

Pre- and Postnatal Exposure to Parental Smoking and Allergic Disease Through Adolescence



WHAT'S KNOWN ON THIS SUBJECT: Exposure to second-hand tobacco smoke during pregnancy and infancy has been linked to development of asthma, rhinitis, and eczema in young children. It is unclear whether these risks persist into adolescence.



WHAT THIS STUDY ADDS: Exposure to second-hand smoke in utero or during infancy influences the development of allergic disease up to adolescence. Excess risks for asthma and rhinitis were seen primarily in early childhood, whereas those for eczema occurred at later ages.

abstract



OBJECTIVES: To examine the role of prenatal and postnatal second-hand tobacco smoke (SHS) exposure on asthma, rhinitis, and eczema development up to 16 years of age.

METHODS: A birth cohort of 4089 children was followed for 16 years. Information on parental smoking habits, lifestyle factors, and symptoms of allergic disease was gathered using repeated parental questionnaires. Generalized estimating equations assessed the overall and age-specific associations between SHS exposure and allergic disease at ages 1 to 16 years.

RESULTS: Exposure to SHS in utero was associated with an overall elevated risk of developing asthma up to 16 years (odds ratio [OR] = 1.45; 95% confidence interval [CI], 1.15–1.83) but not for rhinitis or eczema. After additional adjustment for parental smoking throughout childhood, excess overall risks for asthma remained statistically significant. Moreover, a dose-dependent pattern with SHS was observed. Exposure to SHS during infancy was associated with an overall elevated risk of asthma (OR = 1.23; 95% CI, 1.01–1.51), rhinitis (OR = 1.18; 95% CI, 1.01–1.39), and eczema (OR = 1.26; 95% CI, 1.09–1.45) up to 16 years. When age-specific associations were examined, the elevated risks related to SHS exposure in utero or during infancy were mostly confined to early childhood for asthma and rhinitis, whereas the excess risk of eczema appeared greatest at later ages.

CONCLUSIONS: Our findings indicate that early SHS exposure, in utero or during infancy, influences the development of allergic disease up to adolescence. Excess risks for asthma and rhinitis were seen primarily in early childhood, whereas those for eczema occurred at later ages. *Pediatrics* 2014;134:428–434

AUTHORS: Jesse D. Thacher, MPH,^a Olena Gruzieva, MD, PhD,^a Göran Pershagen, MD, PhD,^{a,b} Åsa Neuman, MD,^{a,c} Magnus Wickman, MD, PhD,^{a,d} Inger Kull, RN, PhD,^{a,d,e} Erik Melén, MD, PhD,^{a,d} and Anna Bergström, PhD^a

^a*Institute of Environmental Medicine, and* ^e*Department of Clinical Science and Education, Stockholm South General Hospital, Karolinska Institutet, Stockholm, Sweden;* ^b*Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden;* ^c*Department of Women's and Children's Health, Uppsala University Hospital, Uppsala, Sweden;* and ^d*Sachs' Children's Hospital, Södersjukhuset, Stockholm, Sweden*

KEY WORDS

asthma, rhinitis, eczema, allergy, children, tobacco smoking, cohort study

ABBREVIATIONS

BAMSE—Children, Allergy, Milieu, Stockholm, Epidemiology
CI—confidence interval
OR—odds ratio
SHS—second-hand tobacco smoke

Mr Thacher performed the data analyses, and drafted the initial manuscript; Dr Gruzieva performed the data analyses; Drs Pershagen and Wickman initiated the BAMSE cohort; Dr Kull supervised the data collection; Dr Bergström planned the current study; and all authors participated in the interpretation of the findings, provided critical review, and approved the final manuscript as submitted.

