Environmental Tobacco Smoke, Parental Atopy, and Childhood Asthma

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We hypothesized that the joint effect of genetic propensity to asthma and exposure to environmental tobacco smoke on the risk of childhood asthma is greater than expected on the basis of their independent effects. We performed a population-based 4-year cohort study of 2,531 children born in Oslo, Norway. We collected information on the child's health and environmental exposures at birth and when the child was 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 at the age of 4 years. Parental atopy was defined as a history of maternal or paternal asthma or hay fever. Exposure to environmental tobacco smoke was defined on the basis of questionnaire information on household smokers at birth. In logistic regression analysis adjusting for confounding, parental atopy alone increased the risk of bronchial obstruction [odds ratio 1.62; 95% confidence interval (CI) 1.10–2.40] and asthma (1.66; 95% CI, 1.08–2.54). In children without parental atopy, there was little effect of exposure to environmental tobacco smoke on bronchial obstruction (1.29; 95% CI, 0.88–1.89) and asthma (0.84; 95% CI, 0.53–1.34). The presence of parental atopy and exposure had a substantial effect both on bronchial obstruction (2.88; 95% CI, 1.91–4.32) and asthma (2.68; 95% CI, 1.70–4.22). The results are consistent with the hypothesized joint effect of parental atopy and exposure to environmental tobacco smoke. This phenomenon—denoted as effect modification of environmental exposure by genetic constitution, or gene by environment interaction—suggests that some genetic markers could indicate susceptibility to environmental factors. *Key words*: asthma, atopy, gene by environment interaction, tobacco smoke. *Environ Health Perspect* 109:579–582 (2001). [Online 22 May 2001]
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Several environmental factors, such as exposure to environmental tobacco smoke (*1–5*), dampness and mold problems (*6–11*), house dust mites (*12–14*), emissions from PVC flooring (*15–16*), and electric heating (*17*) have been suggested to increase the risk of asthma or asthmalike symptoms and signs in childhood. A central role of genetic factors in the development of asthma is suggested by evidence that family history of allergic diseases increases the risk of asthma (*18*).

We hypothesized that the joint effect of genetic propensity to asthma and environmental exposure on the risk of childhood asthma is more than expected on the basis of their independent effects. This phenomenon is commonly described as effect modification (*19*) or gene by environment interaction (*20–21*) and it suggests that some genetic markers impose susceptibility to the effects of environmental factors. We addressed the question of gene by environment interaction using the Oslo Birth Cohort, which was established 1992–1993 to study environmental determinants of respiratory health in children with special emphasis on asthma and asthma-related symptoms and signs (*4,11,16,22–24*). We assumed that parents with asthma or allergic rhinitis give their children a large set of genes that increase the child's susceptibility to the effects of environmental factors on asthma. More specifically, we selected environmental tobacco smoke, one of the best established environmental determinants of childhood asthma, and used parental history of allergic diseases as a measure of genetic propensity to asthma to study independent and joint effects of parental atopy and early-life exposure to environmental tobacco smoke.

Methods

Study population. The source population included children born in the two main birth clinics in Oslo during 15 months in 1992–1993. The eligibility criteria and data collection procedures for the children's first two years are described in detail elsewhere (*4*). Information on the child's health and environmental exposures was collected from parents by self-administered questionnaires at the child's birth and when the child was 6 months, 12 months, 18 months, and 24 months of age. The 2-year follow-up rate was 81% (n = 3,048) (*4*). In November 1996, we conducted a 4-year follow-up in connection with a survey directed at all the 4-year-old children living in Oslo and the members of the birth cohort living outside Oslo (*23–24*). All phases of the study were approved by the Norwegian Data Inspectorate (Oslo, Norway). In the present study, we focused only on the 3,048 children with information on respiratory health from the first 2 years of their life. We obtained a correct mailing address for 2,930 of these children and received a completed questionnaire from families of 2,594 (89%) children. Information on current asthma was available for 2,531 children, who constituted the study population (Table 1). These children had a mean age of 4.3 years (SD 0.3).

