

Atopy in Danish children and adolescents: results from a longitudinal population study

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Background and objective: Atopy is an objectively measurable trait related to the presence of rhinitis and asthma, but our knowledge about its longitudinal predictors is limited. Data from a 6-year follow-up study of a population sample of children and adolescents ($n = 408$), aged 7 to 17 years at enrollment, were analyzed to investigate the prevalence and predictors of atopy.

Methods: Case history, including allergic diseases and smoking habits, was obtained by interview and questionnaire. Skin prick test reactivity to common allergens, total serum IgE, airway responsiveness, and pulmonary function were measured using standard techniques.

Results: The point prevalence of atopy increased from the first to the second survey, 26% and 44%, respectively; 23% of the participants had a positive skin prick test only at the second survey. Sensitization to house dust mite (HDM) ($P < .001$), grass ($P < .001$), dog ($P < .001$), cat ($P < .001$), and birch ($P = .02$) increased significantly in both males and females. No gender differences in the prevalence of positive reactions were found at the first survey, whereas atopy to grass ($P = .01$) and HDM ($P = .02$) were more prevalent in males than in females at the second survey. Confining the analysis to participants who were found to be non-atopic at the first survey showed that exposure to maternal smoking (OR 2, CI 1.3 to 3.1; $P = .002$), increased serum IgE (OR 1.7, CI 1.2 to 2.3; $P = .001$), new asthma (OR 1.6, CI 1.2 to 2.7; $P = .03$), and new rhinitis (OR 2.1, CI 1.2 to 3.6; $P = .01$), but not active smoking, were associated with an increased risk for the presence of a positive skin prick test at the second survey.

Conclusions: This longitudinal population study showed an increase in the point prevalence of atopy in Danish children and adolescents; and, furthermore, that exposure to maternal smoking during childhood, increased serum IgE, and new symptoms of asthma or rhinitis were associated with an increased risk for developing sensitization to common aeroallergens in late adolescence.

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INTRODUCTION

The association between atopy, and rhinitis, asthma and eczema is well established. Our knowledge about risk factors for sensitization to common aeroallergens is limited although a number of genetic and environmental

factors have been implicated. A family history of allergy predisposes to allergic diseases,¹ but a search for reliable genetic markers of atopy has so far been inconclusive.² Smith et al³ have recently reported that allergic disease in an adoptive mother increases the risk for asthma in the adoptee, which may suggest a complex interplay between heredity and maternal environment.

Over the past two decades, the reported prevalence of atopy and allergic diseases has increased dramatically in many countries.^{4–7} Such an increase over a relatively short period of time indicates that environmental factors, or an interplay between genetic susceptibility and environment, may be more

important than heredity. Longitudinal studies of environmental factors therefore remain critical in that they can provide us with the necessary evidence for future effective intervention trials.

Cigarette smoke is the most common indoor pollutant that children are exposed to, and maternal smoking is clearly a risk factor for the development of asthma in the first years of life.^{8–10} It appears, however, that the predominant effect of maternal smoking is due to in utero exposure leading to decreased pulmonary function at birth,¹¹ and the question of whether maternal cigarette smoking facilitates atopic sensitization is controversial.^{11–14} Furthermore, if exposure to parental tobacco smoke can induce or increase sensitization to allergens in children, it remains to be investigated if the effect of this exposure is seen throughout childhood and adolescence or, as has presently been reported, only in infancy and pre-school childhood.

The aim of this longitudinal population study of Danish children and adolescents was to describe the changes over time in prevalence of atopic sensitization and to investigate potential risk factors for the development of atopy. The sample was studied twice 6 years apart, using the same symptom questionnaire and methods for objective assessment of sensitization to common aeroallergens.

METHODS

A sample of 983 children and adolescents living in the area surrounding Rigshospitalet in the city of Copenhagen was drawn at random from the civil registration list.¹⁵ All subjects were born in the first week of each month, and had a mean age of 12 years (range, 7 to 17 years). At both surveys, performed 6 year apart, all subjects ($n = 983$) were invited by letter to a

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study concerning asthma, allergy, and airway hyperresponsiveness.