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Address correspondence to Jesse D. Thacher, MPH, Institute of Environmental Medicine, Karolinska Institutet, Box 210, SE-171 77 Stockholm, Sweden. E-mail: jesse.thacher@ki.se

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Allergic diseases such as asthma, rhinitis, and eczema influence quality of life and contribute significantly to the burden of disease and health care costs.^{1,2} Early life exposures play an important role in the development of these diseases,³ but the etiologic pathway is complex and dynamic, involving environmental exposures and genetic factors. Fetal exposure to smoking during pregnancy is of particular interest, because nicotine and other toxic substances readily cross the placental barrier.⁴ Additionally, maternal smoking during pregnancy affects fetal lung growth and structural development.^{5,6} Many children are exposed to tobacco smoke both in utero and postnatally,⁷ and up to 60% of mothers who quit smoking during pregnancy return to smoking within the first 6 months postpartum, and 80–90% relapse \leq 12 months after delivery.⁸

Tobacco smoke exposure in utero and postnatally have been associated with recurrent wheeze and asthma in early childhood.^{9,10} The results of a recent pooled analysis based on 8 European birth cohorts showed that maternal smoking during pregnancy was related to asthma in preschool age among children whose mothers did not smoke postnatally.¹¹ However, it is unclear how risks persist into adolescence. Studies exploring the association between second-hand smoke (SHS) and rhinitis or eczema show inconsistent results.^{12–17} Few longitudinal studies have been capable of investigating the effects of SHS exposure from birth to adolescence.

The aim of this study was to assess the effect of exposure to SHS on allergic disease in the BAMSE (Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiologic survey) birth cohort from fetal life up to age 16 years. More specifically, the purpose was to investigate whether in utero and postnatal exposure to SHS contributes to the development of asthma, rhinitis, and eczema during the first 16 years of life.

METHODS

Study Subjects

BAMSE is a longitudinal population-based cohort study of children recruited at birth and followed during childhood and adolescence. Details of the study design, inclusion criteria, enrollment, and data collection are described elsewhere.¹⁸ In short, 4089 children born between 1994 and 1996 in certain areas of Stockholm County were recruited. At enrollment, when the infant was \sim 2 months of age, parents completed a questionnaire that assessed residential characteristics and indoor environmental exposures, including maternal smoking during pregnancy and smoking habits of both parents before and after the birth of the child. Additionally, the questionnaire assessed parental allergic disease, socioeconomic status, parental occupations, and lifestyle factors.¹⁸ When children were 1, 2, 4, 8, 12, and 16 years old, the parents completed questionnaires focusing on symptoms of asthma, rhinitis, and eczema in their child and parental smoking habits.¹⁸ The survey response rates were 96%, 94%, 91%, 84%, 82%, and 78%, respectively. The baseline and follow-up studies were approved by the Regional Ethical Review Board, Karolinska Institutet, Stockholm, Sweden, and the parents of all participating children provided informed consent.

Exposure Assessment

In utero exposure to maternal smoking was defined as the mother smoking \geq 1 cigarette daily at any time during the pregnancy. The number of cigarettes the mother smoked per day for each trimester was recorded in the baseline questionnaire.

SHS exposure in infancy (first 2 months of life), and at ages 1, 2, 4, 8, 12, and 16 years was defined as any parent smoking \geq 1 cigarettes daily at the time of completing the respective questionnaire. The number of cigarettes smoked by the mothers and fathers was recorded at each follow-up.

Outcome Assessments

Health outcomes were based on parental questionnaires. Succinctly, asthma, rhinitis, and eczema were defined as follows:

Asthma at 1 and 2 years: \geq 3 episodes of wheeze combined with inhaled steroids or suspected hyperreactivity (wheezing or severe coughing with exertion and cold weather, or disturbed coughing at night) without upper respiratory infection.¹⁹ At 4, 8, 12, and 16 years: \geq 4 episodes of wheeze or \geq 1 episode of wheeze in combination with inhaled steroids.

Rhinitis: eye or nose symptoms after exposure to allergens and a doctor's diagnosis of allergic rhinitis.

Eczema: dry skin, pruritic rashes with age-specific localizations at face, flexures of arms or legs, wrists or ankles, or neck, or a doctor's diagnosis of eczema.

Detailed age-specific definitions for all outcomes are provided in this article's online repository.

Statistical Methods

We used generalized estimating equation models to assess the associations between SHS exposure and repeated measures of asthma, rhinitis, and eczema during the first 16 years of life.²⁰ To evaluate the age-specific association, the models included terms for an interaction between the time indicator variable and exposure. Both overall and age-specific associations from the models were reported. χ^2 tests were used to analyze differences in the distribution of potential confounders in relation to maternal smoking in utero and during infancy.

