(R ₀₁)	2776	86	0.0310	+0.0065‡		1.26 (1.01–1.58)	1.27 (1.01–1.60)	1.22 (0.97–1.54)
	>10	(R ₀₂)	1445	52	0.0360	+0.0115§		1.47 (1.11–1.94)	1.48 (1.11–1.98)	1.44 (1.08–1.92)
Boy	0	(R ₁₀)	24,442	991	0.0405	+0.0160		1.65 (1.49–1.83)	1.68 (1.51–1.87)	1.67 (1.51–1.85)
	<10	(R ₁₁)	2953	148	0.0501	+0.0256¶	+0.0026**	2.04 (1.71–2.44)	2.10 (1.74–2.52)	2.02 (1.68–2.42)
	>10	(R ₁₂)	1610	84	0.0522	+0.0277††	+0.0002‡‡	2.13 (1.70–2.66)	2.19 (1.73–2.77)	2.12 (1.68–2.68)

*Risk in exposure category minus risk in reference category (R₀₀).

†Logistic regression analysis: adjusted for birth order, maternal age, marital status, and index of socioeconomic status.

‡R₀₁ – R₀₀.

§R₀₂ – R₀₀.

||R₁₀ – R₀₀.

¶R₁₁ – R₀₀.

** (R₁₁ – R₀₀) – (R₁₀ – R₀₀) – (R₀₁ – R₀₀).

††R₁₂ – R₀₀.

‡‡ (R₁₂ – R₀₀) – (R₁₀ – R₀₀) – (R₀₂ – R₀₀).

Excluding 2209 children (with 2 cases) without information on maternal smoking (boys: 0/1141, girls 2/1068) + 4 cases of children with undetermined sex (for which one had no information of maternal smoking).

Therefore, the effect estimates calculated for smoking during pregnancy include some of the potential effect of ETS during childhood. However, the distribution of these potential confounders is expected to be similar among boys and girls, and thus assessment of sex differences should be unconfounded.

Previous Literature

Several epidemiologic studies have assessed the relation between maternal smoking during pregnancy and the risk of asthma and wheezing in the child,^{2–14} but only one¹⁴ has explored whether the effect of prenatal tobacco product exposure differs in boys and girls. Alati and colleagues¹⁴ reported consistent sex differences in the relation between maternal heavy smoking and early-life exposure to tobacco smoke and the risk of asthma at the age of 14. Among the girls, the adjusted odds ratio of asthma was 1.98 (95% CI = 1.25–3.33) for maternal smoking at least 20 cigarettes per day, compared with 1.02 (0.62–1.70) in boys. The effect estimates for exposure at the age of 6 months were 1.53 (1.10–2.13) for girls and 1.10 (0.81–1.50) for boys. The authors suggested that smoking exposure in utero may exert more serious damage to airway function in females, which could be explained by sex differences in lung size. There is evidence that maternal smoking during pregnancy influences lung function,² but to our knowledge clear sex differences in lung function have not been shown. In addition, interplay between airway function and sex hormones at pubertal age was suggested to affect the risk of asthma.

Our results suggest that in the presence of maternal smoking during pregnancy, boys and girls have similarly increased risks of developing asthma during the first 7 years of life.

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