Of the 983 subjects, 527 (54%) participated in the first survey and 665 (68%) participated in the second survey; 408 subjects (199 boys and 209 girls) participated in both surveys. Only data for the 408 subjects who participated in both surveys are included in the present analysis.

The question of non-responder bias has been addressed in previous articles.^{16,17} Briefly, apart from a significantly higher number of current smokers among the subjects, who participated only in the second survey, no significant differences were found between the groups (ie, 'stayers', 'drop-outs, and 'newcomers') with respect to anthropometric data, pulmonary function, or prevalences of atopy, airway hyperresponsiveness, and allergic diseases, indicating that the subjects in the present analysis are representative of the entire sample; for further details see Ulrik and colleagues.^{16,17}

Exclusion Criteria

In case the participants were taking medication for asthma or allergy, they were asked not to use theophylline or an antihistamine for at least 24 hours, astemizole for 6 weeks, an oral β_2 -agonist for 18 hours, and an inhaled bronchodilator for 6 hours before the tests; long-acting β_2 -agonists were not available in Denmark at the time of the surveys. They were allowed to continue use of any inhaled or oral corticosteroid they had been taking.

Case History

The participants and, if present, their parents were interviewed by one person about diseases (respiratory and non-respiratory), active and passive smoking, use of medication, and known or suspected allergic disease and allergy.

Furthermore, all participants filled out a questionnaire about asthmatic (attacks of wheezing/shortness of breath with wheezing, chest tightness or dry cough) and allergic symptoms, that is rhinitis (sneezing, running or blocked not associated with a cold) and

eczema (an itchy dry rash on face, arms, or legs), as related to themselves, their siblings, and their parents.

Disposition to allergic disease was recorded if either one or both of the parents had a history, past or present, of asthma, allergic rhinitis, and/or atopic dermatitis. Furthermore, all participants reported whether they were current smokers, ex-smokers or never-smokers, and for the first two categories they reported the duration of smoking. Current and ex-smokers also reported their daily tobacco consumption (in g; one cigarette = 1 g), and an estimate of their lifetime tobacco exposure was calculated as pack-years [current tobacco consumption (g day⁻¹/20) × duration of smoking (yr)]. Smoking history (daily tobacco consumption and duration of smoking) was obtained for both parents and included in the analysis (as a dichotomous variable) as an estimate of passive tobacco exposure (for members of the participant's household only).

Skin Prick Test

Skin prick tests were performed on the volar surface of the forearm, using standard dilutions of allergens in 50% glycerol (ALK, Hørsholm, DK). The allergens used were birch, grass, mugwort, horse, dog, cat, house dust mite (*Dermatophagoides pteronyssinus*, at the second survey also *D. farinae*) and two molds (*Alternaria iridis* and *Cladosporium herbarum*). Histamine HCl (10 mg/mL) in 50% glycerol was used as a positive reference, and a negative reference (50% glycerol) was also included. The reactions were read after 15 to 20 minutes. The reaction to each of the allergens was regarded as positive if the mean wheal diameter [(d1 + d2)/2] was at least 3 mm.¹⁸ In case of reaction to the negative reference, a positive result was recorded when the difference between the mean wheal diameter of the reaction to the allergen and to the negative reference exceeded 3 mm. A positive skin prick test was defined as a positive reaction to at least one of the allergens.¹⁸ Atopy was defined as a positive skin prick test.

Serum IgE

The total serum IgE levels were determined by paper radioimmunosorbent test (PRIST, Pharmacia, Sweden). Determination of total IgE levels were only performed at the first survey.

