

Epidemiology and Health Services Research

The effect of environmental tobacco smoke on eczema and allergic sensitization in children

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Accepted for publication 16 July 2003

Summary

Background The negative impact of environmental tobacco smoke (ETS) on airway diseases in children is well known. Whether there is an effect on atopic eczema is not clear.

Objectives To determine the impact of ETS on atopic eczema, allergic sensitization and allergic airway diseases in 1669 school beginners.

Methods The prevalence of atopy-related health outcomes was assessed by questionnaire, dermatological examination, skin prick testing and specific immunoglobulin E measurement. Exposure assessments were based on measurement of cotinine [expressed as cotinine to creatinine ratio (CCR)] in spot urine samples ($n = 1220$) together with questionnaire and interview data on smoking behaviour of the parents.

Results In the total study group, prevalence of atopic eczema diagnosed on examination was significantly associated with urinary CCR values. The odds ratio (OR) and 95% confidence interval (CI), calculated for an increase of 100 ng mg^{-1} CCR was 1.97 (95% CI 1.23–3.16). The prevalence of skin manifestations according to questionnaire data as well as a history of asthma, wheezing, and hay fever were positively although not significantly associated with ETS exposure. When genetically predisposed children (defined by the presence of parental atopy) were compared with children whose parents had no atopy, the ORs of allergic outcome variables were generally higher in the first group. In the group of predisposed children, significant associations with urinary CCR were found for allergic sensitization against house dust mites as measured by skin prick test (OR 3.10, 95% CI 1.63–5.90).

Conclusions Children are at a higher risk of developing an atopic eczema when exposed to ETS and genetically predisposed children are at higher risk of developing a sensitization against house dust mites.

Key words: eczema, parental atopy, predisposition, respiratory allergies, sensitization, tobacco smoke

Environmental tobacco smoke (ETS) is one of the most common indoor air pollutants. Adverse health effects attributable to ETS include acute and chronic respiratory illness, cardiovascular disease and lung cancer in

nonsmokers. Children are more likely to suffer from ETS-related health effects than adults, and the home is the most important site of such exposure.^{1,2}

Extensive epidemiological literature documents an association between exposure to ETS and increased lower respiratory illness (bronchitis, bronchiolitis, pneumonia and their symptoms) in infancy and early childhood.^{3,4} In a quantitative overview of 38 studies on respiratory outcomes, Strachan and Cook revealed

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pooled odds ratios (ORs) of 1.57 for smoking by either parent and 1.72 for maternal smoking.³ The authors conclude that there is a causal relationship between parental smoking and acute lower respiratory illness, at least in the first 2 years of life. With respect to childhood asthma, a pooled OR of 1.37 for the risk of asthma was reported.⁵ A cohort study in children up to the age of 4 years revealed a joint effect of parental atopy and exposure to ETS on asthma, which was stronger than expected on the basis of their independent effects.⁶ The results of a large population-based study from Italy support the hypothesis that ETS may act as an adjuvant factor in determining persistent bronchial hyperreactivity and asthma in genetically predisposed children, whereas in nonpredisposed individuals parental smoking could be an irritative cofactor provoking wheezing attacks.⁷

In contrast to lower respiratory tract diseases, there is no consistent evidence of an association between parental smoking and atopic eczema and allergic sensitization in children. As reviewed by Strachan and Cook,⁸ some studies indicate an increased risk of developing sensitization to specific allergens, but other studies have found no effect on total or specific immunoglobulin (Ig)E and IgE-mediated allergies. With respect to atopic eczema, the findings are also inconsistent, revealing negative relationships in some studies.^{8–12}

In this study we investigated the influence of ETS on allergic airway diseases, sensitization, and atopic eczema in 6-year-old children. Owing to the evidence of an effect modification by genetic constitution,⁶ the influence was also evaluated in the group of children with and without parental atopy. Exposure assessment was based on urinary cotinine, the major metabolite of nicotine.¹³ In several studies, measurements of cotinine in body fluids have added to the plausibility of associations between passive smoking and disease in children.^{14–17}

