

Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications

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Background: Events occurring during fetal life may affect the development of the immune and respiratory systems and increase the risk of asthma and allergic diseases.

Objectives: We sought to elaborate the relations between the occurrence of pregnancy complications and other pregnancy-related conditions and the risk of bronchial obstruction during the first 2 years of life and the occurrence of asthma and allergic rhinitis by the age of 4 years. Pregnancy complications were considered both as predictors of the health outcomes and as possible effects caused by other prenatal factors.

Methods: A population-based, 4-year, cohort study was carried out involving 2531 children born in Oslo, Norway. We collected information on maternally related (hyperemesis, hypertension, and preeclampsia) and uterus-related complications in pregnancy (antepartum hemorrhage, preterm contractions, insufficient placenta, and restricted growth of the uterus) and the child's health and environmental exposures at birth and at 6, 12, 18, and 24 months and 4 years of age. The outcomes of interest were bronchial obstruction during the first 2 years and asthma and allergic rhinitis at the age of 4 years.

Results: In a logistic regression analysis adjusting for potential confounders, uterus-related, but not other pregnancy-related, complications increased the risk of bronchial obstruction (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.3-3.4), asthma (OR, 3.0; 95% CI, 1.8-5.4), and allergic rhinitis (OR, 2.9; 95% CI, 1.6-5.2). These relations were similar in children of atopic and nonatopic parents.

Conclusions: Uterus-related complications in pregnancy increase the risk of having asthma and allergic rhinitis in childhood. (*J Allergy Clin Immunol* 2000;106:867-73.)

Key words: Pregnancy complications, prenatal conditions, asthma, allergic rhinitis, childhood

The risks of asthma and upper respiratory allergies have been reported to be related to early life events and exposures in several studies,¹⁻¹⁴ but the inference from

Abbreviations used

CI: Confidence interval

OR: Odds ratio

these studies is often difficult for several reasons. There are difficulties in both the measurement of the outcomes and the exposures. In cross-sectional studies retrospective collection of information on early life events and exposures may introduce recall bias. The relatively easy ways to collect data are probably an important reason for why cross-sectional studies of the determinants of asthma and allergy in schoolchildren have become so popular.^{15,16} Because the occurrence of childhood respiratory and allergic diseases varies with age,^{5,13,17-19} studies of preschool children are also needed.

The role of genetic factors^{1,3,4} and prenatal conditions in the development of asthma and upper respiratory allergies is insufficiently understood. However, there is increasing evidence that maternal factors, such as age, smoking, allergies, and pregnancy complications, may play a role in the development of these diseases and that their phenotypic expression frequently begins early in life, even before birth.³ There is some evidence that indicators of fetal growth, as well as maternal factors, predict development of respiratory and allergic diseases.¹⁻⁹ Biologic hypotheses to explain such associations have been proposed.^{3,4,6,8,9} Events occurring during fetal life may affect the developmental pathways followed by the immune system and the lung and airways.³ We analyzed data from the Oslo Birth Cohort^{20,21} to elaborate the relations between the occurrence of pregnancy complications and other pregnancy-related conditions and the risk of bronchial obstruction during the first 2 years of life and asthma and allergic rhinitis by the age of 4 years. We considered pregnancy complications both as predictors of the health outcomes and as possible effects caused by other prenatal factors.

METHODS

Study population

The source population was the Oslo Birth Cohort, which is a cohort of 3754 children born in Oslo, Norway, in 1992-1993.^{20,21} The eligibility criteria and data collection procedure for the children's first 2 years of life are described in detail elsewhere.²⁰ Briefly, the population included children born in the 2 main birth clinics in Oslo dur-

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Supported by grants from the Norwegian Research Council.

Received for publication Apr 19, 2000; revised July 31, 2000; accepted for publication July 31, 2000.

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0091-6749/2000 \$12.00 + 0 1/1/110558

doi:10.1067/mai.2000.110558

ing a 15-month period from 1992-1993. The eligibility criteria were as follows: permanent address within the city of Oslo, no plans of moving from Oslo within the near future, birth weight greater than 2000 g, no serious illness that might impair respiration, no assisted ventilation or oxygen therapy after 6 hours of life, at least one family member able to speak and write Norwegian, at least one biologic parent living together with the child, and no known drug abuse in the family. Information on the child's health and environmental exposures was collected by means of a self-administered questionnaire at birth and when the child was 6, 12, 18, and 24 months old. The follow-up rate was 81% ($n = 3048$) at the age of 2 years.