Pulmonary Function Tests

The FEV₁ and forced vital capacity (FVC) were measured with a 7-L dry wedge spirometer (Vitalograph, Buckingham, UK), which was calibrated weekly. Each measurement consisted of at least three maximal expiratory maneuvers from total lung capacity to residual volume with a variation of less than 5%. The highest FEV₁ and FVC were used in the analyses. Data on pulmonary function were also expressed as a percentage of predicted values (%pred), using prediction equations based on age, sex, and height.¹⁹

Histamine Challenge Test

Airway responsiveness to inhaled histamine was measured using the method described by Cockcroft and colleagues.²⁰ Aerosols of the test solution were generated by a nebulizer (Wright; Aerosol Products, London, UK) operated to give an output of 0.14 mL/min. Each aerosol was inhaled through the mouth by tidal breathing for 2 minutes. The first aerosol was saline (0.9%), and it was followed at 4-minute intervals by twofold increasing concentrations of histamine (0.075 to 8.0 mg/mL). The response was measured by determining the FEV₁ 1 minute after each inhalation. The test was terminated when a >20% decline in FEV₁ from the postsaline value occurred, or at the end of the dose schedule if such a decline did not occur. For all subjects having at least 20% decline in FEV₁ by the end of the dose schedule, the concentration of histamine causing a 20% fall in FEV₁ (PC₂₀) was calculated by linear interpolation from the individual log dose-response curve as follows²¹: PC₂₀ = anti-log[logC₁ + logC₂](20 - R₁)/R₂ - R₁] where C₁ is the second-to-last concentration of histamine (<20% fall in FEV₁), C₂ is the last concentration of histamine (>20% fall), R₁ is the percent fall in FEV₁

(%fall FEV₁) after C₁, and R₂ is the percent fall in FEV₁ after C₂. A positive test was defined as a PC₂₀ FEV₁ of <8.0 mg of histamine per milliliter.

Statistical Methods

Unless stated otherwise, the prevalence figures given are the point prevalence rates at the time of the surveys. Changes in the proportion of subjects with a positive test/symptoms were assessed by means of McNemar's χ^2 test.

Logistic regression analysis were used to assess putative risk factors at the first survey in relation to outcome at the second examination, primarily to the presence or absence of a positive skin prick test, and non-significant variables were deleted by backward elimination. A *P* value less than .05 was considered significant.

RESULTS

Complete data were available for 408 subjects, 199 boys and 209 girls. Characteristics of the examined subjects are displayed in Table 1. Thirty-two percent of the participants were current smokers at the time of the second survey, and 80% of the participants had been exposed to parental smoking during childhood.

The point prevalence of atopy increased from the first to the second survey, 26% and 44%, respectively; 23% of the participants had a positive skin prick test only at the second survey (Fig 1).

The frequency of positive skin tests to each of the allergens at the two surveys is shown by gender in Fig 2; no gender differences in the prevalence of positive reactions were found at the first survey, whereas a positive skin reaction to both grass pollen (*P* = .01) and house dust mite (*P* = .02) was more prevalent in boys than in girls at the second survey.

A significant increase from the first to the second survey in the point prevalence of atopy to house dust mite (*P* < .001), grass pollen (*P* < .001), dog dander (*P* < .001), cat epithelium (*P* < .001), and birch pollen (*P* = .02) was observed in both boys and girls (Table 2), whereas the point preva-

Table 1. Characteristics of Population Sample Comprising 408 Subjects, 7 to 17 Years of Age at Enrollment, Examined Twice 6 Years Apart

	First Survey		Second Survey	
	Males (n = 199)	Females (n = 209)	Males (n = 199)	Females (n = 209)
Age, yr	12.1 (2.9)	12.5 (2.9)	18.1 (2.9)	18.5 (2.9)
Height, m	1.54 (0.18)	1.52 (0.14)	1.79 (0.09)	1.68 (0.06)
Smoking habits				
Never smokers, no.	189	188	143	125
Ex-smokers, no.	0	1	0	10
Current smokers, no. (Pack-yr)	10 [5] —	20 [10] —	56 [28] (2.8) (2.0)	74 [35] (2.1) (1.8)
Parental smoking habits				
Maternal smoking	—	—	112 [56]	116 [56]
Paternal smoking	—	—	136 [68]	127 [61]

* (Standard deviations) and [percentages] in parentheses.

lences of atopy to mugwort, horse, Alternaria, and Cladosporium were unchanged or declined.