Materials and methods

Study population and study design

This investigation was part of the cross-sectional study MIRIAM (Multicentric International Study on Risk Assessment of Indoor and Outdoor Air Pollution and Eczema Morbidity), performed during 1996. A special focus of the study done in Augsburg, a city with 250 000 inhabitants in Southern Germany, was to clarify the relationship between ETS exposure and

allergy and eczema morbidity. The study was approved by the ethics committee of the Bavarian Medical Association (Bayerische Landesärztekammer) and written parental consent was obtained. The source population included all 2444 children registered for admission to school in the year 1996. Data collection was based on questionnaire information, dermatological investigation, analysis of atopic sensitization, biomonitoring of cotinine in spot urine samples and evaluation of residential characteristics by interview. During a re-investigation which took place in 1998, urine samples from 358 children were obtained for cotinine determination; urine samples of 258 children exist for both time points and were used to examine the persistence of the children's ETS exposure over time.

A basic questionnaire was sent to the parents along with the invitation to the school entrance examination. The questionnaire comprised symptoms and diagnosis of airway diseases and allergic manifestations, sources of air pollutants and potential confounding variables.

Covariates

The information on covariates was based on questionnaires and interview data. In agreement with other studies,^{18,19} the covariates in the present analysis included nationality, gender, atopy in parents, education, bedroom sharing, playing predominantly outdoors, month of investigation and housing characteristics (age of the house, type of furniture, wall to wall carpet, and dampness of flat). Nationality was defined as German if at least one of the parents had German nationality. Similarly, atopy in parents was defined as positive if father or mother had ever had bronchial asthma, hay fever or eczema. The residential environment and exposure to ETS was assessed in greater detail with a structured interview of the parents, which was performed during a home visit.

Health outcomes

Primary health outcomes were respiratory allergies, atopic eczema and sensitization to common allergens. All children underwent a standardized dermatological examination by experienced physicians, trained in using the U.K. Diagnostic Criteria²⁰ and the instrument for severity assessment of atopic eczema, SCORAD (Severity Scoring of Atopic Dermatitis).²¹ A standardized skin prick test was performed on the forearm of the children. The common aeroallergens birch pollen, grass pollen, mugwort pollen, house dust mite, cat and

alternaria as well as two food allergens (hen's egg, cow's milk) were tested. In blood sera the concentration of specific IgE antibodies to five aeroallergens (house dust mite, grass pollen, birch pollen, *Cladosporium herbarum*, and cat) was measured by Radio-Allergo-Sorbent-Test (RAST) (CAP-FEIA; Pharmacia, Uppsala, Sweden). Results are given in kU L^{-1} . A sensitization was regarded as positive if the concentration exceeded 0.35 kU L^{-1} . Total IgE values were dichotomized (value $< 180 \text{ kU L}^{-1}$ or value $\geq 180 \text{ kU L}^{-1}$).

Assessment of environmental tobacco smoke exposure

The number of cigarettes (cig.) smoked currently inside the house per day was recorded and categorized as 0, weak ($1\text{--}10 \text{ cig. day}^{-1}$), medium ($11\text{--}20 \text{ cig. day}^{-1}$), and heavy ($> 20 \text{ cig. day}^{-1}$). Cotinine in spot urine samples was determined by radioimmunoassay according to the method of Haley *et al.*²² The limit of detection was 0.5 ng mL^{-1} for cotinine in urine, corresponding to about 0.5 ng mg^{-1} creatinine. Urinary creatinine was determined by the Jaffe method using a commercial test kit (Merck AG, Darmstadt, Germany). All measurements were performed in duplicate. An analysis was repeated when the deviation between two values exceeded 10%.

Statistical analysis

To describe the association between health outcome variables and ETS exposure, logistic regression was used to adjust for confounding. Nationality, gender and atopy in parents were included in every model. Other covariates were included if the association with the health outcome was significant ($P < 0.1$). The effect estimates were transformed to ORs with their respective 95% confidence intervals (CI). Additionally, ORs were calculated for the two subgroups: predisposed children (at least one parent with atopy) and nonpredisposed children (no parental atopy).