In utero exposure to maternal smoking was dichotomized (yes versus no). To assess possible dose–response effects we defined 3 categories (no cigarettes throughout pregnancy, 1–9 cigarettes per day during any trimester, and \geq 10 cigarettes per day during any trimester). Parental smoking in infancy and at age 1, 2, 4, 8, 12, and 16 years was also

dichotomized, and dose–response effects based on infancy exposure were coded in 3 categories (mother and father did not smoke, mother or father smoked 1–9 cigarettes per day, and mother or father smoked ≥ 10 cigarettes per day).

To account for parental smoking throughout childhood, parental smoking was defined based on the response in the questionnaire given before the time of outcome assessment. For example, parental smoking assessed in the questionnaire at year 4 was regressed against outcomes assessed at year 8.

The final models were adjusted for covariates selected based on prior knowledge and on results from exploratory stepwise logistic regression. Thus, we adjusted for covariates shown to lead to $>5\%$ change in odds ratio (OR). These included gender, parental history of allergic disease, and socioeconomic status (see online supplement).

Sensitivity analyses were performed to test the robustness of risk estimates, for example, in relation to inclusion of potential area-level confounders (eg, mean income in the neighborhood). We defined neighborhoods on the basis of small-area market statistics from Statistics Sweden (<http://www.scb.se>). These are the smallest administrative area units in Sweden, with an average population of 1000 to 2000 per unit.

To promote stable and robust longitudinal analyses, we included only children who had information from ≥ 3 of 6 follow-up questionnaires ($N = 3798$, 93%) from age 1 in our study. Analyses were performed with Stata statistical software (release 12; Stata Corp, College Station, TX).

RESULTS

The 3798 (93%) children included in this study were comparable with the children in the whole cohort with respect to baseline characteristics (Supplemental Table 4). Maternal smoking in utero was reported in 483 (12.7%) of families,

and parental smoking during infancy was reported in 785 (20.8%). Maternal smoking during pregnancy was associated with shorter duration of breastfeeding, low socioeconomic status of the parents, and higher prevalence of maternal age <26 years at delivery ($P \leq .01$) (Table 1). The same pattern was observed for parental smoking in infancy (Supplemental Table 5). Parental history of allergic disease was less common (25.5% among children exposed to parental smoking in infancy compared with 31.1% among unexposed) and parental smoking as well as eczema at 16 years were more common among children exposed to SHS during infancy.

The prevalence of parental smoking during the study period is shown in Fig 1. Parental smoking was highest during infancy and the prevalence remained $\sim 18\%$ from ages 1 to 8 years and declined to 13.6% by age 16 years. Children exposed to maternal smoking in pregnancy were more likely to be exposed to

parental smoking later in childhood. For example, 51.9% of these children had ≥ 1 smoking parent at age 16 years. At age 16 years, 4.5% of the children smoked daily and 7.4% smoked sometimes. At this age, 6.3% of the children had asthma, 25.4% had rhinitis and 9.8% had eczema.

The association between in utero exposure to maternal smoking and occurrence of allergic disease is examined in Fig 2A. Exposure to maternal smoking in utero was associated with an overall elevated risk for development of prevalent asthma up to 16 years (OR = 1.45; 95% CI, 1.15–1.83). However, no significant overall effects were observed for rhinitis or eczema. Similar results were observed for incident asthma, rhinitis, and eczema (Supplemental Fig 3A). When we examined age-specific associations, the elevated risks for asthma tended to be strongest early in life (1, 2, and 4 years), and a similar pattern was seen for rhinitis. On the other hand,

