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Maternal smoking during pregnancy and lactation increases the risk for atopic eczema in the offspring

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Background: Maternal smoking during pregnancy has been shown to lead to immunologic changes in the offspring. However, little is known about the influence of this exposure on atopic manifestations.
Objective: Our purpose was to investigate the influence of air pollutants on manifestations of atopy in preschool children.
Methods: Unselected cohorts of a total of 678 5- to 6-year-old preschool children (350 boys, 328 girls) were investigated in areas with different degrees of air pollution in Bavaria. Data on the history of atopic diseases and other relevant factors were obtained by questionnaire. A skin-prick test was performed with common aeroallergens. Manifestation of atopy was defined as personal history of atopic disease or positive prick test to either grass pollen, house dust mite, or cat and analyzed multivariately.
Results: Of all children, 38.9% exhibited at least one manifestation of atopy. Atopic eczema was reported in 7.9% to 15.5%, hayfever in 4.1% to 25.6%, and asthma in 3.0% to 8.1%. Of the mothers, 12.6% smoked during pregnancy or lactation or both. Analysis of the manifestation of atopy including sex, location, nitrogen oxide and sulfur dioxide exposure and maternal smoking as covariates revealed an influence of the maternal smoking during pregnancy/lactation. Of children whose mothers had smoked during pregnancy/lactation, 52.2% exhibited manifestations of atopy in contrast to 35.7% of children of nonsmoking mothers ($p < 0.044$). A history of atopic eczema was the only component of the variable "manifestation of atopy" that was significantly associated with maternal smoking during pregnancy and lactation. A causal interpretation of this finding, however, was not supported by a follow-up study.
Conclusion: Maternal smoking during pregnancy or lactation or both might play a role in the development of atopic eczema and should be avoided.
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Atopic diseases are determined by genetic predisposition in combination with environmental influences. An increase in the incidence of all three atopic diseases (atopic eczema, hayfever, and asthma) has been demonstrated in several studies from different Western countries.[1,2] Environmental contaminants, specifically air pollutants, are suspected to play a role in the sensitization process.[3-6] Pollutants such as sulfur dioxide (SO_2),[7] nitrogen oxide (NOx),[8] tobacco smoke,[9] and others[10-15] increase IgE synthesis and thereby may contribute to the immunologic sensitization. Additionally these adjuvant effects may be increased by chronic inflammation, damage of the mucosal barrier, and changes of the allergenicity of certain allergens.[3,5] The total serum IgE level of active tobacco smokers is higher than that of nonsmokers.[16-18] Exposure to maternal tobacco smoke also leads to immunologic changes in the child.[19] Children of households in which the mother smokes have significantly more upper respiratory tract infections and impaired lung function.[20-24] Maternal smoking during pregnancy is associated with premature birth, low height and low weight at birth, and impaired behavioral capabilities.[25] Nicotine crosses the placenta[26] and is excreted into breast milk.[27] The nicotine metabolite cotinine is elevated in the amniotic fluid of pregnant women exposed to tobacco smoke.[28] Children of mothers who had

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smoked during pregnancy showed elevated levels of IgE, IgA, and IgG_3[29, 30] in their cord blood and other altered immune functions.[31] Elevated levels of cord blood IgE have been linked to a higher risk of atopy.[32] However, little is known regarding the influence of maternal smoking during pregnancy on atopic manifestations in the child.

SUBJECTS AND METHODS

Time and locations

The study was conducted in different regions of Bavaria between the spring of 1988 and the summer of 1990. Study sites were chosen to present different air-pollution patterns. Two regions (I and II) located in Upper Palatinate (Schwandorf) and Upper Franconia (Selb, Arzberg, and Wunsiedel) had high outdoor exposure, especially to SO_2 and NOx. Region III (Schwabach) in Central Franconia was close to a toxic waste incinerator. A control region (IV) with a lower degree of air pollution included two areas (Bad Reichenhall and Berchtesgaden) in Upper Bavaria.