Results

Study population

The response rate (completed questionnaire and dermatological investigation) was 68% ($n = 1669$). The mean age of the 1669 participants (48% boys, 52% girls) was 6.5 years; 72% of the children had at least one German parent. Spot urine samples were obtained from 1221 of the 1669 children enrolled in the study, cotinine to creatinine ratio (CCR) values from 1220 children.

Description of exposure

According to the questionnaire information, approximately one-third of the children were currently exposed to cigarette smoke in their homes (Table 1). In most cases, smoke exposure was reported to be weak ($< 10 \text{ cig. day}^{-1}$) or medium ($11\text{--}20 \text{ cig. day}^{-1}$), with only 57 children (3.5%) experiencing exposure to more than 20 cigarettes a day. Table 2 shows the distribution of urinary CCR in the four exposure groups. Although the distribution of CCR in the exposed and nonexposed subpopulations overlapped, there is a strong overall agreement between single-point measurements of CCR and parental reports of exposure to tobacco smoke. Children living in nonsmoking homes had significantly lower CCRs than children exposed to ETS at home. There was an almost linear increase in CCR from weak ($1\text{--}10 \text{ cig. day}^{-1}$) to heavy ($> 20 \text{ cig. day}^{-1}$) passive smoking. Urinary CCRs of the 258 children, who supplied urine samples both in 1996 and 1998, were significantly correlated ($r = 0.67$, $P < 0.001$).

Association of health outcome variables with environmental tobacco smoke exposure

Atopic eczema was found in 4.7% and bronchial asthma and hay fever in about 4% of the children (Table 3). Approximately one-third of the children

Table 1. Description of exposure to environmental tobacco smoke (ETS)

Exposure		<i>n</i>	% yes ^a or mean (SD) ^b
ETS	None	1644	65.9
	Weak ($1\text{--}10 \text{ cig. day}^{-1}$)		19.5
	Medium ($11\text{--}20 \text{ cig. day}^{-1}$)		11.1
	Heavy ($> 20 \text{ cig. day}^{-1}$)		3.5
Urinary cotinine	ng mL^{-1}	1221	22.8 (32.04)
Cotinine to creatinine ratio	ng mg^{-1}	1220	29.13 (40.53)

^a% positive answers. ^bArithmetic mean (standard deviation).

		Cotinine to creatinine ratio (ng mg ⁻¹)				
		<i>n</i>	Arithmetic mean (SD)	Median (range)	5th percentile	95th percentile
Total		1220	23.13 (40.53)	15.32 (1.18–409.31)	3.42	101.93
ETS	None	790	14.67 (17.38)	8.91 (1.18–189.74)	3.09	46.01
	Weak	232	45.82 (50.22)	30.21 (5.45–409.31)	10.4	130.82
	Medium	132	64.79 (55.33)	46.95 (4.91–318.74)	15.67	197.39
	Heavy	43	83.43 (68.05)	53.2 (11.54–277.24)	23.19	221.23

Table 2. Association of reported exposure to environmental tobacco smoke (ETS) and urinary cotinine to creatine ratio

Table 3. Prevalence of allergic diseases, symptoms and sensitization in 6–8-year-old children and association with environmental tobacco smoke exposure

		Prevalence			
		All cases		Cases with CCR determination	
Health outcome variable		<i>n</i>	%	<i>n</i>	% yes
Atopic disease or symptom (questionnaire information)					
Bronchial asthma ever ^b		1640	3.7	1088	3.5
Wheeze ^c		1561	4.2	1038	4.7
Hay fever ever ^b		1639	4.6	1131	4.9
Sneezing attacks, running nose ^c		1661	12.9	1107	13.4
Additionally with reddened eyes ^c		1660	4.2	1140	4.1
Itching skin rash ^c		1655	4.0	1094	4.3
Actual examination					
Atopic eczema		1656	4.7	1132	4.7
Prick 1 positive result ^d		1481	30.8	1020	29.6
House dust mite		1477	15.2	1002	13.9
Pollen		1477	21.6	1019	20.7
RAST 1 positive result ^d		1125	37.1	777	36.2
House dust mite		1124	14.6	752	14.4
Pollen		1123	20.0	775	19.4
Total serum IgE > 180 IU L ⁻¹		1124	14.4	773	14.2

CCR, Cotinine to creatine ratio; RAST, Radio-Allergo-Sorbent-Test. ^aAdjusted odds ratio with 95% confidence interval (CI). ^bDoctor diagnosed. ^cIn the last 12 months. ^dAt least.

were sensitized against one or more common allergens, predominantly against pollen and mites. The associations of these health parameters with passive smoking at home were calculated for a steady increase of urinary cotinine values and OR given for an increase of 100 ng mg⁻¹ (Table 3).