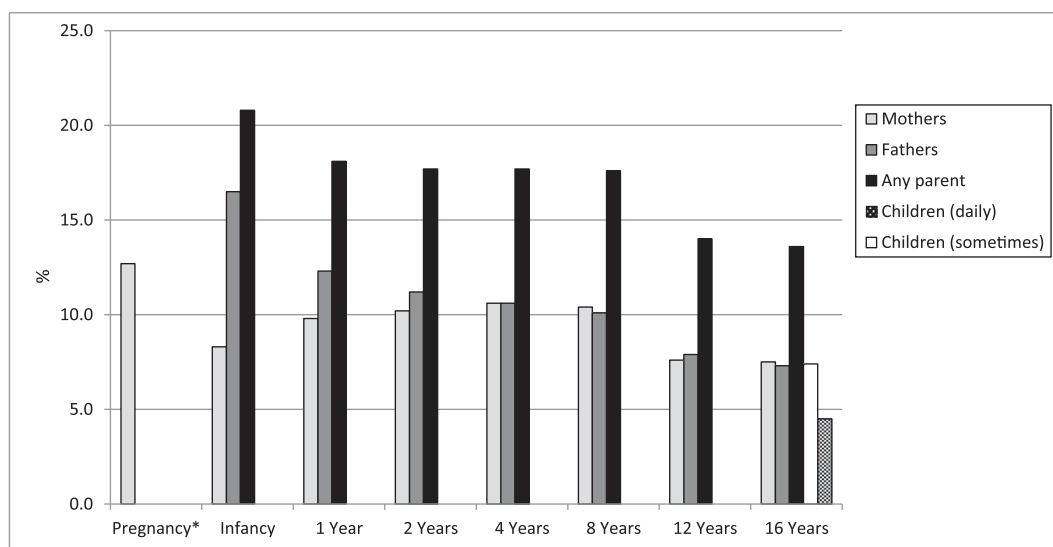
TABLE 1 Distribution of Exposure Characteristics in Relation to Maternal Smoking During Pregnancy Among Children in the BAMSE Birth Cohort ($n = 3798$)

	In Utero Exposure to Maternal Smoking ^a			
	No, $n = 3314$ (87.3%)		Yes, $n = 483$ (12.7%)	
	<i>n</i>	%	<i>n</i>	%
Gender				
Male	1675	50.5	245	50.7
Breastfeeding				
≥ 4 mo	2647	81.3	329	69.1
Socioeconomic status ^b				
Low	482	14.8	145	30.6
High	2781	85.2	329	69.4
Parental allergic disease				
Yes	1001	30.4	130	27.8
Maternal age at birth				
<26 y	225	6.8	60	12.4
Parental smoking at 16 y ^c				
Yes	221	8.3	189	51.9
Asthma at 16 y				
Yes	172	6.3	27	7.1
Rhinitis at 16 y				
Yes	697	25.7	87	22.9
Eczema at 16 y				
Yes	256	9.3	48	12.5

^a The mother smoked ≥ 1 cigarette per day at any time during pregnancy.

^b Children were categorized on the bases of the parents' occupations. Manual workers were classified as having low socioeconomic status and nonmanual workers as having high socioeconomic status. Detailed definitions can be found in the online supplement.

^c Any parent smoked ≥ 1 cigarette per day.