We conducted a follow-up study by using a self-administered questionnaire mailed at the end of 1996 to all 4-year old children living in Oslo and children of the cohort living outside Oslo.^{22,23} The home addresses of the participating children were updated by information from the Central Population Registry. Only the 3048 children with complete information on respiratory health in the first 2 years of their lives were included. A correct mailing address was obtained for 2985 of these children, and a completed questionnaire was received from families of 2594 children (87% of the 2-year cohort and 67% of the baseline study population). Information on current asthma and allergic rhinitis was available for 2531 children, and those children comprised the study population. The children had a mean age of 4.3 years (SD 0.3) at the last follow-up contact. The study was approved by the Norwegian Data Inspectorate.

Health outcomes

The primary outcomes were bronchial obstruction during the first 2 years of life and current asthma and allergic rhinitis at the age of 4 years. Bronchial obstruction during the first 2 years of life was defined as 2 or more episodes with symptoms and signs of obstruction or one episode lasting more than 1 month during the first 2 years of life.²⁰ Several procedures were used to identify and confirm these episodes. At least one of the episodes had to be diagnosed by a physician, and the guidelines were that at least 3 of 5 symptoms or signs (wheezing, chest recession, rhonchi during auscultation, forced expiration, and rapid breathing) should be observed. Current asthma and allergic rhinitis (nose- or eye-related allergy, including hay fever) were defined on the basis of answers to the 4-year follow-up questionnaire. Both outcomes had to be diagnosed by a physician, and current disease meant that the child had to have experienced symptoms of the disease during the previous 12 months.

Pregnancy complications

We obtained information on the experience and type of pregnancy complications in a questionnaire administered at the maternity wards soon after birth. We hypothesized a priori that complications related to the pathophysiology of the uterus influence the fetus differently from maternally related complications, which represent systemic diseases. Accordingly, we categorized the complications into those that were maternally related ($n = 141$), including hyperemesis ($n = 45$), hypertension ($n = 55$), and preeclampsia ($n = 56$), and those that were uterus related ($n = 121$), including antepartum hemorrhage ($n = 62$), preterm contractions ($n = 56$), insufficient placenta ($n = 12$), and restricted growth of the uterus ($n = 20$). Information on the type of delivery was collected from hospital records and dichotomized according to experience of cesarean delivery (yes/no).

Covariates

We obtained information on covariates and potential confounders from the questionnaire and hospital records. Parental atopy (parental asthma or hay fever) and sex were used as indicators of genetic propensity (ie, the presence of genetic markers that predict the disease of interest); maternal age at delivery, birth order, maternal education (number of years), family income per year (Norwegian kro-

ner), maternal smoking at the end of pregnancy (yes/no), and an episode of lower respiratory tract infections during the first year of life²¹ were used as indicators of social and environmental exposures; and birth weight was used as an indicator of fetal growth.

Statistical methods

First, we assessed the relation between the covariates and the occurrence of pregnancy events. Second, we studied the relation of uterus-related complications to the covariates and health outcomes. Third, we elaborated to what extent pregnancy complications are in the causal pathway of the effects of the other prenatal factors on the risk of asthma and allergies and if the effect of pregnancy complications was mediated through early life infections. We used odds ratios (ORs) as a measure of association and effect. Logistic regression analysis was applied, and these relations were elaborated in models including different covariates, as well as in stratified analyses in children with and without parental atopy. Because of missing values for some of the variables, we included in the model a category for missing values for variables with that problem. Results of logistic regression analyses with and without the missing strata gave point estimates, which did not differ more than 0.1 from each other. Only the results of the first approach are presented.

RESULTS

Children in the cohort who were followed up to the age of 4 years had older and more educated mothers and came from families with higher incomes than that of the total cohort, and a normal pregnancy was equally common (Table I). During the first 2 years of life, 8.9% of the children experienced bronchial obstruction, and by the age of 4 years, 9.6% had received a physician's diagnosis of asthma and 5.5% had received a diagnosis of allergic rhinitis. Current asthma was reported for 6.5% of the children, and current allergic rhinitis was reported for 4.6% of the children.