Allergies of the respiratory tract

There were no significant associations between children's urinary CCR values and bronchial asthma, wheezing, hay fever and other symptoms related to respiratory allergies. With an increase in urinary CCR of 100 ng mg⁻¹ the observed ORs were between 0.86 and 1.34 (Table 3). The ORs were higher although not significantly different from one (between 1.24 and 1.82

for the five variables) in the subpopulation of predisposed children (Table 4).

Atopic eczema

Actual dermatological examination revealed eczema in 4.7% of the children in agreement with questionnaire information on itching skin rash in the last 12 months. Severity assessments according to SCORAD (range 0–103) resulted in scores between 9 and 58 with a median of 25, indicating moderate eczema. There was a significant association between the degree of ETS exposure and prevalence of atopic eczema on examination (OR 1.97, $P \leq 0.01$). The OR for the raw association between atopic eczema and urinary CCR was 1.68. This changed to 1.92 when including atopy

Table 4. Association of allergic diseases, symptoms and sensitization to urinary cotinine to creatinine ratio values in children of parents with atopy and in children of parents without atopy

Health outcome variable	Parents with atopy			Parents without atopy		
	<i>n</i>	% yes	OR (95% CI)*	<i>n</i>	% yes	OR (95% CI)*
Atopic disease or symptom (questionnaire information)						
Bronchial asthma ever†	433	4.4	1.58 (0.53, 4.67)	647	2.9	0.68 (0.16, 2.88)
Wheeze‡	405	7.2	1.82 (0.81, 4.10)	625	3.2	1.15 (0.47, 2.80)
Hay fever ever†	450	5.8	1.51 (0.51, 4.54)	671	4.2	0.57 (0.14, 2.39)
Sneezing, running nose‡	443	17.6	1.24 (0.61, 2.51)	655	10.5	0.96 (0.52, 1.76)
Additionally reddened eyes‡	452	5.8	1.27 (0.37, 4.30)	679	3.1	0.91 (0.30, 2.79)
Itching skin rash‡	438	7.1	1.68 (0.73, 3.88)	648	2.5	1.41 (0.55, 3.62)
Actual examination						
Atopic eczema	451	6.7	2.40 (1.11, 5.15)	673	3.4	1.84 (0.98, 3.45)
Prick 1 positive result§	415	34.2	1.65 (0.94, 2.91)	603	26.5	1.03 (0.68, 1.54)
House dust mite	404	14.9	3.10 (1.63, 5.90)	596	13.3	0.67 (0.33, 1.36)
Pollen	412	26.0	1.50 (0.81, 2.78)	605	17.2	1.16 (0.75, 1.79)
RAST 1 positive result§	312	41.8	1.39 (0.70, 2.73)	454	32.4	0.88 (0.56, 1.40)
House dust mite	314	16.2	1.59 (0.68, 3.73)	435	13.1	0.90 (0.46, 1.74)
Pollen	321	26.8	1.62 (0.77, 3.37)	453	14.1	0.51 (0.21, 1.24)
Total serum IgE > 180 IU L ⁻¹	320	16.3	1.24 (0.48, 3.22)	451	12.8	1.38 (0.81, 2.33)

RAST, Radio-Allergo-Sorbent-Test. *Adjusted odds ratio per 100 ng mg⁻¹ with 95% confidence interval (CI). †Doctor diagnosed. ‡In the last 12 months. §At least.

in parents in the model. Only very minor changes occurred when introducing sex (OR 1.92) and nationality (OR 1.97) (Table 3, final model), additionally. The effect of inclusion of parental education, which might be a strong confounder, was negligible. After additionally including this variable the OR was 1.95. CCR values were positively but not significantly associated with questionnaire data on itchy skin rash in the last 12 months (OR 1.45) (Table 3). With respect to atopic eczema, there was a tendency towards higher OR in the subgroup of predisposed children compared with children whose parents had no atopy (Table 4).

