
Change in prevalence of asthma in Danish children and adolescents

Simon F. Thomsen, MD*; Charlotte S. Ulrik, MD, DMSci†; Klaus Larsen, MSc, PhD‡; and Vibeke Backer, MD, DMSci*

Background: There is evidence suggesting that the prevalence of asthma has increased, especially in industrialized countries.

Objective: To investigate whether the prevalence of asthma in Danish children and adolescents has changed during the past 15 years.

Methods: Serial cross-sectional studies of 2 different random population samples of children aged 7 to 17 years, living in urban Copenhagen, Denmark, were performed 15 years apart. The first cohort was investigated in 1986 (n = 527) and the second in 2001 (n = 480). The same methods were applied at both occasions. Skin test reactivity was measured using standard techniques. Asthma was defined on the basis of questionnaire responses and was regarded as nonatopic (intrinsic) if no positive reactions were observed on the skin test and as atopic (extrinsic) if at least 1 positive reaction was noted. Current asthma was defined as symptoms within the preceding 12 months.

Results: The prevalence of current asthma increased from 5.3% in 1986 to 11.7% in 2001. This was primarily due to an increase in intrinsic asthma, which was 4.2-fold (1.5% to 6.4%), compared with extrinsic asthma, which increased only 1.4-fold (3.8% to 5.5%). The changes were more pronounced in girls.

Conclusions: The prevalence of asthma has increased substantially during the past 15 years. The observed striking increase in intrinsic asthma suggests the possibility of a more heterogeneous disorder, involving more important factors than atopy. Furthermore, our findings suggest that asthma might be shifting toward female predominance in childhood.

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INTRODUCTION

Several studies have reported an increase in the prevalence of asthma during the past decades, especially in industrialized countries and in children and adolescents.^{1–4} Despite large reported regional differences worldwide, there is nevertheless a consistent reporting of an increase in wheezing illness.

Furthermore, most asthmatic cases among children and adolescents are often imputed to atopy, and the prevalence of asthma seems to be correlated with skin test reactivity to allergens and levels of serum IgE.^{5,6} Some reports, however, suggest that the proportion of asthma cases attributable to atopy may have been overestimated and that this could have led to underrecognition of other possible etiological mechanisms for asthma.⁷ Also, it is known that the proportion of boys with asthma is greater in early childhood compared with girls and that this sex difference diminishes with increasing age due to boys becoming less frequent wheezers and girls beginning to wheeze at a later age.^{8,9}

This study aimed to determine whether there has been a change in the prevalence of current asthma among Danish

children and adolescents aged 7 to 17 years. We studied 2 different and independent population samples interspaced by 15 years.

METHODS

Subjects

Two different random samples of children and adolescents were studied. All subjects lived in the area surrounding the National University Hospital (Rigshospitalet) in urban Copenhagen, Denmark. The first study population was examined in 1986¹⁰ and the second in 2001. All subjects were drawn at random from the civil registration list before each study. All were born in the first week of each month and were white. The mean age of the subjects was 12 years (age range, 7–17 years). At both occasions, subjects were invited by letter to participate in a study concerning asthma and allergy.

In 1986 and 2001, a total of 1,000 and 1,500 subjects, respectively, were mailed a written invitation. Due to incorrect information on postal addresses, only 983 and 1,440 subjects were eligible for participation in 1986 and 2001, respectively. In 1986, 527 (53.6%) participated in the survey, including 262 boys (49.7%), whereas in 2001, 480 (33.3%) agreed to participate, including 222 boys (46.3%). We chose to include 1,500 subjects in 2001 instead of 1,000, which was the projected number in 1986. The reason for this was and still is a declining willingness to participate in clinical studies in Denmark. In that regard, we wanted to make sure that we obtained enough children with complete questionnaire data and skin test results to estimate differences in asthma rates.

* Department of Internal Medicine, Bispebjerg Hospital, Copenhagen, Denmark.

† Department of Respiratory Medicine, Hvidovre Hospital, Copenhagen, Denmark.

‡ Clinical Research Unit, Hvidovre Hospital, Copenhagen, Denmark.