The results of the multiple logistic regression analysis predicting the presence or absence of atopy, ie, a positive skin prick test, at the second survey as a function of variables measured at the first survey and changes in these variables during the observation period are shown in Table 3. The longitudinal multiple logistic regression analysis did not reveal a significant association between gender, age, birth weight, breast feeding, month of birth, disposition to allergic disease, tobacco ex-

posure (active or passive), a history of wheezy bronchitis before the age of 2 years self-reported eczema, or airway hyperresponsiveness at the first survey and the presence of atopy at the second survey.

To investigate further the association between potential risk factors measured at the first survey and changes in these risk factors during the observation period and the presence or absence of atopy at the second survey, the data were reanalyzed after exclusion of subjects with atopy, ie, positive skin prick test, at the first survey. This analysis revealed that exposure to ma-

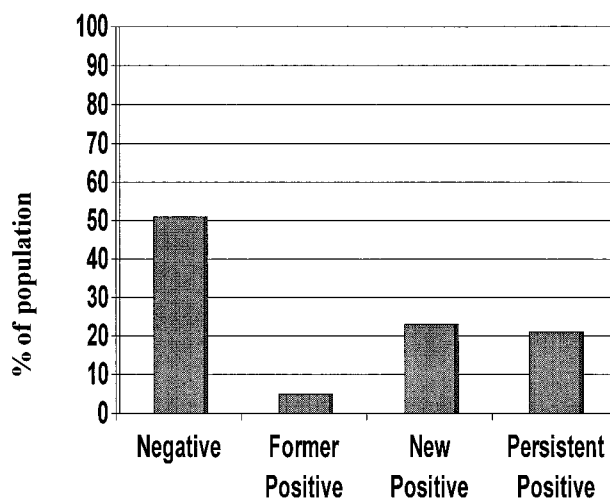


Figure 1. Distribution of skin prick test reactivity in population sample comprising 408 subjects, 7 to 17 years of age at enrollment, examined twice 6 years apart.

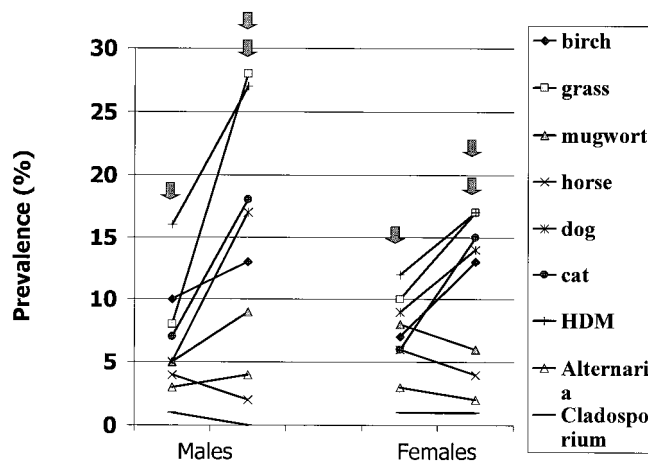


Figure 2. Point prevalence (%) of positive skin reactions to common aeroallergens by gender in population sample comprising 408 subjects, 7 to 17 years of age at enrollment, examined twice (— = first survey and —○— = second survey) 6 years apart.

Table 2. Point Prevalences of Atopy, Asthma, Eczema, Rhinitis, and Airway Hyperresponsiveness in the Population Sample Comprising 408 Subjects

	First survey		Second survey	
	Males (n = 199)	Females (n = 209)	Males (n = 199)	Females (n = 209)
Atopy, no. (%) [*]	55 (28)§	51 (24)§	96 (48)§	82 (39)§
Rhinitis, no. (%)	27 (14)‡	31 (15)‡	46 (23)‡	44 (21)‡
Asthma, no. (%)	12 (6)§	10 (5)§	30 (15)§	31 (15)§
Eczema, no. (%)	12 (6)	15 (7)‡	18 (9)	28 (13)‡
AHR†, no. (%)	44 (22)‡	36 (17)‡	10 (5)‡	14 (7)‡

* Positive skin prick test, † airway hyperresponsiveness, ‡ $P < .001$, and § $P < .01$ (χ^2 -test).