Sensitization

Atopic sensitization to common environmental allergens was not significantly associated with the degree of passive smoking in the total study group (Table 3). However, analysis of the subgroups defined by atopy of parents revealed markedly higher ORs in children of parents with atopy compared with nonpredisposed children. In the former group, there was a significant association of positive skin prick testing against at least one common allergen (OR 1.65, $P \leq 0.1$) as well as house dust mite (OR 3.10, $P < 0.01$). Allergen-specific IgE antibodies were also positively associated with the CCR concentrations (ORs between 1.39 and 1.62) but without statistical significance (Table 4). Total serum

IgE levels were not significantly influenced by passive smoking in either group.

Discussion

Data from this study provide evidence that exposure to ETS has an adjuvant effect on atopic eczema and allergic sensitization in children. The effect of ETS was more pronounced in children with allergic parents and strongest for sensitization against house dust mite, the most common indoor allergen.

Of 2444 families registered, 1669 responded. It seems very unlikely that the result of the main question of the study might be distorted by selection. The possible participants did not know that one main aim of the study was to investigate the effect of passive smoking. However, it seems possible that the prevalence of diseases and symptoms in the whole population differs from the prevalence in the families studied. This was not investigated. Exposure assessment was based on urinary CCR as an objective marker in addition to parental reports on cigarette consumption at home. As shown in Table 3, the prevalence of health outcome variables in the entire study group is not different from the prevalence in the group of children with available cotinine values, making selection bias by restriction to the latter group less likely. Cotinine measurements in body fluids is considered at present to be the gold

standard of ETS exposure assessment. Cotinine has a half-life of approximately 20 h²³ and is therefore a biomarker of recent exposure. In our study, a second assessment in 258 children almost 20 months later revealed a good correlation of the CCR measurements at the two time points, indicating that smoking habits were relatively stable over time. Generally, a CCR cut-off level of 10 ng mg⁻¹ is used to distinguish between nonexposed and ETS-exposed children.¹⁵ In the present study, mean (14.7 ng mg⁻¹) and median (8.9 ng mg⁻¹) CCR values measured in children with no reported ETS exposure are in good agreement with this value. Overall, there was a steady increase in CCR concentrations in the four exposure groups, with mean CCR of 83.4 ng mg⁻¹ when consumption of more than 20 cig. day⁻¹ was reported.

Discrepancies between parental reports and cotinine measurements may be explained by information bias (difference in reporting exposure among parents of healthy and sick children), sampling error (some parents may not smoke the same amount every day and on some days they might open the windows) or incomplete knowledge of exposure. Cook and Strachan¹⁰ previously demonstrated the importance of exposure outside the home in determining cotinine levels in 5–7-year-old children and Weaver *et al.*²⁴ reported substantial ETS exposure (mean CCR = 45 ng mg⁻¹) in inner-city children without known individual exposure. Studies of biomarkers in urine and hair of Scandinavian children indicate that those children living in homes without smokers are also exposed to some ETS and are therefore not a true unexposed group. This misclassification could have contributed to an underestimation of the health effect of passive smoking.¹⁹ To avoid reporting bias or misclassification of exposure, we based the calculation of ETS-associated health risks on CCR concentration in spot urine samples. However, it has to be stated that cotinine measurements can be affected by intersubject variability in the metabolic conversion of nicotine; consumption of nicotine-containing food, on the other hand, remains negligible except in the case of vegetarians.²⁵