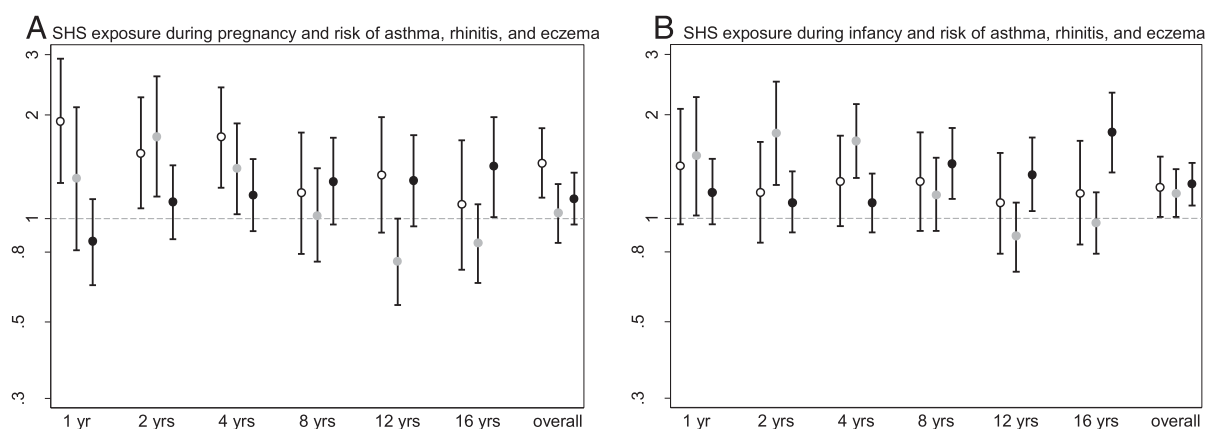
**FIGURE 1**

Prevalence of parental smoking from pregnancy to age 16 and children's own smoking at age 16 years among children in the BAMSE birth cohort ($n = 3798$). *Information on fathers' smoking habits during pregnancy was not collected.

excess risks for eczema were found primarily as children reached adolescence. Exposure to parental smoking during infancy (Fig 2B) was associated with an overall elevated risk of prevalent asthma (OR = 1.23; 95% CI, 1.01–1.51), rhinitis (OR = 1.18; 95% CI, 1.01–1.39), and eczema (OR = 1.26; 95% CI, 1.09–1.45). Similar associations were observed for incident asthma, rhinitis, and eczema (Supplemental Fig 3B). The age-specific associations resembled the pattern for in utero exposure.

Analyses of the effect of SHS exposure throughout childhood indicated a positive overall association with prevalent eczema (OR = 1.14; 95% CI, 1.01–1.29), but no significant associations were observed for asthma (OR = 1.07; 95% CI, 0.89–1.28) or rhinitis (OR = 1.03; 95% CI, 0.90–1.18). Inclusion of maternal smoking in utero in the model had no major influence on the observed association between parental smoking and prevalent eczema (OR = 1.12; 95% CI, 0.98–1.27).

When in utero exposure was adjusted for parental smoking throughout childhood, prevalent and incident asthma remained statistically significant (OR = 1.45; 95% CI, 1.12–1.87 and OR = 1.34; 95% CI, 1.04–1.73, respectively), but no significant associations were observed for rhinitis or eczema (Table 2). After adjustment for parental smoking throughout childhood in the analyses of SHS exposure during infancy, elevated risks for prevalent asthma, rhinitis, and eczema remained apparent.

**FIGURE 2**

Association between exposure to SHS during pregnancy or infancy and prevalent asthma, rhinitis, and eczema during the first 16 years of life among children in the BAMSE birth cohort ($n = 3798$). Adjusted for gender, parental allergic disease, and socioeconomic status. ○, Asthma; ◐, Rhinitis; ●, Eczema.

TABLE 2 Maternal Smoking During Pregnancy or Parental Smoking During Infancy and Overall Risk of Developing Asthma, Rhinitis, or Eczema up to 16 y of Age Among Children in the BAMSE Birth Cohort (*n* = 3798)^a

	Maternal Smoking During Pregnancy ^b		Parental Smoking During Infancy ^b	
	Prevalent Cases	Incident Cases	Prevalent Cases	Incident Cases
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Asthma	1.45 (1.12–1.87)	1.34 (1.04–1.73)	1.26 (0.99–1.61)	1.10 (0.83–1.46)
Rhinitis	1.03 (0.84–1.27)	1.08 (0.88–1.33)	1.22 (1.02–1.46)	1.19 (0.98–1.45)
Eczema	1.07 (0.89–1.30)	0.99 (0.82–1.20)	1.24 (1.04–1.47)	1.03 (0.83–1.29)

^a ORs and 95% CIs obtained from generalized estimating equation analyses.

^b Adjusted for gender, parental allergic disease, socioeconomic status, and parental smoking throughout childhood.

We explored the dose–response association between SHS exposure in utero or infancy and development of asthma, rhinitis, and eczema (Table 3). The highest risk of asthma, rhinitis, and eczema up to 16 years were seen among children whose mothers smoked ≥ 10 cigarettes per day while pregnant. A significant trend was observed for asthma ($P_{\text{trend}} = .001$) but not for rhinitis ($P_{\text{trend}} = .34$) or eczema ($P_{\text{trend}} = .24$). Children had an elevated risk of rhinitis or eczema if either parent smoked ≥ 10 cigarettes per day in the child's first 2 months after birth. The trends for rhinitis ($P_{\text{trend}} = .008$) and eczema ($P_{\text{trend}} = .03$) were both significant.