Table 3. Longitudinal Multiple Logistic Regression Analysis Predicting Atopy^{*}

	Odds Ratio	95% Confidence Interval	P Value
Atopy, first survey	1.6	1.1–2.3	.008
Log serum IgE	1.4	1.1–1.7	.013
Persistent asthma	1.5	1.1–2.0	.04
New asthma	1.5	1.1–2.0	.01
Persistent rhinitis	1.7	1.1–2.7	.02
New rhinitis	1.7	1.1–2.6	.01

* A positive skin prick test at the second survey as a function of variables measured at the first survey and changes in these variables. The sample comprised 408 subjects (7 to 17 years of age at enrollment) examined twice, 6 years apart.

teral smoking during childhood (OR 2.0, CI 1.3 to 3.1; $P = .002$), increased total serum IgE (OR 1.7, CI 1.2–2.3; $P = .001$), new asthma (OR 1.6, CI 1.2–2.7; $P = .03$), and new rhinitis (OR 2.1, CI 1.2–3.6; $P = .01$), but not active smoking, were associated with

an increased risk for having a positive skin prick test at the second survey.

DISCUSSION

This longitudinal population study of children and adolescents revealed an increase with age in the point preva-

lence of sensitization to common aeroallergens; and, furthermore, that, in participants who were found to be non-atopic at the time of enrollment, exposure to maternal smoking during childhood, increased total serum IgE, and new symptoms of asthma or rhinitis were associated with an increased risk for having a positive skin prick test at the time of the second survey.

The present study design does not permit a valid conclusion concerning the question of whether or not the prevalence of atopy has increased in Danish children and adolescents. The observation of an increase in the prevalence of atopy from the first to the second survey most likely reflects the age-related change in the prevalence of atopy, ie, the natural history of sensitization to common aeroallergens.

The question of whether maternal smoking can alter the response to allergen exposure is controversial.¹¹ The present study revealed an association between exposure to maternal smoking during childhood and subsequent development of sensitization to common aeroallergens in late adolescence, whereas we found no association between a history of wheezy bronchitis during the first 2 years of life, birth weight and breast feeding, and later development of a positive skin prick test. Some longitudinal studies of infants and small children have reported an association between exposure to parental smoking and atopy,^{13,22–24} while a Norwegian cross-sectional study of older children (mean age 9.5 years) reported that postnatal maternal smoking increases the prevalence of asthma but not of atopy and airway hyperresponsiveness in the offspring.¹⁴ The apparent discrepancies between the findings could be due to differences in study design, longitudinal versus cross-sectional, but another possible explanation could be that smoke exposure facilitates allergic sensitization only very early in life. The present longitudinal study shows, in contrast to previous published reports, that maternal smoking may also facilitate sensitization to common aeroallergens in older children and adolescents (mean

age of the participants at the first survey 12 years). Our findings therefore may indicate that it should be possible, through counseling parents with regard to smoking habits, to reduce the risk for atopic sensitization in adolescents, and by that possibly future development of asthma and allergic diseases.

Iversen et al²⁵ have previously reported an increased risk for sensitization to house dust mites and animals with fur in smoking farmers. This study did not reveal a significant association between active smoking and risk for atopic sensitization. The lack of association could be caused by a combination of misclassification of participants as nonsmokers due to selective underreporting of active smoking and the participants relatively low active life-time tobacco exposure.