Health outcomes. The primary outcomes were bronchial obstruction in the first 2 years of life and current asthma. Current asthma was defined on the basis of answer to the 4-year follow-up questionnaire as a history of asthma diagnosed by a physician and experience of symptoms of asthma during the previous 12 months. Bronchial obstruction in the first 2 years of life was defined as two or more episodes with symptoms and signs of obstruction or one episode lasting more than one month (*4*). We also used a combination of bronchial obstruction in the first 2 years of life and current asthma as the secondary outcome.

Genetic and environmental determinants of interest. Parental atopy was defined as a history of maternal or paternal asthma or hay fever. Information on parental asthma and hay fever was collected in the birth questionnaire. We based our assessment of exposure to environmental tobacco smoke on questionnaire information at birth about the smoking habits of the parents and other persons living in the child's home. Use of information on smoking habits at birth prevented bias that could be introduced by a change in parental smoking habits caused by appearance of symptoms and signs of asthma in the child. We evaluated the validity of questionnaire information by using the levels of cotinine and thiocyanate in umbilical cord serum in 202 randomly selected mothers. There was an excellent agreement between high and low levels of biomarkers and daily and nonsmoking mothers (*25*).

Covariates. We obtained information on potential confounders from the hospital records and the questionnaires. The covariates in the present analyses included sex of the child, maternal age at delivery, length of breast-feeding, care in a day care center at 1

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year (> 10 hr per week), maternal education, family income, and single parenthood. Length of breast-feeding was categorized as 0–6 months and > 6 months.

Statistical methods. First, we studied independent and joint effects of parental atopy and exposure to environmental tobacco smoke on an additive scale (*26*,*27*). We compared the risk of experiencing bronchial obstruction in the first 2 years and asthma at 4 years of age in four exposure categories: *a*) no parental atopy and no exposure to environmental tobacco smoke (R_{00}, reference category); *b*) parental atopy and no exposure to environmental tobacco smoke (R_{10}); *c*) no parental atopy and exposure to environmental tobacco smoke (R_{01}); and *d*) parental atopy and exposure to environmental tobacco smoke (R_{11}). On an additive scale, we quantified the interaction (*IA*) or joint effect of two factors by calculating the risk that is more than expected based on the independent effects of these factors (*26*):

$$IA = (R_{11} - R_{00}) - (R_{10} - R_{00}) - (R_{01} - R_{00}).$$

Second, we used the odds ratio as a measure of effect and estimated adjusted odds ratios applying logistic regression analysis. The odds ratios were adjusted for the covariates described above. We also assessed how each allergic disease, including maternal and paternal asthma and hay fever, alone predicts the risk of developing the primary outcomes. To assess the joint effect of parental atopy and exposure to environmental tobacco smoke, we calculated odds ratios contrasting each of the three exposure categories to the reference category. Estimates for the independent effects of parental atopy and environmental tobacco smoke exposure and their joint effect was derived from the same logistic regression model adjusting for the covariates.

Results

Study population. The characteristics and early exposure of the children followed for 4 years and those of the baseline and 2-year cohort were similar (Table 1). A total of 225 children (8.9%) experienced bronchial obstruction during the first 2 years of life, and 164 children (6.5%) had current asthma at the age of 4 years.

Independent effects of parental atopy and exposure to environmental tobacco smoke. Early-life exposure to environmental tobacco smoke increased the risk of bronchial obstruction [adjusted odds ratio 1.43; 95% confidence interval (CI), 1.07–1.90], but had little effect on the risk of asthma in the complete cohort (1.10; 95% CI, 0.79–1.53), as shown in Table 2. Parental atopy was a significant determinant of both bronchial obstruction (1.84; 95% CI, 1.39–2.44) and asthma (2.17; 95% CI, 1.57–3.00). Table 2 also presents maternal and paternal asthma and hay fever as predictors of bronchial obstruction and asthma. Maternal asthma was the strongest predictor of both bronchial obstruction (adjusted odds ratio 2.65; 95% CI, 1.72–4.10) and asthma (adjusted odds ratio 3.11; 95% CI, 1.97–4.90). The association of paternal asthma was clearly weaker both with the risk of bronchial obstruction (adjusted odds ratio 1.52; 95% CI 0.91–2.53) and asthma (adjusted odds ratio 1.57; 95% CI 0.88–2.82).