The ORs for having both asthma and allergic rhinitis ($n = 44$ [1.7%]), given the child had either asthma or allergic rhinitis, were similar (both 11.7). The ORs for having asthma or allergic rhinitis if the child had experienced bronchial obstruction during the first 2 years of life were 12.9 (95% confidence interval [CI], 9.1-18.2) and 2.2 (95% CI, 1.4-3.7), respectively.

Determinants of pregnancy complications

All the pregnancy events were more common among old mothers and mothers who had children with low birth weights (Table II). Parental atopy and the child's sex did not show strong associations with the pregnancy events. First pregnancies had a lower risk of uterus-related complications, and maternal smoking decreased the risk of maternally related complications. Socioeconomic conditions showed various patterns. Incidence of cesarean delivery was related to the mother's low education and high family income. The differences were less marked for the other complications. Uterus-related complications were less common in the families with the lowest incomes.

Predictors of bronchial obstruction, asthma, and allergic rhinitis

Children with uterus-related complications had a higher risk of bronchial obstruction (crude OR, 2.1; 95% CI,

TABLE I. Characteristics of the Oslo Birth Cohort at birth and at 2 and 4 years' follow-up

	At birth, % (n = 3754)	2 years' follow-up, % (n = 2985)	4 years' follow-up, % (n = 2531)
Sex (M)	51.8	51.3	51.3
Parental atopy	33.7	33.9	34.6
Normal pregnancy	82.1	82.1	82.2
Cesarean delivery	11.9	11.5	11.3
Birth weight			
<2500 g	12.6	12.3	12.0
2500-3499 g	32.4	31.6	31.5
≥3500 g	55.1	56.1	56.4
Birth order			
First	51.4	52.6	52.6
Second	36.3	35.7	35.7
Third or later	12.2	11.7	11.7
Maternal age at delivery			
<25 y	12.2	10.5	9.5
25-29 y	36.2	35.7	35.5
≥30 y	51.6	53.8	55.0
Maternal smoking at the end of pregnancy	24.4	22.5	21.4
Maternal education			
<12 y	7.3	5.6	4.7
12-15 y	39.5	38.0	36.4
≥15 y	53.2	56.4	58.9
Family income per year			
<200,000 NOK	17.0	14.1	13.2
200,000-500,000 NOK	64.7	66.8	66.8
≥500,000 NOK	18.3	19.1	20.0

Maximal number of subjects with missing data in the baseline questionnaire was 78 (family income per year), in the 2-year questionnaire was 48 (family income), and in the 4-year questionnaire was 35 (family income).

NOK, Norwegian kroner (7 NOK were about one US dollar in 1992).

1.3-3.4), asthma (crude OR, 3.0; 95% CI, 1.8-5.0), and allergic rhinitis (crude OR, 2.9; 95% CI, 1.6-5.2) compared with the children without such complications (Table III). For children with both asthma and allergic rhinitis at the age of 4 years contrasted against those with none of the diseases, the corresponding figure was a crude OR of 5.7 (95% CI, 2.7-12.2). No statistically significant associations were found between the other pregnancy complications and the studied health outcomes.

Parental atopy increased the child's risk of experiencing both bronchial obstruction during the 2 first years of life and the risk of asthma and allergic rhinitis at the age of 4 years (ORs, 1.6-2.7). Both maternal and paternal atopy increased the risk of the studied outcomes.

Compared with the first-born child, the second- and later-born children had an increased risk of bronchial obstruction during the first 2 years of life (ORs, 2.3 and 2.0) but showed a decreased risk of asthma (ORs, 1.1 and 0.5) and allergic rhinitis (ORs, 0.8 and 0.7) at the age of 4 years. The risk of asthma and allergic rhinitis, but not that of bronchial obstruction, decreased by increasing maternal age at delivery. For allergic rhinitis, there was even a linear decrease (OR, 0.92; 95% CI, 0.87-0.96) per year. This was also the case for children with both asthma and allergic rhinitis contrasted with those with none of the diseases (OR, 0.89; 95% CI, 0.83-0.95). Only the

risk of bronchial obstruction was increased statistically significantly by maternal smoking in late pregnancy. Even if not statistically significant, high maternal education and family income decreased the risk of having asthma and allergic rhinitis at the age of 4 years. For bronchial obstruction before the age of 2 years, the associations were in the opposite directions.