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Due to the low number of participants, we conducted interviews with an identical questionnaire by telephone among 100 and 116 randomly selected subjects from the group of nonresponders in 1986 and 2001, respectively, to ensure the robustness of the sampled population. For every household, the interview was performed with the child, and subsequently a parent was consulted to reach consensus. The subjects interviewed by telephone did not differ significantly from the subjects originally included with respect to sex, age, disposition to atopy, or symptoms that met the criteria for a diagnosis of asthma, but at both occasions there were significantly fewer children with atopy among the group of nonresponders.¹¹ We chose not to include the additional children interviewed by telephone in the final analyses, since skin prick test results were not obtained. Evaluation of the age- and sex-specific participation rates in the 2 cohorts revealed a similar pattern, which provides us with a rationale for comparing asthma prevalence rates between the 2 cohorts without adjusting for these variables.

Questionnaire

All participants were interviewed by one of the authors (V.B. or S.F.T.) by means of an identical questionnaire concerning respiratory symptoms at both occasions, and the accompanying parent was consulted to obtain agreement. The definition of asthma was adopted from the American Thoracic Society, Division of Lung Disease of the National Heart, Lung, and Blood Institute,^{12,13} and Hopp et al.¹⁴ The validity of the questionnaire to determine the presence of asthma has been reported in detail elsewhere.^{15,16} Asthma was defined by questionnaire criteria based on responses to the following questions: (1) Have you ever had asthma? (2) Does your breathing ever sound wheezy or whistling? (3) Do you ever have attacks of shortness of breath with wheezing? (4) Do you experience wheezing, chest tightness, cough, or breathlessness with any of the following: at rest, with exertion, with emotional stress, with exposure to cold air, or with chest infections or head cold? (5) Do you experience wheezing after exposure to: dust, fumes, molds, pollen, food, pets, or drugs? (6) Have you ever been hospitalized or observed and treated by a doctor for asthma? (7) Have you ever received medication for your asthma? (8) What was the medication used? (9) Did it help? (10) How many attacks of wheezing have you had during the last year? (11) Have you ever had attacks of wheezing, shortness of breath, or dry cough at night? Asthma was defined on the basis of positive responses to questions 2, 3, 4, and/or 5. Current asthma was defined as attacks of shortness of breath with wheezing within the preceding 12 months in addition to positive responses to questions 2, 3, 4, and/or 5. Asthma was regarded as extrinsic if it was associated with at least 1 positive reaction on the skin prick test and as intrinsic if no positive responses were noted.

Skin Prick Tests

Skin prick tests were performed using standard dilutions of 10 common aeroallergens. The allergens used were birch,

grass, mugwort, horse, dog, cat, house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), and 2 molds (*Alternaria iridis* and *Cladosporium herbarium*), with positive and negative references being histamine, 10 mg/mL, in 50% glycerol and glycerol, 50%, respectively. The allergens used were identical apart from *D. farinae*, which was not used in 1986. Reactions were read after 15 minutes. A positive test result was defined as a positive reaction to at least one of the allergens. The reaction to each of the allergens was regarded as positive if the mean wheal diameter $[(D1 + D2) \times \frac{1}{2}]$ was at least 3 mm.¹⁷ The participants were told to stop using medications that contained antihistamine at least 3 days before skin testing.

Statistical Analysis

Data were analyzed with the statistical package R.¹⁸ We applied logistic regression modeling to investigate associations between risk factors for having asthma. We included cohort (being examined in 1986 or 2001), atopy (positive or negative skin prick test result), age (7–12 years or 13–17 years), sex, and body mass index (BMI) as explanatory variables and asthma as the response variable. A model with main effect of age, atopy, and cohort provided the best fit to the data. The results are reported as odds ratios (ORs). $P < .05$ was considered statistically significant. Only subjects who had skin prick test results were included in the analyses, and a further 15 subjects were excluded from the analyses of BMI, since data on height and weight were not obtained. BMI was calculated as weight in kilograms divided by the square of height in meters. The protocol was evaluated and approved by the local ethical committee, and informed consent was obtained from all participating subjects and their parents.

