

Original article

Severe asthma in childhood: assessed in 10 year olds in a birth cohort study*

Background: Limited information is available regarding the prevalence of severe asthma in children. The present study aimed at investigating the prevalence of severe asthma in an urban child population; secondarily evaluating the applicability of the chosen definition by clinical characteristics.

Methods: Children enrolled in the prospective birth cohort; the Environment and Childhood Asthma Study in Oslo; were reinvestigated at the age of 10 years ($n = 1019$). A representative population based cohort of 616 children [mean age 10.9 (SD 0.9) years] with lung function measurements at birth was used for prevalence estimates, whereas all 1019 children (154 with current asthma) attending the 10-year follow-up were included for verification of the definition of severe asthma. Clinical investigations included spirometry, tests of bronchial hyperresponsiveness, skin prick tests and exhaled nitric oxide. Severe asthma was defined as poorly controlled asthma despite treatment with $\geq 800 \mu\text{g}$ budesonide or equivalent; assessed by a detailed structured interview.

Results: The population point prevalence at age 10 years of current severe asthma was 0.5% (three of 616) and among children with current asthma 4.5% (three of 67). The 10/154 children identified as suffering from severe asthma more often had severe bronchial hyperresponsiveness (PD_{20} methacholine $< 1 \mu\text{mol}$) (60% vs 22%, $P = 0.015$), lower median forced expiratory volume in 1 s/forced vital capacity ratio (93% vs 99%, $P = 0.04$) and higher body mass index (mean BMI 22.3 vs 18.3, $P < 0.001$) than nonsevere current asthmatics.

Conclusions: The prevalence of severe asthma was 0.5% in all 10-year olds, and 4.5% among current asthmatics. The severe asthma definition applied in this study is supported by results of clinical investigations.

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Asthma is a heterogeneous disease of varying severity, posing differing demands on the patient, the physician and health care services. A variety of terms (severe asthma, difficult to treat asthma, refractory asthma, brittle asthma) are used alluding to the subset of asthma patients with the most severe disease; frequently quoted to represent 5–10% of the total adult asthma population (1, 2). Whereas much attention and scientific effort has been placed on tracking epidemiological changes in the overall asthma prevalence during recent decades (3–5), few population-based studies map the frequencies of different categories of asthma severity (6, 7). Consequently, the prevalence of severe or difficult to treat asthma remains largely un-described, particularly in the childhood population.

Formulating an acceptable definition of severe asthma, which may also be used for epidemiological purposes, is challenging. Consensus statements such as the Global

Initiative for Asthma (GINA) guidelines represent one approach to classifying asthma symptom severity (8). Yet in a cross-sectional study setting where many patients are established on controller medication, classifications of disease severity based on clinical features in the treatment naïve patient are impractical. Subsequently; modifications of the GINA classification system are necessary when applying them for epidemiological purposes (9).

Some authors emphasize a distinction between asthma severity and asthma control (10, 11), yet in a cross-sectional study different levels of asthma severity and asthma control will coexist, and the two may be difficult to differentiate. Others have therefore suggested that by encompassing both level of treatment (as an expression of underlying disease severity) and disease or symptom control, one can reach pragmatic definitions of asthma severity that may also prove useful for epidemiological purposes (9, 12).

The primary objective of the present study was to determine the prevalence of severe asthma within a population-based cohort of children by applying a definition of severe asthma combining information on symptom control with treatment intensity. We secondly wished to investigate whether the chosen definition of severe asthma could be supported by results of clinical investigations.

Subjects and methods

Study design

The present study includes children from the 10-year follow-up of the 'Environment and Childhood Asthma' (ECA) study in Oslo, described comprehensively elsewhere (3). Briefly, a birth cohort of 3754 healthy infants was established in Oslo 1992–1993. Written informed consent was obtained from parents of all subjects, and the regional medical ethics committee and the Norwegian Data Directorate approved the study. For all 3754 infants enrolled in the ECA study detailed questionnaires were completed by the parents every 6 months for the first 2 years of life (3).