Subjects

A total of 950 5 to 6-year-old preschool children were recruited from preschool examination groups. The parents were contacted by letters that described the study and requested participation. After a written formal consent was obtained from the parents, 678 children (71.4%) participated in this study (350 boys and 328 girls). There were 132 children in region I, 189 in II, 102 in III, and 255 in IV.

Questionnaire

A questionnaire was distributed and reviewed with the parents at the time of examination. Personal and family history of atopic and allergic diseases was determined, as were certain sociodemographic factors. Cases of atopic diseases were ascertained by asking whether a physician had ever diagnosed atopic eczema, hay fever, or asthma in the child. Parental history was considered positive if at least one parent gave at least one positive answer. The original questionnaire has been published.[33, 34]

Skin-prick test

A prick test with four common aeroallergens (birch and grass pollen, house dust mite, and cat) and two food allergens (hen's egg and cow's milk) was performed with a multipuncture device (Stallerkit, Allmed-Pharma, Alpen, Germany) on the volar aspect of the forearm. Codeine phosphate and saline served as positive and negative controls, respectively. Reactions were determined after 15 minutes and assessed to be positive for wheal diameters of 2 mm or more.

Exposure to SO_2 and NOx

The outdoor and indoor exposure to SO_2 and NOx was measured with a passive sampler. A special plastic tube/device containing a filter was placed in the children's bedrooms and near the kindergartens for 7 days. The method for the analyses of the air pollutants was described earlier.[35]

Follow-up study

The study was repeated with the same instruments during the years 1991 through 1994 in regions III and IV (only 1991 and 1992) and in another region also close to a waste incinerator (Kempten).

Statistical analyses

Bivariate calculations were performed by means of the chi-square test and the results were expressed by the p value or the crude odds ratios (ORs) with the corresponding 95% confidence intervals. Indoor exposures to NOx and SO_2 were categorized in quartiles (NOx: $<4.2 < 6.0 < 8.2 <$; SO_2: $<4.1 < 5.2 < 6.1 < \mu g/m^3$). Multivariate analysis was carried out with the technique of classification and regression trees (CART) for the detection of risk factors of the child's manifestations of atopy. Manifestation of atopy was defined as an individual history of atopic eczema, hayfever, or asthma or a positive skin-prick test to grass pollen, house dust mite, or cat. Sex, location, exposure to SO_2 and NOx, and maternal smoking during pregnancy and lactation were included as risk factors. The CART analysis shows graphically and hierarchically the influence of these covariates on the selected variable. More detailed information on the statistical methods has been published.[36, 37]

RESULTS

Descriptive data

Exposure to SO_2 and NOx. The mean values for measures of the indoor and outdoor exposure to SO_2 and NOx in 1989 and 1990 are listed for the different study sites in Table I. The most polluted areas with respect to outdoor SO_2 were regions I and II. The outdoor exposures are not fully reflected by the measured indoor levels.

Atopic diseases and sensitization. The region-specific frequencies of atopic disease and the sensitization to grass pollen, house dust mite, and cat are summarized in Table II. The sensitization to grass pollen and cat and the frequency of atopic eczema and hayfever tended to be higher in polluted areas. Within the total cohort, 38.9% of the children had a manifestation of atopy.

Table I. Mean levels of indoor and outdoor measures of NOx and SO_2 in different Bavarian study sites (1989, 1990)

Mean ($\mu g/m^3$)	Region			
	I	II	III	IV
Indoor SO_2	5.0	5.2	7.2	4.4
Indoor NOx	6.2	7.4	5.3	5.6
Outdoor SO_2	21.9	37.1	5.2	8.2
Outdoor NOx	4.9	17.4	6.7	7.9

Table II. Cumulative incidence of atopic diseases and prevalence of skin-prick test reactions to common aeroallergens in different Bavarian study sites (1988 to 1990)

Parameter (%)	Region			
	I	II	III	IV
Atopic disease				
Atopic eczema	14.6	14.8	15.5	7.9
Hayfever	4.1	10.9	25.6	6.3
Asthma	8.1	5.1	3.0	4.8
Prick test				
Grass pollen	16.7	11.9	15.7	9.8
House dust mite	11.5	12.4	5.9	12.8
Cat	9.2	9.7	8.4	6.0