The effects of uterus-related complications on the main health outcomes were further explored in different logistic regression models controlling for various combinations of potential confounders (Table IV) and stratified by the history of parental atopy (Table V). The adjusted effect estimates remained similar in different models, with one exception. The relation of uterus complications to bronchial obstruction was weakened when we controlled for early life lower respiratory tract infection.

The estimated associations between the health outcomes and the other covariates did not change substantially when all the covariates were included in the logistic regression model (data not shown). Parental atopy and the child's sex remained statistically significant determinants of all 3 health outcomes. Maternal age remained a statistically significant determinant of allergic rhinitis (OR, 0.92; 95% CI, 0.87-0.97), whereas the associations between maternal education and family income and asthma and allergic rhinitis remained nonsignificant (data not shown).

TABLE II. The percentage of pregnancy complications by indicators of genetic propensity, pregnancy exposures, and fetal growth

	n	Pregnancy events		
		Maternally related complications, % (n = 141)	Uterus-related complications, % (n = 124)	Cesarean delivery, % (n = 348)
Parental hay fever and/or asthma				
Mother –/father –	1656	5.5 (4.4-6.6)	4.4 (3.4-5.4)	11.5 (10.0-13.1)
Mother +/father –	349	6.9 (4.2-9.6)	5.2 (2.9-7.6)	11.1 (7.7-14.4)
Mother –/father +	408	5.1 (3.0-7.3)	5.9 (3.6-8.2)	10.5 (7.5-13.5)
Mother +/father +	118	4.2 (0.1-7.9)	7.6 (2.8-12.5)	11.4 (5.5-17.3)
Sex				
F	1233	5.6 (4.3-6.9)	5.1 (3.9-6.4)	10.5 (8.7-12.2)
M	1298	5.6 (4.3-6.8)	4.7 (3.6-5.9)	12.1 (10.3-13.9)
Birth weight				
<2500 g	303	9.3 (6.0-12.6)	14.6 (10.6-18.6)	21.8 (17.1-26.6)
2500-3499 g	794	6.5 (4.7-8.2)	4.3 (2.9-5.7)	10.1 (8.0-12.3)
≥3500 g	1421	4.3 (3.2-5.4)	3.2 (2.3-4.2)	9.7 (8.2-11.3)
Birth order				
First	1332	6.5 (5.2-7.8)	4.2 (3.1-5.3)	11.4 (9.6-13.1)
Second	904	4.3 (3.0-5.6)	5.9 (4.3-7.4)	11.4 (9.3-13.5)
Third or later	295	5.4 (2.8-8.1)	5.1 (2.6-7.6)	10.5 (6.9-14.1)
Maternal age at delivery				
<25 y	241	3.3 (1.0-5.6)	3.3 (1.0-5.6)	6.9 (3.6-10.2)
25-29 y	898	7.4 (5.7-9.1)	4.7 (3.3-6.1)	8.5 (6.7-10.4)
30-34 y	950	4.7 (3.3-6.0)	4.8 (3.4-6.1)	12.9 (10.7-15.1)
≥35 y	442	5.2 (3.1-7.3)	6.6 (4.3-8.9)	15.9 (12.3-19.2)
Maternal smoking				
No	1987	6.5 (5.4-7.5)	4.8 (3.9-5.7)	10.9 (9.5-12.3)
Yes	541	2.4 (1.1-3.7)	5.4 (3.5-7.3)	12.8 (9.9-15.6)
Maternal education				
<12 y	119	2.5 (0.0-5.4)	4.2 (0.5-7.9)	15.5 (8.8-22.2)
12-15 y	914	5.6 (4.1-7.1)	4.7 (3.3-6.1)	11.8 (9.7-13.9)
≥15 y	1479	5.8 (4.6-7.0)	5.1 (4.0-6.3)	10.5 (8.9-12.1)
Family income per year				
<200,000 NOK	330	4.3 (2.1-6.4)	1.8 (0.4-3.3)	6.6 (3.8-9.3)
200,000-500,000 NOK	1668	6.3 (5.1-7.5)	5.3 (4.3-6.4)	11.7 (10.2-13.3)
≥500,000 NOK	498	4.4 (2.6-6.2)	5.6 (3.6-7.7)	12.1 (9.2-15.0)

Maternally related complications include hyperemesis, hypertension, and preeclampsia. Uterus-related complications include antepartum hemorrhage, preterm contractions, insufficient placenta, and restricted growth of the uterus. There was missing information on maternally and uterus-related complications for 8 subjects and missing information on cesarean delivery for 59 subjects. There was missing information on the covariates of birth weight for 13 subjects, maternal smoking for 3 subjects, maternal education for 19 subjects, and family income for 35 subjects.