Joint effect of parental atopy and exposure to environmental tobacco smoke. Tables 3 and 4 show risks of bronchial obstruction and asthma in the four categories. On additive scale, the excess risk of bronchial obstruction caused by parental atopy was 0.033 and that caused by environmental tobacco smoke exposure was 0.024, and the effect caused by interaction of these two determinants was 0.044 (Table 3). In terms of relative risks, parental atopy alone

Table 1. Characteristics of the Oslo Birth Cohort at birth and at 2- and 4-year follow-up surveys.

Characteristic	At birth (*n* = 3,754)	2-Year cohort (*n* = 2,985)	4-Year cohort (*n* = 2,531)
Sex, male	51.8	51.3	51.3
Parental atopy	33.7	33.9	34.6
Breast-feeding after 6 months	–	70.1	71.2
Maternal age at delivery (years)			
< 25	12.2	10.5	9.5
25–29	36.2	35.7	35.5
> 30	51.6	53.8	55.5
Maternal education (years)			
< 12	7.3	5.6	4.7
12–15	39.5	38.0	36.4
> 15	53.2	56.4	58.9
Family income per year (Norwegian kronor)			
< 200,000	17.0	14.1	13.2
200,000–500,000	64.7	66.8	66.8
> 500,000	18.3	19.1	20.0
Single parenthood	11.4	7.7	7.1
Care in a day care center at 1 year[a]	–	15.0	15.0
Early-life exposure to environmental tobacco smoke	46.3	41.3	39.8

Values shown are percentages. Number of subjects with missing data is very low: In the baseline questionnaire, 78 (family income per year) did not respond; in the 2-year questionnaire, 101 (breast-feeding); and in the 4-year questionnaire, 79 (breast-feeding).
[a]>10 hr per week.

Table 2. Independent effects of parental atopy and exposure environmental tobacco smoke on the risks of bronchial obstruction by 2 years of age and asthma at 4 years of age.

		Bronchial obstruction by 2 years of age				Asthma at 4 years of age			
			Crude	Adjusted[a]			Crude	Adjusted[a]	
	No.	Risk	OR	OR	95% CI	Risk	OR	OR	95% CI
Environmental tobacco smoke									
Early-life exposure									
No	1,520	0.075				0.061			
Yes	1,003	0.111	1.53	1.43	1.07–1.90	0.071	1.17	1.10	0.79–1.53
Parental allergic diseases									
Parental atopy (maternal or paternal)									
No	1,656	0.072				0.048			
Yes	875	0.120	1.75	1.84	1.39–2.44	0.096	2.09	2.17	1.57–3.00
Maternal asthma									
No	2,372	0.082				0.057			
Yes	159	0.189	2.60	2.65	1.72–4.10	0.176	3.51	3.11	1.97–4.90
Maternal hay fever									
No	2,149	0.086				0.060			
Yes	382	0.107	1.28	1.39	0.97–2.00	0.089	1.52	1.66	1.11–2.48
Paternal asthma									
No	2,384	0.086				0.063			
Yes	147	0.129	1.67	1.52	0.91–2.53	0.095	1.57	1.57	0.88–2.82
Paternal hay fever									
No	2,086	0.085				0.060			
Yes	445	0.108	1.30	1.35	0.96–1.91	0.085	1.45	1.54	1.05–2.28

[a]Logistic regression controlling for sex, maternal age at delivery, maternal education, family income, single parenthood, and length of breast-feeding.

increased the risk of bronchial obstruction, with an adjusted odds ratio of 1.62 (95% CI, 1.10–2.40). The effect of environmental tobacco smoke in children of nonatopic parents was weaker: 1.29 (95% CI, 0.88–1.89). The adjusted odds ratio of bronchial obstruction was 2.88 (95% CI, 1.91–4.32) in children with atopic heredity and exposure to environmental tobacco smoke, compared with children in the reference category. The 95% CIs of these effect estimates were exclusive, indicating that the stronger effect of environmental tobacco smoke in children of atopic parents could not be explained by chance.