RESULTS

Questionnaire data were available for all 527 and 480 subjects in 1986 and 2001, respectively. Skin test reactivity was measured for 519 subjects (98%) in 1986 and for 470 (98%) in 2001. We observed no significant differences in sex, age, height, weight, or BMI between 1986 and 2001 when comparing the 2 studied populations (Table 1). In 1986, none of the asthmatic patients were either current or ever smokers, whereas in 2001, 2 of the subjects with asthma were current smokers. The results of the logistic regression analysis are presented in Table 2. We found that year of examination, having a positive skin prick test result, and being in the age group 7 to 12 years were independent risk factors for asthma. On the contrary, we did not find a statistically significant impact of sex and BMI on asthma. Further, we did not find any statistically significant differential effect of atopy or age on asthma when comparing the 2 cohorts.

When looking at the specific prevalence rates for asthma, a substantial increase was observed during the intervening 15-year period from 1986 to 2001. In 1986, 28 subjects (5.3%) were classified as having current asthma. Among boys, 17 (6.5%) fulfilled the criteria for current asthma, as did 11 (4.2%) of the girls. In 2001, we found 56 subjects (11.7%)

Table 1. Comparison of Cohorts Studied in 1986 and 2001 with Respect to Sex and Anthropometrical Values

	1986 (n = 527)	2001 (n = 480)	Difference (95% CI)	P value
Boys, No. (%)	262 (49.7)	222 (46.3)	-3.5 (-9.6 to 2.7)	.30
Girls, No. (%)	265 (50.3)	258 (53.8)	3.5 (-2.7 to 9.6)	.30
Age, y*	12.2	12.1	-0.1 (-0.24 to 0.46)	.54
Height, cm*	153.3	152.1	-1.2 (-0.72 to 2.93)	.22
Weight, kg*	45.6	45.1	-0.5 (-0.9 to 2.3)	.55
BMI*	18.8	19.0	0.2 (-0.2 to 0.56)	.36

Abbreviations: BMI, body mass index; CI, confidence interval.

* Geometric mean values.

Table 2. Associations between Explanatory Variables and Risk for Current Asthma among Danish Children Aged 7 to 17 Years

	χ^2 test (df)	OR	P value
Cohort	16.02 (1)		<.001
1986		1	
2001		2.7	
Atopy	54.91 (1)		<.001
Negative skin test result		1	
Positive skin test result		6.2	
Age, y	5.35 (1)		.02
7-12		1.8	
13-17		1	
Sex	0.18 (1)		.67
BMI	1.68 (1)		.20
Differential effect of atopy on asthma in the 2 cohorts	2.11 (1)		.15
Differential effect of age on asthma in the 2 cohorts	0.29 (1)		.59

Abbreviations: BMI, body mass index; OR, odds ratio.

with current asthma. Among those, 24 (10.8%) were boys and 32 (12.4%) were girls (Table 3). Dividing the participants into 2 age groups, 7 to 12 years and 13 to 17 years, respectively, showed that the prevalence of asthma in girls increased from 3.6% to 13.9% in the younger age group, whereas it increased from 4.8% to 10.5% in the older age group. In boys, the prevalence of asthma increased only from 8.0% to 12.5% and 4.0% to 7.1%, respectively, in the younger and the older age groups (Table 3).

Table 3. Change in Prevalence of Current Asthma among Danish Children Aged 7 to 17 Years between 1986 and 2001

	No. (%) of children	
	1986	2001
Asthma (total)	28/527 (5.3)	56/480 (11.7)
Boys	17/262 (6.5)	24/222 (10.8)
7-12 years	13/162 (8.0)	19/152 (12.5)
13-17 years	4/100 (4.0)	5/70 (7.1)
Girls	11/265 (4.2)	32/258 (12.4)
7-12 years	5/140 (3.6)	20/144 (13.9)
13-17 years	6/125 (4.8)	12/114 (10.5)