NOK, Norwegian kroner (7 NOK were about one US dollar in 1992).

DISCUSSION

In our prospective cohort study we found that the risk of bronchial obstruction during the first 2 years of life and that of asthma and allergic rhinitis at the age of 4 years were associated with uterus-related complication in pregnancy but not with maternally related pregnancy complications or cesarean delivery. Increasing maternal age at delivery was negatively associated with the risk of asthma and allergic rhinitis at the age of 4 years.

The current study had a strong and suitable design for the objectives of this article. It included information on most of the relevant conditions or exposures. This enabled control for a large number of confounders. Information on the basis of hospital records or parental reports may lead to some misclassification. However, our data were collected prospectively and before the children had any signs of asthma or allergic rhinitis, and it has been

shown that pregnancy-related events are reported quite correctly.²⁴ Low statistical power made it difficult to study separately the effects of each type of pregnancy event. Therefore we defined 2 types of pregnancy complications, complications related to symptoms and signs from the uterus and complications affecting the mothers health in general.

Reduced smoking caused by preeclampsia, hyperemesis symptoms, or both could explain the rather surprising negative association between maternal smoking and maternally related pregnancy complications. Pregnancy events were also associated with some of the other covariates, but only uterus-related complications in pregnancy were associated with the studied health outcomes.

Birth weight and other conditions indicating fetal growth have been shown to be related to the risk of atopic diseases.^{1,2,6,7} Our study did not indicate such associations. Our inclusion criteria (birth weight, >2000 g) may

TABLE III. Risks, ORs, and 95% CIs of having bronchial obstruction at 0 to 2 years of life and atopic diseases at 4 years by birth-related conditions*

	n	Bronchial obstruction at 0-2 y (n = 221)			Asthma at 4 y (n = 164)			Allergic rhinitis at 4 y (n = 116)		
		Risk	OR	95% CI	Risk	OR	95% CI	Risk	OR	95% CI
Pregnancy events										
Maternally related complications										
No	2382	0.090			0.063			0.046		
Yes	141	0.071	0.8	0.4-1.5	0.092	1.5	0.8-2.7	0.050	1.1	0.5-2.4
Uterus-related complications										
No	2399	0.085			0.060			0.043		
Yes	124	0.161	2.1	1.3-3.4	0.161	3.0	1.8-5.0	0.113	2.9	1.6-5.2
Cesarean delivery										
No	2193	0.087			0.064			0.045		
Yes	279	0.100	1.2	0.8-1.8	0.072	1.1	0.7-1.8	0.054	1.2	0.7-2.1
Indicators of genetic propensity										
Parental hay fever and/or asthma										
Mother -/father -	1656	0.072			0.048			0.033		
Mother +/father -	349	0.126	1.8	1.3-2.7	0.106	2.3	1.5-3.5	0.074	2.3	1.4-3.8
Mother -/father +	408	0.113	1.6	1.1-2.3	0.081	1.7	1.1-2.6	0.064	2.0	1.2-3.2
Mother +/father +	118	0.127	1.9	1.1-2.3	0.119	2.7	1.5-4.8	0.076	2.4	1.2-5.0
Sex										
F	1233	0.072			0.044			0.028		
M	1298	0.104	1.5	1.1-1.9	0.085	2.0	1.4-2.8	0.062	2.3	1.5-3.4
Pregnancy-related conditions										
Birth weight										
<2500 g	303	0.086			0.083			0.033		
2500-3499 g	794	0.084	1.0	0.6-1.6	0.062	0.7	0.4-1.2	0.049	1.5	0.7-3.1
≥3500 g	1421	0.092	1.1	0.7-1.7	0.063	0.7	0.5-1.2	0.047	1.5	0.7-2.9
Birth order										
First	1332	0.059			0.067			0.051		
Second	904	0.126	2.3	1.7-3.1	0.071	1.1	0.7-1.5	0.042	0.8	0.5-1.2
Third or later	295	0.112	2.0	1.3-3.1	0.037	0.5	0.3-1.0	0.034	0.7	0.3-1.3
Maternal age										
<25 y	241	0.075			0.095			0.066		
25-29 y	898	0.092	1.3	0.7-2.1	0.069	0.7	0.4-1.2	0.060	0.9	0.5-1.6
30-34 y	950	0.088	1.2	0.7-2.0	0.058	0.6	0.4-1.0	0.040	0.6	0.3-1.1
≥35 y	442	0.090	1.2	0.7-2.2	0.054	0.5	0.3-1.0	0.018	0.3	0.1-0.6
Maternal smoking										
No	1987	0.083			0.063			0.047		
Yes	541	0.113	1.4	1.0-1.9	0.073	1.2	0.8-1.8	0.041	0.9	0.5-1.4
Socioeconomic factors										
Maternal education										
<12 y	119	0.067			0.084			0.076		
12-15 y	914	0.107	1.3	0.7-2.1	0.079	0.7	0.4-1.2	0.055	0.9	0.5-1.6
≥15 y	1479	0.080	1.2	0.7-2.0	0.055	0.6	0.4-1.0	0.039	0.6	0.3-1.1
Family income per year										
<200,000 NOK	330	0.103			0.076			0.048		
200,000-500,000 NOK	1668	0.089	0.8	0.6-1.3	0.067	0.9	0.6-1.4	0.046	0.9	0.5-1.6
≥500,000 NOK	498	0.072	0.7	0.4-1.1	0.046	0.6	0.3-1.1	0.044	0.9	0.5-1.8