The ECA study design involved clinical investigations of two main study populations from within the birth cohort. Initially lung function measurements were obtained in 803 unselected children at birth (13). These children were representative of the entire birth cohort ($n = 3754$) with regards to demographic characteristics (3). Of the 803 children with lung function measurements at birth, 616 (76%) were reinvestigated at the 10-year follow-up (mean age 10.9 ± 0.8 years). This population is used for prevalence estimates of severe asthma in the current study.

At 2 years of age a nested case-control study was established including children with physician confirmed recurrent bronchial obstruction ($n = 306$) and age-matched controls ($n = 306$). Two clinical investigations between 0 and 2 years were performed, with at least one investigation in 562 (92%) children (14). The 10-year follow-up study, initiated in 2001, included 1019 (84%) of the 1215 children with either lung function measurements at birth and/or a clinical 2-year investigation (Fig. 1). The investigations included a detailed parental structured interview, blood sampling, skin prick tests (SPT) for allergic sensitization, spirometry, methacholine challenge test, exhaled nitric oxide (FE_{NO}) measurements and clinical examinations on day 1, and an exercise test by treadmill running on the second day within 1 week of the first examination.

Subjects

The present study describes two different selections of children from the ECA study (Fig. 1). For the purpose of assessing the prevalence of severe asthma, the 616 children attending the 10-year examination from the population-based cohort of infants with lung function measurements at birth were included.

When comparing the clinical characteristics of children with severe vs nonsevere current asthma, data from the entire 10-year study population ($n = 1019$) was included.

Methods

The structured parental interview at 10-year follow-up included central ISAAC questions related to airway symptoms (validated in Norwegian language) (3). Detailed questions regarding family

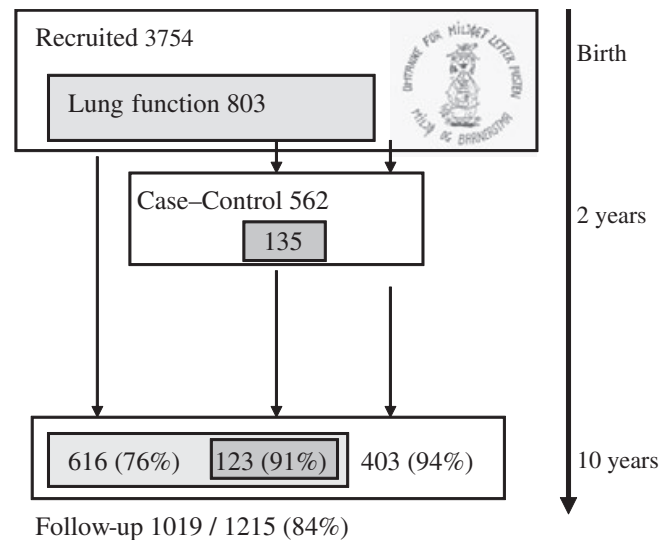


Figure 1. Flow chart of children included in the 'Environment and Childhood Asthma Study in Oslo.' The overall attendance rate for the 10-year follow-up was 84%, with the respective rates being 76% for children with lung function measurements at birth, 91% for children with lung function at birth who were included in the nested case-control study and 94% for children in the nested case-control study who did not have lung function measured at birth.

medical history, current and previous asthma medication, hospital admissions for asthma and asthma symptoms in daily life were also included. Two clinical examinations were performed 2–7 days apart, at least 4 weeks after any suspicion of respiratory tract infection.

Forced expiratory flow (FEF) volume loops were measured according to European standards (15) [reference values of Zapletal et al. (16)] on a Sensor Medics V_{max} 20°C (SensorMedics Diagnostics, Yorba Linda, CA, USA) prior to and after methacholine and exercise challenge tests, on separate days. The reported values were the best baseline values obtained before challenge testing and include forced expiratory volume in 1 s (FEV₁), FEF at 50% of forced vital capacity (FVC) (FEF₅₀) and the FEV₁/FVC ratio.