Smoking habits. Of the mothers, 84 (12.6%) of 666 reported that they had smoked during pregnancy (62; 73.2%) or lactation (22; 26.8%). All but 10 of these mothers still smoked at the time of the study, and no woman had started smoking after pregnancy. Current smoking was highly associated with former smoking and with actual indoor NOx levels ($p < 0.0001$). Indoor NOx exposure in the households of women who reported to have smoked during pregnancy was significantly higher than that in households of women who had not (8.0 vs 5.5 $\mu g/m^3$; $p < 0.0001$). The quantity of cigarettes consumed during pregnancy was probably not recalled precisely; therefore no quantitative analysis was done. At the time of investigation, 33.5% of the mothers smoked, and within this group, those who smoked during pregnancy tended to smoke more heavily (38.8% vs 9.8%, >11 cigarettes/day, OR, 5.8; 95% confidence interval [CI] 2.9-11.8). The current smoking habits or the exposure to NOx and SO_2 were, however, not positively associated with any manifestation of atopy in the children.

Mothers who smoked during pregnancy/lactation were less well educated, had a higher percentage of blue-collar jobs, and had a lower monthly income. Those characteristics, however, did not statistically explain differences in the atopic outcomes. The family history of atopic diseases did not differ significantly within the groups of smoking and nonsmoking mothers.

CART analysis

For a total of 421 children, complete data were available for analysis. Of these children, 158 (37.5%) showed manifestations of atopy. The variable, manifestation of atopy, was primarily influenced by two factors, the maternal smoking during pregnancy/lactation and the indoor NOx exposure. The factor with the strongest influence led to the first split in this CART, and this was maternal smoking during pregnancy or lactation. Twenty-four (52.2%) of 46 children whose mothers smoked during pregnancy showed manifestations of atopy versus 134 (35.7%) of 375 for nonsmoking mothers ($p < 0.044$). The primary p value for the influence of NOx (Q1 vs Q2-4) on the depending variable was 0.021. This had to be corrected because this was a categoric variable and led to the definite p value of 0.052 that was not significant but demonstrated a possible influence. In the final CART analysis, the NOx exposure led to the second split, a separation in the group of mothers who did not smoke during pregnancy/lactation. In

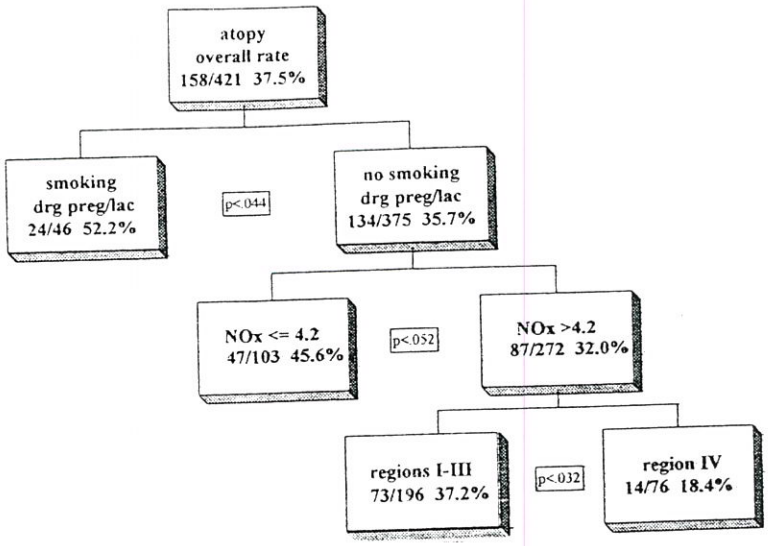

Fig. 1. Classification and Regression Tree for manifestations of atopy in 421 Bavarian preschool children. *drg preg/lac*, During pregnancy and lactation.

contrast to the a priori hypothesis, more children with manifestations of atopy were found in the lowest category of indoor NOx exposure (45.6% Q1 vs 32% Q2-4). The quartiles 2-4 of the NOx exposure were separated in a third split by the influence of the investigation site. In this group the children of the so-called clean air areas (group IV) had significantly fewer manifestations of atopy (14 [18.4%] of 76) compared with all other groups (73 [37.2%] of 196; $p < 0.032$; Fig. 1).