Maternally related complications include hyperemesis, hypertension, and preeclampsia. Uterus-related complications include antepartum hemorrhage, preterm contractions, insufficient placenta, and restricted growth of the uterus.

NOK, Norwegian kroner (7 NOK were about one US dollar in 1992).

*The first category is always the reference category.

have contributed to this, but Bråbäck and Hedberg⁶ reported the same associations also for conscripts with normal birth weights. If the development of asthma and allergic rhinitis is related to birth weight in the normal range, this most likely indicates genetic propensity or is a result of some pregnancy exposure or complication. We found that

reports of uterus-related complications in pregnancy, but not maternally related pregnancy complications, increased the risk of all the studied outcomes. Hemorrhage during pregnancy could be of special importance,⁵ but low statistical power made it difficult to explore this further. Our findings are consistent with the hypothesis that pathophys-

TABLE IV. OR of having bronchial obstruction at 0 to 2 years of life and asthma or allergic rhinitis at 4 years by uterus-related complications during pregnancy, with adjustment for possible confounding factors

	Bronchial obstruction at 0-2 y*		Asthma at 4 y†		Allergic rhinitis at 4 y‡	
	OR	95% CI	OR	95% CI	OR	95% CI
No adjustment	2.1	1.3-3.4	3.0	1.8-5.0	2.9	1.6-5.2
Adjusted for genetic propensity	2.0	1.2-3.4	3.0	1.8-5.1	2.8	1.6-5.2
Adjusted for other pregnancy and socioeconomic factors	2.0	1.2-3.5	3.1	1.8-5.2	3.5	1.9-6.6
Adjusted for genetic propensity and other pregnancy and socioeconomic factors	1.9	1.1-3.3	2.9	1.7-5.0	3.3	1.8-6.2
Adjusted for genetic propensity and other pregnancy and socioeconomic factors and an episode of early life lower respiratory tract infection	1.2	0.7-2.2	2.5	1.4-4.2	3.1	1.7-5.9

Uterus-related complications include antepartum hemorrhage, preterm contractions, insufficient placenta, and restricted growth of the uterus. Reference categories: no bronchial obstruction,* no asthma,† or no allergic rhinitis.‡