Bronchial hyperresponsiveness (BHR) was limited to subjects with a baseline FEV₁ > 70% and measured according to international guidelines (17) by determining the inhaled cumulative dose causing a reduction in FEV₁ of 20% (PD₂₀ methacholine) compared to values after inhaled saline, using an inspiration triggered Spira nebuliser (Spira Respiratory Care Centre, Hämeenlinna, Finland). Severe BHR was defined as an inhaled methacholine dose of less than 1 µmol causing a 20% reduction in FEV₁ (18). Low baseline FEV₁ prevented BHR challenge in one current asthmatic patient; and some participants chose to abstain from this test because of personal preference.

A standardized exercise test (19) was performed with a treadmill run with an exercise load equivalent to 95% of maximal heart rate for at least 4 min (3). A fall in FEV₁ ≥ 10% of baseline FEV₁ measured 3–20 min after running was considered diagnostic for exercise-induced bronchoconstriction (EIB). Successful measurements were obtained in 878 (86%) children, 139 with current asthma. Exercise-induced bronchoconstriction tests were considered unsuccessful when the child failed to complete the treadmill run according to protocol, or if test results were discarded because of

inadequate spirometric technique. In participants failing to attend the second study appointment EIB tests were not performed.

Fractional exhaled nitric oxide (FE_{NO}) was measured by an Eco Medics CLD 88 Exhalyzer® (Eco Medics AG, 8635 Duernten, Switzerland). The measurement of exhaled nitric oxide (FE_{NO}) was performed before spirometry with a standardized expiratory flow rate of 50 ml/s according to international recommendations (20). As a result of late arrival of the equipment, successful measurements were obtained in 500 (49%) subjects only, 97 with current asthma.

Skin prick tests to 15 common inhalant and food allergens (3) were performed with Soluprick® allergens (ALK Abello, Hørsholm, Denmark), and sensitization considered positive with a wheal diameter ≥ 3 mm larger than the negative control (NaCl). Results of SPT were recorded as a dichotomous variable 'any positive SPT' to minimum one allergen (yes/no).

A severity score was calculated for all children in the ECA study on the basis of pulmonary symptoms during age 0–2 years and has previously been published by our group (21). Children without airway symptoms by age 2 years received a score of 0; the maximum score was 12. Severity scores for children identified as severe/non-severe current asthmatics at age 10 are included in the present analysis.

Outcomes

As described previously (3), a diagnosis of *history of asthma* was made if a child had ever met at least two of the following three criteria: reported dyspnea, chest tightness or wheezing; a diagnosis of asthma by a doctor; or reported use of asthma medication [e.g. β_2 -agonist, cromolyn sodium, corticosteroids, leukotriene antagonists (LTA) and aminophylline]. In order to be defined as having *current asthma* the child required a history of asthma *plus* at least one of the following: reported dyspnea, chest tightness or wheezing during the last 12 months; use of asthma medication (as above) during the last 12 months; or a positive EIB test.

Severe asthma was defined as current asthma (by definition above) *plus*

- use of high-dose inhaled corticosteroid (ICS) treatment (budesonide/beclomethasone ≥ 800 μ g/day or fluticasone ≥ 400 μ g/day) at investigation and for at least six of the preceding 12 months.

In addition at least one of the following minor criteria signifying lack of asthma control (assessed by parental responses to questionnaire) had to be met:

- Acute admission to hospital due to an asthma exacerbation during the preceding 12 months.
- Use of systemic steroid treatment because of an asthma exacerbation during the preceding 12 months.
- ≥ 12 periods with increased asthma symptoms during the previous 12 months.
- Frequent limitations of physical activity because of asthma symptoms.
- Characterization of the child's health as 'frequently ill' or 'very ill' with respect to asthma.