The excess risk of asthma related to parental atopy was 0.030, but the risk was not related to environmental tobacco smoke exposure in children without parental atopy (Table 4). The interaction of parental atopy and environmental tobacco smoke was 0.049. In logistic regression, parental atopy without environmental tobacco smoke exposure increased the risk of asthma with an odds ratio of 1.66 (95% CI, 1.08–2.54), but environmental tobacco smoke exposure without atopy had no effect on the risk of asthma (0.84; 95% CI, 0.53–1.34). The adjusted odds ratio of asthma was 2.68 (95% CI, 1.70–4.22) in children with atopic heredity and exposure to environmental tobacco smoke compared with children in the reference category. Also for asthma, the 95% CIs of these two effect estimates were exclusive.

In all, the adjusted odds ratios for the four categories did not differ substantially from the corresponding crude odds ratios, which indicated that the joint effects in additive scale are accurate (Tables 3 and 4).

Finally, we defined an additional outcome, early-onset asthma, which constituted both experience of early-life bronchial obstructions and presence of asthma at the age of 4 years. Seventy-six children met these outcome criteria. The effect of environmental tobacco smoke on this early-onset asthma was 0.74 (95% CI, 0.35–1.58) in children without parental atopy, and 3.86 (95% CI, 2.04–7.28) in children whose either or both parents were atopic.

Discussion

The findings of our prospective cohort study are consistent with the hypothesis that the joint effect of parental atopy and early-life exposure to environmental tobacco smoke on the risk of childhood asthma is greater than expected on the basis of their independent effects. The results also indicated independent effects of parental atopy on the risks of both bronchial obstruction and asthma. We found a small independent effect of exposure to environmental tobacco smoke on bronchial obstruction, but no effect on asthma at age 4—the effect of environmental tobacco smoke on asthma was seen mainly among children of atopic parents.

Validity of results. A prospective cohort study offers a suitable approach to assess the effect of hereditary and early-life environmental factors on development of asthma later in life. We were able to follow 67% of the 3,754 newborns for 4 years. Losses to follow-up were not likely to compromise the validity of the results because distributions of parental atopy and exposure to environmental tobacco smoke at baseline were similar to those of 2- and 4-year cohorts.

Information on environmental tobacco smoke exposure and parental asthma was based on parental reports. The exposure information was collected before the onset of the outcome of interest, so any bias due to awareness of the disease of interest was avoided. We evaluated the questionnaire information on maternal smoking by biomarker concentrations in cord serum and found that smoking habits were reported accurately (*25*).

A committee of specialists evaluated data from clinical examinations by specialists and available health records and made the diagnosis of bronchial obstruction in the first 2 years of life. To detect all the cases, we reminded the parents with each follow-up questionnaire to contact the project pediatrician in case of respiratory problems, asked outpatient clinics to refer all possible cases to the project pediatrician, and contacted families reporting respiratory symptoms in the questionnaires. A physician-conducted telephone interview with 100 parents of nonsymptomatic children revealed that no episodes of bronchial obstruction had been overlooked. The definition of current asthma was based on a diagnosis of a physician and an experience of asthmalike symptoms and signs during the previous 12 months. Free access of families to health services in Norway and our frequent contacts with the families during the first 2 years were likely to minimize underdiagnosis of asthma. Any misclassification of the outcomes was likely to be nondifferential.

We were able to take into account most known potential confounders such as sex, length of breast-feeding, maternal age at delivery, care in a day care center at 1 year, and indicators of socioeconomic status including maternal education, family income, and single parenthood. Adjustment did not change the measure of effect substantially.

Definition of interaction. We used the absolute effects on an additive scale in the definition of interaction. This is justified by the idea that the public health impact of

Table 3. Independent and joint effects of hereditary atopy and exposure to environmental tobacco smoke on the risks of bronchial obstruction by 2 years of age.

		Bronchial obstruction by 2 years of age					
Exposure	No.	Risk	Risk difference[a]	Interaction[e]	Crude OR	Adjusted OR[f]	95% CI
No parental atopy No ETS exposure (R_{00}) (reference)	959	0.063	–	–	1.00	1.00	
Parental atopy No ETS exposure (R_{10})	561	0.096	0.033[b]	–	1.60	1.62	1.10–2.40
No parental atopy ETS exposure (R_{01})	692	0.087	0.024[c]	–	1.42	1.29	0.88–1.89
Parental atopy ETS exposure (R_{11})	311	0.164	0.101[d]	0.044	2.94	2.88	1.91–4.32

[a]Risk in exposure category minus risk in reference category. [b]$R_{10}–R_{00}$. [c]$R_{01}–R_{00}$. [d]$R_{11}–R_{00}$. [e]$(R_{11}–R_{00})–(R_{10}–R_{00})–(R_{01}–R_{00})$. [f]Logistic regression controlling for sex, maternal age at delivery, maternal education, family income, single parenthood, and length of breast-feeding.