In a sensitivity analysis, adjustment for area-level socioeconomic indicators and

birth weight did not influence the association between SHS exposure and the examined outcomes (data not shown). Additionally, we restricted our analyses to children born at term (≥ 37 weeks), but this had little influence on results. Because children of current or former smokers are more likely to begin smoking themselves,²¹ we additionally adjusted for children's own smoking at age 16 years, but the risk estimates were not affected to any major extent. Furthermore, we investigated possible effect modification by including interaction terms between SHS exposure in utero or during infancy and gender or allergic heredity, but none were statistically significant.

TABLE 3 SHS Exposure Intensity During Pregnancy or Infancy and Overall Risk of Prevalent Asthma, Rhinitis, or Eczema up to 16 y of Age Among Children in the BAMSE Birth Cohort (*n* = 3798)^a

	Maternal Smoking During Pregnancy ^b	Parental Smoking During Infancy ^b
	OR (95% CI)	OR (95% CI)
Asthma		
No smoking	Referent	Referent
Total of 1–9 cigarettes/d	1.19 (0.81–1.75)	1.27 (0.92–1.76)
Total of ≥ 10 cigarettes/d	1.68 (1.23–2.29)	1.25 (0.93–1.67)
	$P_{\text{trend}} = .001$	$P_{\text{trend}} = .10$
Rhinitis		
No smoking	Referent	Referent
Total of 1–9 cigarettes/d	0.81 (0.59–1.12)	1.07 (0.82–1.38)
Total of ≥ 10 cigarettes/d	1.21 (0.94–1.56)	1.35 (1.09–1.67)
	$P_{\text{trend}} = .34$	$P_{\text{trend}} = .008$
Eczema		
No smoking	Referent	Referent
Total of 1–9 cigarettes/d	0.92 (0.70–1.21)	1.22 (0.97–1.54)
Total of ≥ 10 cigarettes/d	1.19 (0.94–1.51)	1.25 (1.01–1.53)
	$P_{\text{trend}} = .24$	$P_{\text{trend}} = .03$

^a ORs and 95% CIs obtained from generalized estimating equation analyses.

^b Adjusted for gender, parental allergic disease, socioeconomic status, and parental smoking throughout childhood.

DISCUSSION

We provide evidence for an association between SHS exposure in utero and an elevated overall risk of asthma, but not rhinitis or eczema, over the first 16 years of life. The association remained after adjustment for parental smoking throughout childhood, and a dose–response relationship was observed. Exposure to SHS during infancy was associated with an elevated overall risk of asthma, rhinitis, and eczema. A dose–response association was noted for rhinitis and eczema. Age-specific analyses suggested that the effect of SHS exposure was most pronounced for asthma up to 4 years of age. For rhinitis, the strongest associations appeared in ages 1 through 4, whereas for eczema the excess risks were seen primarily for ages eight through 16.

Strengths of this study include its prospective and population-based design, large sample size, limited loss to follow-up, and detailed repeated assessment of SHS exposure and symptoms of allergic disease. Moreover, information on in utero and infancy exposure was collected in the few months after delivery, reducing the risk of a child's disease status influencing parental answers on smoking status.

Some limitations of this study deserve mention. Because the information was gathered via parental questionnaires, some exposure misclassification is likely. Regarding SHS exposure, parents may underreport smoking habits, especially in the context of children's exposure, because of the known negative effects of tobacco smoke. However, self-reported data are comparable with cord blood, urinary cotinine, or indoor air nicotine measurements.^{22,23} Additionally, exposure information was collected at baseline, before onset of disease symptoms. Thus, any misclassification is likely to be nondifferential and would tend to underestimate the true association. Because asthma, rhinitis, and

eczema were assessed by parental questionnaires, misclassification of outcome could result from the heterogeneity of asthma, differing diagnostic practices among physicians, and parental recall. Results from a Dutch cohort showed that mothers who smoke appear to underuse health care for their children with respiratory symptoms.²⁴ This could potentially lead to differential misclassification, biasing our results toward the null. Furthermore, it is difficult to distinguish the effect of prenatal SHS exposure from the effect of postnatal SHS exposure because women who smoke during pregnancy are likely to continue after the child's birth.⁷