Statistical analyses

Data are presented using mean, SD or minimum and maximum values for continuous data, or as median and interquartile range (IQR) in the case of non-normality; categorical data are presented as frequencies. ANOVA tests were used for comparing two or multiple groups, for normally distributed data. For non-normality,

the Kruskal–Wallis test was used, whereas the Mann–Whitney–Wilcoxon test was used for two-group comparison. ANCOVA was used to compare body mass index (BMI) between groups correcting for gender; Cook's *d* and Jackknife residuals were used to assess the appropriateness of the model. Categorical variables were compared by Pearson's chi-square test or Fishers exact test. The exact binomial distribution was used to calculate the confidence interval of the binomial estimates. The level of significance was set to 0.05. Statistical analyses were performed with Statistical Package for Social Sciences Version 15.0 (SPSS Inc., Chicago, IL, USA) and Number Cruncher Statistical System 2006 (NCSS, Kaysville, UT, USA).

Results

Three out of 616 children were identified as suffering from severe asthma in the population-based cohort, equivalent to 0.5 % (95% CI of estimate 0.1–1.4%) of all the subjects in the present population. Within the 67 children defined as having current asthma (3), the prevalence of severe asthma was 4.5 %. Background data for the population-based cohort in ECA is displayed in Table 1.

When extending the analysis to include all children ($n = 1019$) reinvestigated at the 10-year follow-up, a further seven children were identified as having severe asthma. Background data for the total ECA study population is shown in Table 2, whereas the individual characteristics of all 10 severe asthmatic children are provided in Table 3.

Regular use of other controller medication (long acting beta agonists and/or LTA) in addition to ICS was more often reported in children with severe asthma (nine of the 10) than in nonsevere current asthma (46/144) ($P < 0.001$); whereas the difference in daily use of short acting beta agonists (reported in six of the 10 severe asthmatics *vs* 45/144 nonsevere asthmatics) was only borderline significant ($P = 0.08$).

Pooled clinical and laboratory characteristics of severe and nonsevere current asthmatic children are presented in Table 4. Children with severe asthma had significantly more often severe BHR than children with nonsevere current asthma; the FEV₁/FVC ratio and FEF₅₀ measurements were also significantly lower in these subjects. Rate of allergic sensitization or EIB positivity was not significantly different between the two groups. The low number of successful FE_{NO} measurements in severe asthmatic subjects made statistical comparisons between the groups with regard to FE_{NO} levels unfeasible (Table 4).

A male preponderance was observed in the nonsevere current asthmatic population (104 boys, 72%), but not among children with severe asthma (five boys, 50%) ($P = 0.16$).

Body mass index was significantly higher in severe asthmatic children than in nonsevere current asthma (mean BMI 22.3 *vs* 18.3, $P < 0.001$), the difference remaining significant after correction for gender. A

Table 1. Demographic characteristics of children included in the ECA population-based cohort ($n = 616$) at 10-year follow-up

	Current asthma ($n = 64$)	History of asthma; not current ($n = 57$)	All ($n = 616$)
Boys, n (%)	45 (70)	28 (49)	331 (54)
Age (years)	10.6 (9.2–12.5)	10.6 (9.3–12.3)	10.9 (9.2–12.5)
Height (cm)	145 (128–167)	147 (121–172)	147 (121–172)
BMI	18.1 (12.8–25.6)	18.0 (13.9–26.2)	18.0 (12.8–30.2)
SPT, any positive (%)	36 (57)	15 (27)	178 (29)
Parental asthma (%)	20 (31)	7 (12)	93 (15)
Parental RhC (%)	41 (64)	26 (46)	297 (48)

Data are expressed as mean (minimum–maximum) or frequencies (%).

ECA, Environment and Childhood Asthma; BMI, body mass index; SPT, skin prick test; RhC, rhinoconjunctivitis.