REFERENCES

- Räsänen M, Laitinen T, Kaprio J, et al. Hay fever—a Finnish nation-wide study of adolescent twins and their parents. *Allergy* 1998;53:885–890.
- Hopkin JM. Genetics of atopy. *Pediatr Allergy Immunol* 1995;6:139–144.
- Smith JM, Cadoret RJ, Burns TL, Troughton EP. Asthma and allergic rhinitis in adoptees and their adoptive parents. *Ann Allergy Asthma Immunol* 1998;81:135–139.
- Magnus P, Jaakkola JJK. Secular trends in the occurrence of asthma among children and young adults: critical appraisal of repeated cross sectional surveys. *Br Med J* 1997;314:1795–1799.
- Robertson CF, Heycock E, Bishop J, et al. Prevalence of asthma in Melbourne schoolchildren: changes over 26 years. *Br Med J* 1991;302:1116–1118.
- Omran M, Russel G. Continuing increase in respiratory symptoms and atopy in Aberdeen schoolchildren. *Br Med J* 1996;312:34–37.
- Mutius Ev, Weiland SK, Fritzsche C, et al. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet* 1998;351:862–866.
- Bisgaard H, Dalgaard P, Nyboe J. Risk factors for wheezing during infancy. A study of 5953 infants. *Acta Paediatr Scand* 1987;76:719–726.
- Halken S, Høst A, Husby S, et al. Recurrent wheezing in relation to environmental risk factors in infancy. *Allergy* 1991;46:507–514.
- Infante-Rivard C. Childhood asthma and indoor environmental risk factors. *Am J Epidemiol* 1993;137:834–844.
- Weiss ST. Environmental risk factors in childhood asthma. *Clin Exp Allergy* 1998;28:29–34.
- Tariq SM, Matthews SM, Hakim EA, et al. The prevalence of and risk factors for atopy in early childhood: A whole population birth cohort study. *J Allergy Clin Immunol* 1998;101:587–593.
- Wickman M, Nordval SL, Pershagen G. Risk factors in early childhood for sensitization to airborne allergens. *Pediatr Allergy Immunol* 1992;3:128–133.
- Søyseth V, Kongerud J, Boe J. Postnatal maternal smoking increases the prevalence of asthma but not of bronchial hyperresponsiveness or atopy in their children. *Chest* 1995;107:389–394.
- Backer V. Bronchial hyperresponsiveness in children and adolescents (thesis). *Dan Med Bull* 1995;42:397–409.
- Ulrik CS, Backer V, Hesse B, Dirksen A. Risk factors for development of asthma in children and adolescents: findings from a longitudinal population study. *Respir Med* 1996;90:623–630.
- Ulrik CS, Backer V. Increased bronchial responsiveness to exercise as a risk factor for symptomatic asthma: findings from a longitudinal population study of children and adolescents. *Eur Respir J* 1996;9:1696–1700.
- Dreborg S. The Skin Prick Test: Methodological Studies and Clinical Applications. Medical Dissertation No. 239, 1987. Linköping, Sweden, 1–148.
- Nysom K, Ulrik CS, Hesse B, Dirksen A. Published models and local data can bridge the gap between reference values of lung function for children and adults. *Eur Respir J* 1997;10:1591–1598.
- Cockcroft DW, Killian KN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977;7:235–243.
- Juniper EF, Cockcroft DW, Hargreave FE. Histamine and Methacholine Tests: Tidal Breathing Method, Laboratory Procedure and Standardization. *Can Thorac Soc* 1991;28.
- Ronchetti R, Bonci E, Cutrera R, et al. Enhanced allergic sensitization related to parental smoking. *Arch Dis Child* 1992;67:496–500.
- Kulig M, Luck W, Lau S, et al. Effect of pre- and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first 3 years of life. *Allergy* 1999;54:220–228.
- Weiss ST, Tager IB, Munoz A, Speitzer FE. The relationship of respiratory infections in early childhood to the occurrence of increased levels of bronchial responsiveness and atopy. *Am Rev Respir Dis* 1985;131:573–578.
- Iversen M, Pedersen B. The prevalence of allergy in Danish farmers. *Allergy* 1990;45:347–353.

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