TABLE V. Risks, ORs, and 95% CIs of having bronchial obstruction at 0 to 2 years of life and asthma or allergic rhinitis at 4 years by uterus-related complications during pregnancy in different categories of parental atopy

	n	Bronchial obstruction at 0-2 y			Asthma at 4 y			Allergic rhinitis at 4 y		
		Risk	OR	95% CI	Risk	OR	95% CI	Risk	OR	95% CI
I										
Parental atopy –/pregnancy complications –	1578	0.07	Ref		0.04	Ref		0.041	Ref	
Parental atopy –/ pregnancy complications +	73	0.111	1.6	0.8-3.5	0.127	3.5	1.7-7.1	0.127	3.4	1.5-7.8
II										
Parental atopy +/ pregnancy complications –	821	0.051	Ref		0.052	Ref		0.054	Ref	
Parental atopy +/ pregnancy complications +	51	0.114	2.4	1.2-4.8	0.119	2.5	1.2-5.1	0.115	2.3	1.0-5.3

Uterus-related complications include antepartum hemorrhage, preterm contractions, insufficient placenta, and restricted growth of the uterus. Ref, Reference category.

iology of the uterus increases the risk of atopy-related diseases.⁹ It might be that uterus complications affect the development of the immune system. However, it might also be that such complications indicate other pregnancy exposures, such as infections, which have been shown to increase the risk of atopic diseases in childhood.^{11,25} Another explanation is that a more pronounced T_H2 response during gestation is associated with less complications and more favorable pregnancy outcome.²⁶

Parental atopy and the child's sex were not strongly associated with pregnancy conditions and did not affect the associations between pregnancy conditions and outcomes. Neither did any of the other prenatal or socioeconomic conditions. This could indicate that the pathophysiology of the uterus affects the risk of these diseases in general or that there are other genotypes for which uterus growth is more important.

Overly hygienic conditions in early life have been hypothesized to increase the risk of atopy.²⁷ Contamination from maternal microflora along the birth canal could thus be an advantage. We could not find any support for this hypothesis because children born by means of cesarean delivery did not differ in risk from other children.

Increasing maternal age at delivery seemed to lower the risk of asthma somewhat and clearly reduced the risk of allergic rhinitis. The latter finding is in opposition to the results of Bråbäck and Hedberg.⁶ However, we

believe that our findings are reasonable. We have controlled for a number of possible confounders. Reduced follow-up among the youngest mothers could have introduced some selection bias, but the association was the same also for the older age groups. Maternal age could in some way be related to biology of fetal development, but it could also reflect social conditions and environmental exposures. The relation of maternal age in pregnancy to the child's risk of asthma and allergic rhinitis could even vary in magnitude between different populations, depending on how maternal age reflects differences in environmental exposures. We have not controlled for siblings' diseases, but it is likely that parents with asthmatic or allergic children are more prone to create a low-exposure environment for their next child, or it could be that having an allergic or asthmatic child even reduces the chance of having more children. Both arguments favor our findings. The population in the study by Bråbäck and Hedberg was born about 2 decades before the children in this study, and the outcomes were measured when the population was about 18 years old. Because asthma and allergic diseases seem to vary in occurrence by both time and age, this could also explain differences in findings. The positive association between bronchial obstruction and increasing birth order could be explained by increased exposure to early life infections in children with older siblings. Adjustment for early life lower respiratory tract infection

mainly weakened the effect that uterus-related pregnancy complications had on bronchial obstruction. This supports the idea that some of this effect is mediated through post-natal infections and that early life bronchial obstruction is more often a manifestation of infections than asthma and allergic rhinitis at the age of 4 years.

Epidemiologic studies have provided evidence of the relations of several early life events and exposures to the risk of asthma and allergic rhinitis or their indicators.¹⁻⁹ These epidemiologic findings need biologic explanations that can lead to more sophisticated hypotheses for further epidemiologic studies. The genetic propensities to asthma and allergic rhinitis are considered to be similar because these diseases overlap each other. In spite of this, the relations of asthma and allergic rhinitis to early life events are not always similar, which makes the interpretation of these relations even more difficult. Our study supported the hypothesis that the pathophysiology of the uterus, sometimes manifesting in complications, increases the risk of childhood asthma and allergic rhinitis. Furthermore, increasing maternal age decreased the risk of asthma and particularly allergic rhinitis. The latter is in contrast to some other studies, but there are several arguments that make this finding reasonable. However, the contrasting findings between studies clearly demonstrated the need for more biologic and epidemiologic evidence.