Table 2. Demographic characteristics of children from the total ECA study population ($n = 1019$) at 10-year follow-up

	Current asthma ($n = 154$)	History of asthma; not current ($n = 149$)	All ($n = 1019$)
Boys, n (%)	109 (71)	83 (56)	549 (54)
Age (years)	10.5 (8.8–12.5)	10.5 (9.0–12.3)	10.8 (8.8–12.5)
Height (cm)	144 (126–167)	144 (126–171)	146 (121–172)
BMI	18.6 (11.7–31.2)	18.0 (13.9–30.2)	18.0 (11.7–31.2)
SPT, any positive (%)	80 (52)	37 (25)	293 (29)
Parental asthma (%)	57 (37)	29 (20)	183 (18)
Parental RhC (%)	95 (62)	75 (50)	489 (48)

Data are expressed as mean (minimum–maximum) or frequencies (%).

ECA, Environment and Childhood Asthma; BMI, body mass index; SPT, skin prick test; RhC, rhinoconjunctivitis.

Table 3. Characteristics of children included as severe asthmatics at 10-year follow-up

No.	Gender (M/F)	BMI	Atopic status	Controller treatment	Severe asthma symptom criteria	FEV ₁ (% pred.)	FEF ₅₀ (% pred.)	PD ₂₀ (μmol)	EIB test (ΔFEV ₁ %)	FE _{NO} (ppb)
1*	M	17.5	Neg	ICS, LTA	4	86	66	Neg	–	5.9
2*	F	22.7	Neg	ICS, LABA	2, 4	128	141	Neg	Pos (–19)	17.4
3*	M	21.2	Pos	ICS, LABA	3, 4	91	54	0.27	Pos (–14)	4.4
4	F	17.1	Pos	ICS, LABA	1, 4	93	80	6.99	Neg	–
5	F	31.2	Pos	ICS, LABA	1, 2, 4	112	77	0.22	Pos (–15)	–
6	F	23.0	Pos	ICS, LTA, LABA	4	86	62	0.30	Pos (–38)	–
7	M	28.5	Neg	ICS	1, 2, 4, 5	91	75	0.52	Pos (–10)	–
8	M	17.0	Pos	ICS, LTA, LABA	1, 4	84	52	0.10	Neg	31.9
9	F	27.2	Pos	ICS, LABA	1, 4	80	42	0.51	Pos (–21)	20.1
10	M	17.2	Neg	ICS, LTA, LABA	4	81	60	7.18	–	–

ICS, high-dose inhaled corticosteroids; LTA, leukotriene antagonist; LABA, long acting beta agonist; FEV₁, forced expiratory volume in 1 s; FEF₅₀, forced expiratory flow at 50% of forced vital capacity; PD₂₀, dose of metacholine causing a 20% fall in FEV₁; EIB, exercise induced bronchoconstriction; ΔFEV₁%, maximal reduction in FEV₁ after treadmill run; FE_{NO}, fractional exhaled nitric oxide.

Severe asthma symptom categories: 1 – acute hospital admittance last 12 months due to asthma; 2 – systemic steroid treatment last 12 months due to asthma; 3 – >12 asthma exacerbations last 12 months; 4 – frequent limitations of physical activity due to asthma; 5 – characterisation of child by parent as frequently ill/very ill of asthma.

*Patient included in population-based cohort.

significant interaction was however observed between gender, BMI and severity of asthma: girls had lower mean BMI than boys in the nonsevere current asthma group (mean BMI 17.7 in girls vs 18.6 in boys); but among severe asthmatics the girls had higher BMI (mean BMI 24.2 vs 20.3 respectively) ($P = 0.009$). Exercise limitations were more often reported in severe than nonsevere asthmatic children [10/10 (100%) vs 38/144 (26%), $P < 0.001$].