We observed an overall excess risk of asthma in children exposed to SHS in utero and from infancy up to 16 years. This is in line with a recent report from a German birth cohort, where maternal smoking during pregnancy was associated with asthma up to age 20 years using time-to-event analyses.²⁵ In our study, the influence of SHS exposure was strongest on asthma in preschool age, whereas there was no elevated risk for incident cases of asthma at later ages. Recent findings from an Australian birth cohort reported an elevated risk for current asthma at 14 years associated with maternal smoking during pregnancy,²⁶ which is not supported by our findings.

In utero SHS may contribute to the risk of asthma in children through a combination of changes in lung growth, airway responsiveness, and impaired adaptive immune response to viral pathogens.^{27,28} Animal studies have implicated nicotine, a key constituent of cigarettes, to increase collagen accumulation in airway and alveolar walls after in utero exposure.²⁹ A lessening effect of SHS exposure over time may indicate the critical effect of early cigarette smoke exposure on developing lungs. Alternatively, children spend less time with their parents

as they grow older, resulting in reduced exposure.

Current literature on SHS exposure and the development of rhinitis in children provides a mixed picture.^{12,13,30} Our findings indicated an elevated risk of rhinitis primarily related to postnatal SHS exposure, and this was limited to preschool-age children. This finding is partly in line with those of an international cross-sectional study that found that maternal and paternal smoking was associated with elevated risk of rhinitis symptoms in children.¹³ Moreover, the International Study of Asthma and Allergies in Childhood reported an elevated risk of rhinitis in children aged 9 to 11 years who had been exposed to in utero SHS.³¹ The waning risks for rhinitis in late childhood seen in our study are in line with the findings of a Danish cohort study that reported no association among 14- to 18-year-old children.¹²

Although the evidence for an association between early SHS exposure and eczema appears inconsistent,^{12,16,17,32} our results, suggesting an elevated risk of eczema in children exposed to SHS during infancy, are in accord with those of other studies.^{13,14,33} We observed the highest risks among school-age and adolescent children exposed to SHS during infancy, a finding similar to the results of a large international cross-sectional study.¹³ The occurrence of excess risks at later ages may have several explanations. First, it may reflect a shift in eczema phenotypes into a larger proportion of children with eczema in combination with allergic sensitization over time, because there is an increasing number of sensitized children in this cohort.³⁴ Furthermore, studies have indicated that SHS negatively affects skin barrier function, allowing the ingress of high-molecular weight structures such as allergens, bacteria, and viruses and thereby influencing the development of

eczema.^{35,36} Finally, postnatal parental smoking may contribute to eczema development by impairing immune function, and Tebow et al³⁷ found that parental smoking in childhood negatively affects interferon γ responses of school-age children.

In Sweden, nurses at antenatal and child health care clinics encourage parents to abstain from smoking. At the start of our cohort in 1994, the prevalence of smoking during pregnancy was around 17%, compared with about 5% currently.³⁸ In parallel, the prevalence of smoking among Swedish parents has decreased and is currently 11% among parents of 12-year-olds in a national sample.³⁹ A decreasing prevalence over time is also shown in our study. A ban on smoking in public places, primarily indoors, has been in place in Sweden since 2005, and children's SHS exposure in public places has decreased.³⁹ However, the prevalence of parental smoking at the latest follow-up of our cohort was 13.6%, and >4% of adolescents in this study smoked daily, and another 7% smoked occasionally. This indicates that there is still potential for decreasing the prevalence of smoking among parents and their offspring.

CONCLUSIONS

Our findings indicate that early life exposure to SHS, in utero or during infancy, have persistent adverse effects and influence the development of allergic disease up to adolescence. Excess risks for asthma and rhinitis were seen primarily in early childhood, whereas those for eczema occurred at later ages.

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