We thank Dr Lennart Bråbäck for his comments on the manuscript.

REFERENCES

1. Sears M. Epidemiology of childhood asthma. *Lancet* 1997;350:1015-20.
2. Fergusson DM, Crane J, Beasley R, Horwood LJ. Perinatal factors and atopic disease in childhood. *Clin Exp Allergy* 1997;27:1394-401.
3. Martinez FD. Maternal risk factors in asthma. *Ciba Found Symp* 1997;206:233-43.
4. Björkstén B. Risk factors in early childhood for the development of atopic diseases. *Allergy* 1994;49:400-7.
5. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;312:1195-9.
6. Bråbäck L, Hedberg A. Perinatal risk factors for atopic disease in conscripts. *Clin Exp Allergy* 1998;28:936-42.
7. Weitzman M, Gortmaker S, Walker DK, Sobol A. Maternal smoking and childhood asthma. *Pediatrics* 1990;85:505-11.
8. Leadbitter P, Pearce N, Cheng S, Sears MR, Holdaway MD, Flannery EM, et al. Relationship between fetal growth and the development of asthma and atopy in childhood. *Thorax* 1999;54:905-10.
9. Xu B, Järvelin MR, Pekkanen J. Prenatal factors and occurrence of rhinitis and eczema among offspring. *Allergy* 1999;54:829-36.
10. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999;354:541-5.
11. Pekkanen J, Remes S, Kajosaari M, Husman T, Soininen L. Infections in early childhood and risk of atopic disease. *Acta Paediatr* 1999;88:710-4.
12. von Mutius E, Illi S, Hirsch T, Leupold W, Keil U, Weiland SK. Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J* 1999;14:4-11.
13. Ponsonby AL, Couper D, Dwyer T, Carmichael A, Kemp A. Relationship between early life respiratory illness, family size over time, and the development of asthma and hay fever: a seven year follow up study. *Thorax* 1999;54:664-9.
14. von Mutius E. The environmental predictors of allergic disease. *J Allergy Clin Immunol* 2000;105:9-19.
15. ISAAC Steering Committee. ISAAC International Study of Asthma and Allergies in Childhood Manual (ISAAC Document 006). 2nd ed. Auckland, New Zealand: ISAAC Steering Committee; 1993.
16. ISAAC Steering Committee. Phase II modules of the International Study of Asthma and Allergies in Childhood Manual (ISAAC), Munster: International Study of Asthma and Allergies in Childhood; 1998.
17. Martinez FD, Cline M, Burrows B. Increased incidences of asthma in children of smoking mothers. *Pediatrics* 1992;89:21-6.
18. Åberg N, Engström I. Natural history of allergic diseases in children. *Acta Paediatr Scand* 1990;79:206-11.
19. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998;101:587-93.
20. Nafstad P, Kongerud J, Botten G, Hagen JA, Jaakkola JJK. The role of passive smoking in the development of bronchial obstruction the first 2 years of life. *Epidemiology* 1997;8:293-7.
21. Nafstad P, Jaakkola JJK, Hagen JA, Botten G, Kongerud J. Breastfeeding, maternal smoking and lower respiratory tract infections. *Eur Respir J* 1996;9:2623-9.
22. Nafstad P, Hagen JA, Øie L, Magnus P, Jaakkola JJK. Day-care centers and respiratory health. *Pediatrics* 1999;103:753-8.
23. Nafstad P, Magnus P, Jaakkola JJK. Early respiratory infections and childhood asthma [online]. *Pediatrics* 2000;106:e38.
24. Tomeo CA, Rich-Edwards JW, Michels KB, Berkey CS, Hunter DJ, Frazier AL, et al. Reproducibility and validity of maternal recall of pregnancy-related events. *Epidemiology* 1999;10:774-7.
25. Xu B, Pekkanen J, Järvelin MR, Olsen P, Hartikainen AL. Maternal infections in pregnancy and the development of asthma among offspring. *Int J Epidemiol* 1999;28:723-7.
26. Nilsson L, Kjellman NI, Löfman O, Björkstén B. Parity among atopic and non-atopic mothers. *Pediatr Allergy Immunol* 1997;3:134-6.
27. Björkstén B. The intrauterine and postnatal environments. *J Allergy Clin Immunol* 1999;104:1119-27.

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