The prevalence of subjects with asthma in relation to atopic status is shown in Table 4. Although we did not find a statistically significant differential effect of atopy on asthma when comparing the 2 cohorts, a pronounced increase was seen in the prevalence of nonatopic (intrinsic) asthma from 1.5% in 1986 to 6.4% in 2001, whereas the rates for atopic (extrinsic) asthma only showed minor changes (ie, from 3.8% to 5.5%). In 1986, 28% of the asthmatic patients had a negative skin prick test result, whereas 54% had so in 2001. The number of subjects with a positive reaction on the skin prick test in 1986 [125 of 519 (24.1%)] did not differ significantly from 2001 [91 of 470 (19.4%); difference, 4.7; 95% confidence interval (CI), -0.4 to 9.9; $P = .09$]. The fraction of subjects with a negative reaction to the histamine control in 1986 was 24 (4.6%) of 519 compared with 14 (3.0%) of 470 in 2001 (difference, 1.6; 95% CI, -0.7 to 4.0; $P = .24$), which we interpret as evidence against a selection of children in 2001 with a false-negative test result (ie, taking drugs containing antihistamine). Only 2 subjects had a positive skin prick test result due to a solitary reaction to *D farinae*, which was used for testing in 2001 only.

DISCUSSION

The main finding of this study was a 2.2-fold increase in the prevalence of current asthma among children and adolescents from 1986 to 2001. This was primarily due to an increase among girls. Previously, it has been shown that the male-to-female ratio for the prevalence of asthma symptoms decreases with rising age and shifts toward a female predominance in late adolescence and early adulthood.^{8,9} Our data suggest that this shift may already take place in middle to late

Table 4. Change in Prevalence of Current Intrinsic and Extrinsic Asthma among Danish Children Aged 7 to 17 Years between 1986 and 2001

	No (%) of children	
	1986	2001
Intrinsic asthma (total)	8/523 (1.5)	30/470 (6.4)
Boys	4/257 (1.6)	11/218 (5.0)
Girls	4/262 (1.5)	19/252 (7.5)
Extrinsic asthma (total)	20/523 (3.8)	26/470 (5.5)
Boys	13/257 (5.1)	13/218 (6.0)
Girls	7/262 (2.7)	13/252 (5.2)

childhood. In 1986, we found a male-to-female ratio for asthma of 1.6, and in 2001 this ratio had reversed, being only 0.9. Further, we found a more pronounced increase in asthma prevalence among girls in the age group 7 to 12 years compared with boys of the same age. The incidence of asthma among girls must therefore surpass that of boys at an earlier age than this.

Some studies support this hypothesis and question whether asthma really is more prevalent among boys in the younger age groups. Fagan et al¹⁹ demonstrated a significantly higher prevalence of current asthma among girls than boys (age range of studied cohort, 13–18 years). In addition, some studies indicate that asthma might previously have been unrecognized and unreported in girls.^{20,21} This lack of a sex difference in asthma prevalence may, as noted in the previously mentioned studies, be due to sex-specific symptoms, suggesting that girls may have more nonspecific symptoms of asthma, such as chronic night cough, whereas boys more often experience wheezing.^{20,21} Because our definition of asthma uses emphasis on attacks of wheezing and shortness of breath and relies only to a small extent on more nonspecific symptoms, such as chest tightness and cough, there could be a tendency to overlook a subgroup of asthmatic patients who only experience nonspecific symptoms, especially in girls in early-to-middle childhood. Also, there could be a tendency toward underdiagnosis of asthma in boys, since there is evidence that girls are better at reporting symptoms than boys, when using the self-administered International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.²² However, only a faint parallel can be drawn, since we did not use the ISAAC questionnaire and the questionnaire used in our study was completed by the physician on the basis of answers given by the child or adolescent and the parent and hence was not self-administered.

A methodological limitation of the study when interpreting the data is the potential spurious results that arise from the low response rates. We attempted to correct for this by conducting additional telephone interviews among the nonresponders. This approach enhanced the robustness of the data, but we did not collect information on skin prick test status of the nonresponders. Neither did we obtain data on socioeconomic status of both the responders and the nonresponders, which would have further increased interpretability. On that behalf, we cannot entirely count out that at least part of the observed changes in asthma prevalence may be due to selection bias.

Furthermore, we are aware of the fact that a further portion of the observed increase in prevalence rates, as proposed by Magnus and Jaakkola,²³ may be due to an enhanced awareness of symptoms as a consequence of asthma being discussed extensively in public and physicians giving better information. This could shift the emphasis from feeling well toward recognizing and aggravating natural sensations of breathing, resulting in a downward shift in tolerance of mild respiratory symptoms. Additionally, the word *wheezing* may

have been used and understood differently over time and among different social groups.