Explorative bivariate analysis. The influence of the maternal smoking habits on the individual measures of atopy was analyzed bivariately. Smoking during pregnancy or lactation or both was not associated with the child's skin-prick test reactivity or a history of respiratory atopic diseases but only with a positive history of atopic eczema. Of the children whose mothers did not smoke, 98 (18.1%) of 541 had a history of atopic eczema, whereas in 26 (33.8%) of 77 of the children whose mothers had smoked during pregnancy or lactation or both, atopic eczema was reported (OR, 2.30; CI, 1.32-3.12).

Results of the follow-up study. The hypothesis of an association between maternal smoking during pregnancy and lactation and manifestations of atopy in the offspring was tested also for the consecutive years 1991 through 1994. No statistically significant result was obtained except for the year 1992, for which we found an inverse association in univariate and multivariate analyses. This was the result mainly of an extreme distribution in the subgroup of girls. Only one girl of 21 of smoking mothers showed manifestations of atopy compared with 46 of 109 of nonsmoking mothers. Because this result is based on a single case, we interpreted it with caution. In the following year, a positive association in the subgroup of girls was obtained. Two of four girls with smoking mothers and 23 of 87 nonsmoking mothers had signs of atopy. Again a rather small number of affected girls with smoking mothers was observed. Table III summarizes the distribution of manifestations of atopy and maternal smoking status over the years 1988 through 1994. Whereas the proportion of atopic children in the group of nonsmoking mothers remained quite constant over the years, in recent years fewer children with signs of atopy were observed in the group of smoking mothers.

DISCUSSION

Maternal smoking during pregnancy/lactation was found to be associated with an increased risk of 2.3 (1.3 to 3.1) of atopic eczema in the offspring. Our data result from CART analysis of an earlier investigation with preliminary publications.[33,38,39] Here the definition of manifestation of atopy included positive prick-test reactivity in addition to positive history of atopic disease. All valid cases between 1988 and 1990 were included. Smoking by the mother during pregnancy or lactation or both was associated with later manifestations of atopy, leading to the first split in the CART. Further analyses demonstrated that this effect was related only to the his-

Table III. Manifestations of atopy by maternal smoking status during pregnancy and lactation from 1988 through 1994

Year	Atopic children/total (%)		
	Smoking mothers	Nonsmoking mothers	OR (95% CI)
1988-1990	24/46 (52.2)	134/375 (35.7)	1.96 (1.02-3.79)*
1991	10/30 (33.3)	88/257 (34.2)	0.96 (0.40-2.27)
1992	8/39 (20.5)	90/222 (40.5)	0.38 (0.15-0.89)*
1992 (girls, multivariate)	1/47 (2.1)	20/83 (24.1)	0.07 (0.00-0.47)*
1993	4/18 (22.6)	56/161 (34.8)	0.54 (0.12-1.82)
1994	7/21 (33.3)	44/117 (37.6)	0.83 (0.28-2.42)
1991-1994	29/108 (26.1)	278/757 (36.6)	0.63 (0.39-1.01)

tory of atopic eczema and not to respiratory atopy. The degree to which the effects of prenatal exposure to components of tobacco smoke on the immune system are side effects or are causally linked to the later outcome cannot be answered. Earlier studies by Rantakallio et al.[40] associated smoking during pregnancy to alterations in the child's skin. The cumulative incidence during the first 5 years of life for hospital admissions for diseases of the skin and the subcutaneous tissue was 22.5/1000 live births in the group of mothers who smoked during pregnancy ($n = 1821$) and 8.2/1000 in the nonsmoker group ($n = 1823$, $p < 0.0001$). Eczema and urticaria were observed 4.7 times more often in the smoker group. It has also been shown that children with atopic eczema whose mothers smoke are more likely to develop asthma.[41]