Table 4. Independent and joint effects of hereditary atopy and exposure to environmental tobacco smoke on the risks of asthma at 4 years of age.

		Asthma at 4 years of age					
	No.	Risk	Risk difference[a]	Interaction[e]	Crude OR	Adjusted OR[f]	95% CI
No parental atopy No ETS exposure (R_{00}) (reference)	959	0.050	–	–	1.00	1.00	
Parental atopy No ETS exposure (R_{10})	561	0.080	0.030[b]	–	1.66	1.66	1.08–2.54
No parental atopy ETS exposure (R_{01})	692	0.046	–0.004[c]	–	0.92	0.84	0.53–1.34
Parental atopy ETS exposure (R_{11})	311	0.125	0.075[d]	0.049	2.72	2.68	1.70–4.22

[a]Risk in exposure category minus risk in reference category. [b]$R_{10}–R_{00}$. [c]$R_{01}–R_{00}$. [d]$R_{11}–R_{00}$. [e]$(R_{11}–R_{00})–(R_{10}–R_{00})–(R_{01}–R_{00})$. [f]Logistic regression controlling for sex, maternal age at delivery, maternal education, family income, single parenthood, and length of breast-feeding.

independent effects and their possible interaction follows additive rather than, for example, multiplicative scale (*26*,*27*). This can be illustrated by a rough calculation of excess number of children experiencing bronchial obstruction caused by parental atopy, exposure to environmental tobacco smoke, and interaction of these factors from the risk differences (Table 3). Parental atopy resulted in 33 excess cases per 1,000 children and exposure to environmental tobacco smoke 24 excess cases per 1,000 children. The independence of effects would implicate 57 additional cases in the presence of both determinants. Table 3 indicates that children with both parental asthma and exposure had 101 excess cases per 1,000 with asthma; on additive scale the interaction represented 44 additional cases.

Synthesis with previous knowledge. Several recent studies have provided evidence of the role of environmental tobacco smoke as a determinant of childhood asthma (*1–4*). A recent meta-analysis reported a pooled estimate of 1.37 for the risk of asthma if either parent smoked (*5*). Our study provides additional confirmation that exposure to environmental tobacco smoke increases the risk of childhood asthma, although the effect is stronger in genetically susceptible individuals.

Our findings strengthen the evidence that hereditary allergic diseases are important determinants of childhood asthma, and are consistent with a study by Mutius and colleagues (*18*). Maternal asthma was the strongest determinant of both bronchial obstruction and asthma at the age of 4 years. These findings suggest strongly that genetic background is an important determinant of asthma. Because the pathophysiological and clinical manifestations of asthma are complex, studies of genetic markers have focused on specific features (phenotypes) of asthma, such as atopic immunoglobulin E (IgE) responsiveness, other inflammatory responses, and bronchial hyperresponsiveness, rather than on genetic markers of clinical asthma. Presence of high levels of IgE and bronchial hyperresponsiveness predict asthma in subjects without diagnosed asthma and occur more commonly in asthmatic than in nonasthmatic subjects. For each of these manifestations of asthma (phenotypes), there may be a gene or set of genes that confer susceptibility or predisposition (*28–31*). However, the inheritance patterns of the disease indicate that it is not a simple Mendelian trait; rather, asthma is a complex disease involving several genetic and environmental factors (*29*). We used parental asthma and hay fever to represent the complex genetic background of asthma that is inherited by the child from the parents. The strong relations between paternal and particularly maternal asthma and the development of childhood asthma provide empirical support for the use of hereditary asthma to represent the genetic determinants of asthma.

Concluding remarks. The results show that the joint effect of hereditary atopy representing genetic constitution and environmental tobacco smoke is stronger than expected on the basis of their independent effects. This phenomenon—effect modification of environmental exposure by genetic constitution, or gene by environment interaction—suggests that some genetic markers could indicate susceptibility to environmental factors. Identification of these markers is an interesting challenge for future studies.

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