In this study, we found no significant effects of passive smoking on asthma, wheezing and other airway diseases. For the five diseases under investigation, predisposed children (defined by parental atopy) were at higher risk when compared with children whose parents had no atopy, although the difference was not significant. These findings are not surprising as the well-known respiratory effects of ETS are most pronounced in infancy and early

childhood and less pronounced or even absent in older children.⁴

Prevalence of actual atopic eczema diagnosed on examination was significantly associated with CCR values (OR 1.97). Additionally, significant associations to CCR were found for sensitization (according to skin prick test) to house dust mite (OR 3.10) in the subgroup of predisposed children, but not in the whole study population. The results were based on atopic eczema diagnosis on examination and objective parameters (urinary cotinine, skin prick test). When associations were calculated with respect to parental reports, they were also higher in predisposed children, but the difference between groups was not significant. In a recent review of 36 studies, Strachan and Cook⁸ disclosed no overall significant association of passive smoking with skin test positivity, total or specific serum IgE concentration, or allergic rhinitis or atopic eczema. The failure to demonstrate an association in these studies may at least in part be explained by recall bias and a tendency of parents to stop smoking when the child is diagnosed as allergic. The latter was demonstrated for example by Jaakkola *et al.*,²⁶ who found a significant lower risk of exposure to ETS at home for atopic children (OR 0.61) compared with unaffected children.

Despite a number of negative findings (reviewed by Strachan and Cook),^{8,10} some studies support our observation and demonstrate an adjuvant effect of ETS on atopic eczema and allergic sensitization. According to an earlier study, maternal smoking during pregnancy and lactation doubled the risk of the offspring developing atopic eczema (OR 2.3).²⁷ Results from another multicentre German study indicate that during early childhood, prenatal and postnatal ETS-exposed children had a significantly higher risk (OR 2.2) of sensitization to food allergens compared with children never exposed to ETS.²⁸ In young asthmatic children, ETS promoted atopic sensitization to cat allergens with synergistic effects between ETS and other risk factors.²⁹ Two studies from the U.K.³⁰ and the Baltic region³¹ showed an association of ETS with sensitization to indoor allergens (cat dander and house dust mite) but not to other common outdoor air allergens. It must be noted in this context that in adults, active smoking is associated with sensitization to some occupational allergens, but associations with common environmental allergens except to house dust mite are unclear.³²

These observations give rise to the speculation that the indoor air pollutant ETS might directly interact with indoor allergens by promoting allergenicity and thus enhancing immune responses to these allergens. In a

murine model of allergy, ETS was an adjuvant for T-helper-2 (Th2) responses and elicited a rapid and prolonged exaggerated response with respect to IgE, IgG1, eosinophils, and Th2 cytokines.³³ Additionally, ETS, like other air pollutants, may have irritant effects on skin and mucous membranes, thereby facilitating the penetration of potential allergens and causing more eczema symptoms and an elevated risk of sensitization. The effect of ETS on atopic eczema may be triggered by a different mechanism than the effect of ETS on sensitization. For atopic eczema solely, the effect could be seen in predisposed as well as in nonpredisposed children.

Three intervention studies investigated the influence of parental smoking on allergic manifestations in infants of atopic parents. Smoking by either parent was associated with an increased risk of physician-assessed atopic eczema (OR 2.4, 95% CI 0.7–7.9) in one study, with no association in another study and an increased risk of aeroallergen sensitization (OR 2.9, 95% CI 1.1–7.7) and an increased risk of atopic disorders excluding asthma (OR 1.7, 95% CI 0.7–4.4) in the third.⁸ With respect to childhood asthma, the joint effect of genetic propensity to asthma and exposure to ETS was greater than expected on the basis of their independent effects.⁶

In conclusion, our study supports the hypothesis that ETS is an adjuvant factor for atopic eczema and enhances allergic sensitization, at least in children with a genetic disposition to allergies.

Acknowledgments

The study was supported by a grant (01EE9501/2) from the German Federal Ministry of Education and Research (BMBF), the determination of cotinine additionally by the Forschungsgesellschaft Rauchen und Gesundheit, Hamburg, Germany. We thank the team in the Health Department of Augsburg for their excellent cooperation and organization of the study, the physicians from the Department of Dermatology who investigated the children and contributed to the acceptance of the study, and Johanna Grosch from the same department for analysing the specific IgE. Additionally we thank Roger Duffin for language corrections and Gabriele Seitner-Sorge for help with the manuscript.

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