Positive associations between maternal smoking status during pregnancy and lactation and manifestations of atopy in the offspring were not obtained in the follow-up studies from 1991 through 1994. In contrast we observed an inverse correlation for the group of girls in 1992. We believed that this result should be considered a product of chance because only one affected girl was reported in the group of smoking mothers. The lack of a positive association in the follow-up study, however, must be considered in the interpretation of the earlier data. The differences in the study sites might have influenced the outcome. As discussed in the paragraph on exposure assessment, another explanation could be a change in the smoking behavior in families with atopic background as a consequence of public health education and recognition. This is reflected by the lower fractions of atopic children in the group of smoking mothers in more recent years, whereas nonsmoking mothers had about the same number of children with manifestations of atopy over the years. The inconsistency of the results over different periods regarding the prevalence of atopy in children of mothers who smoked or did not smoke during pregnancy does not support a causal interpretation of the significant association.

An association between maternal smoking during pregnancy or lactation or both and sensitization in prick tests or frequency of respiratory atopic diseases was not found in our study. This, however, cannot rule out a potential adverse effect of maternal smoking on atopic respiratory diseases because our study population was restricted to 5- to 6-year-old children. Ownby and McCullough[42] analyzed sera of children whose mothers smoked at home and controls. They found elevated IgD levels but no higher contents of IgE specific to six aeroallergens in the tobacco smoke–exposed group. Skin-prick test reactivity to common aeroallergens was found to be increased in children exposed after birth to maternal tobacco smoke.[43] Another study demonstrated this effect for boys only.[23] Active smokers also showed increased reactions to skin-prick tests in one study,[44] but this was not confirmed by others.[45]

As shown in Table I, the outdoor levels of NOx and SO_2 are not fully reflected by the measured indoor exposure. The unexpected inverse correlation between indoor NOx exposure and manifestations of atopy within the group of mothers who did not smoke cannot be fully explained. We suspect that parents of obviously atopic children refrained from smoking, the major indoor NOx source, as a preventive measure, but data confirming this hypothesis are not available.

A family history of atopic diseases, which was not included in the model, might have influenced the relation as confounder. There was, however, no statis-

tically significant difference in the various exposure groups.

There might have been some cases of improper handling of the sampling devices because no NOx was detectable in 41 (8.3%) of 497 investigated filters. These cases were categorized in the first quartile. Because an exposure level of 0 is unlikely, the plastic devices might not have been opened during the entire period or not at all, so that these cases could have been misclassified. Because there was no evidence of differential misclassification between diseased and nondiseased children, the resulting bias would have driven the estimated effects toward the null value.

We controlled for major possible confounders in our analysis. Maternal smoking during pregnancy was found to be associated with certain outcomes of socioeconomic status. These, however, could not explain the association of interest. Nutritional data for the period of pregnancy and lactation were not obtained and would have probably been prone to inaccuracy and recall bias. Therefore alcohol consumption, as confounder, was not included in the final model. Taking into account the evidence of the effects of maternal smoking,[9, 16, 18, 29-31] we believe that alcohol consumption is not likely to explain much of the observed association.

The response rate always raises concerns about the introduction of selection bias and restrictions to generalizability. In this study 71.4% responded positively to the invitation to participate. Reasons for nonparticipation were given occasionally on request and included acute illnesses and difficulty with the time schedule or location. A differential selection of cases affecting both the exposure and outcome of interest seems unlikely. Because the study did not focus primarily on maternal smoking habits during pregnancy and because it is unlikely that participants could have assumed a relation between the investigated exposure and outcome, a selection bias concerning exposure status can be excluded.

Bias may have been introduced by differential selection of the cases included in the CART analysis. For 421 (62.1%) of the total group of 678 children, complete data were available. However, with respect to the outcome variable or the exposure, no significant differences were found between the total group and those included in the analysis (atopy, 38.9% vs 37.5%; maternal smoking, 12.4% vs 10.9%).

The third split in the CART confirms the original expectations for the remaining subgroup in that fewer manifestations of atopy were found in the so-called clean-air regions.

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