Asthma symptoms are reported to be associated with increasing BMI in middle and late childhood among girls,²⁴ and a linear relation has been reported between the prevalence of asthma and increasing BMI in females 12 years and older.²⁵ We noted a tendency toward higher BMIs from 1986 to 2001, which, however, were not statistically significant among asthmatic girls. Also, the mean values of BMI were not indicative of overweight. We do therefore not believe that changes in BMI can explain the increase in asthma prevalence in our survey.

We looked at the relationship between asthma and atopy and defined asthma as being either extrinsic or intrinsic. We found that the observed increase in the prevalence of asthma was greater among subjects with intrinsic asthma (4.2-fold) compared with subjects with extrinsic asthma (1.4-fold). We therefore observed a change in the ratio of extrinsic to intrinsic asthma from 2.5 to 0.9 in 1986 and 2001, respectively. This finding is not in keeping with the previously proposed hypothesis that asthma is primarily related to atopy.^{26–28} Similar findings have been reported in another study from Scandinavia in which a more pronounced increase in the prevalence of non-atopy-related asthma was observed, being indicative of an increased prevalence of exposures that influence the occurrence of respiratory symptoms without affecting the etiology of hay fever or eczema.²⁹ Furthermore, in a comparative study of the prevalence of asthma and atopy among 9- to 11-year-old children in Albania and the United Kingdom, it has been demonstrated that large variations in the prevalence of asthma can occur without differences in the frequency of atopy.^{30,31} Also, in a systematic review of population-based surveys, it has been shown that only a weak and inconsistent association exists between the prevalence of asthma and atopy and that the proportion of asthmatic cases that are attributable to atopy may not exceed 50%.⁷ In addition to this, recent evidence has been presented that inflammatory mechanisms other than eosinophilic inflammation may be involved in producing the final common pathway of enhanced bronchial reactivity and reversible airflow obstruction that characterizes asthma, suggesting that allergic mechanisms may not be the only and/or the most important underlying mechanism for asthma.³⁰ In line with this, it has been shown that various nonallergic exposures, such as particulate air pollution, bacterial endotoxin, viral infections, and ozone, are able to induce airway inflammation and symptoms of asthma.³⁰ Also, Stein et al³² have reported that, up to the age of 13 years, infection with respiratory syncytial virus in the first years of life is an independent risk factor for the development of wheezing and is not related to atopic status.

However, in a study by Burrows et al,⁵ the concept of dividing asthma into extrinsic and intrinsic phenotypes is challenged. This is based on the observation that the prevalence of asthma is correlated to the level of serum IgE irrespective of the subject being atopic or nonatopic, as judged by skin test reactivity, and that no asthma is found

among subjects with extremely low IgE levels. These findings might indicate that most asthma is related to some type of IgE-related reaction and thus has an allergic basis. Unfortunately, we did not measure the levels of serum IgE or the presence of eosinophils in the airways among our subjects; thus, our conclusions with respect to this are merely speculative. However, irrespective of the definition, our observation of a relatively large proportion of subjects with intrinsic asthma may point to other substances than those tested with the skin prick test (perhaps able to elicit an IgE response) as the cause of the increase in asthma prevalence. These might be substances encountered in an environment associated with western lifestyle involving dietary factors, increased fetal growth, smaller family size, reduced number of infections, and increased use of antibiotics.³³

Dividing asthma into intrinsic and extrinsic phenotypes identifies a group of adult asthmatic patients with intrinsic asthma who probably have a poorer prognosis, including a more rapid decline in lung function.³⁴ This, too, underlines the importance of not only focusing on asthma as an atopic disease but also pointing to the possibility of a more heterogeneous disorder, which, based on our findings, may be shifting toward female predominance in childhood.

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- Requests for reprints should be addressed to:*
Simon F. Thomsen, MD
Department of Internal Medicine I
Bispebjerg Hospital
DK-2400 Copenhagen NV, Denmark
E-mail: sft@city.dk
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