No significant differences were seen between the groups with regard to age of doctor's diagnosis of asthma (mean age 2.3 vs 2.5 years); however children with a history of respiratory symptoms by the age of 2 years (severity score > 0) and who were defined as severe asthmatic at age 10 had a significantly higher severity score at age of 2 years (six children; mean score 7.5) than those with later nonsevere asthma (89 children; mean score 4.9) ($P = 0.002$).

Table 4. Clinical characteristics of children with severe and nonsevere current asthma at ECA 10-year follow-up ($n = 1019$)

	Severe asthma ($n = 10$)	Nonsevere asthma ($n = 144$)	<i>P</i> -value
Boys n (%)	5 (50)	104 (72)	0.16
Spirometry, subjects n	10	144	
FEV ₁ % pred., median (95% CI)	88.5 (81–112)	96 (93–97)	0.11
FEF ₅₀ % pred., median (95% CI)	64 (52–80)	78.5 (74–82)	0.04
FEV ₁ /FVC % pred., median (95% CI)	93 (85–105)	99 (98–100)	0.04
Methacholine challenge test, subjects n	10	141	
Severe BHR n (%)	6 (60)	31 (22)	0.015
Exercise challenge test, subjects n	8	131	
EIB positive n (%)	6 (75)	55 (42)	0.14
Fractional exhaled NO, subjects n	5	92	
FE _{NO} median (IQR)	17.4 (20.8)	7.8 (12.4)	0.53
Skin prick test, subjects n	10	143	
Any positive n (%)	6 (60)	74 (52)	0.74

Where low numbers prevent calculation of 95% CI of the median; non-normally distributed data are presented as median and interquartile range (IQR). Severe BHR is defined as a methacholine challenge dose of $<1 \mu\text{mol}$ leading to a 20% reduction in FEV₁. Bold indicates *P*-value of statistical significance of differences between severe and nonsevere asthma (significance level <0.05).

FEV₁, forced expiratory volume in 1 second; FEF₅₀, forced expiratory flow at 50% of forced vital capacity; BHR, bronchial hyperresponsiveness; EIB, exercise-induced bronchoconstriction; FE_{NO}, fractional exhaled nitric oxide.

Discussion

The prevalence of severe asthma was 0.5% within this population-based cohort examined at age 10 years; the prevalence of severe asthma among children with current asthma was 4.5%. Bronchial hyperresponsiveness and lung function measurements performed in the current study indicate that the chosen definition of severe asthma successfully identifies a subpopulation of asthmatic children with more severe disease.

The present study is to our knowledge the first study to report the prevalence of severe uncontrolled asthma in an urban childhood population. In a large population-based telephone survey the Asthma Insights and Reality in Europe study classified 15.1% of the pediatric participants as having severe persistent asthma symptoms according to a symptom index similar to the GINA severity scale (7). The aim of that study was, however, primarily to assess asthma control rather than disease severity, and medication was not considered in the classification of these patients. There is also sparse data on severe asthma prevalence in adults. In an English cross-sectional investigation of computerized general practice records ($n = 3373$), Walsh et al. (6) found that 4.6% of adult asthma patients received steps 4 or 5 treatment according to British guidelines.

The definition of severe asthma applied in the present study is an accommodation of the ERS Task Force severe asthma definition; namely asthma that is not controlled despite regular treatment with high dose ICS (12). Similar definitions have been applied in clinical studies on severe/difficult asthma in both adults (1, 22) and children (23–25), the greatest discrepancy between these studies being in the definition of lack of disease control. In the present study children were defined as having uncontrolled

asthma if any one of five minor criteria were met. Minor criteria 1–3 are measures of asthma exacerbation frequency and severity, and are comparable to inclusion criteria in other severe asthma definitions (1, 26). Minor criteria 4 and 5 were included into the severe asthma definition in an attempt to identify children with persistent limitations in day-to-day life because of asthma; but it must be conceded that they are less well defined and more difficult to interpret. With regards to the question on exercise limitations, EIB was confirmed in six of eight severe asthmatic children (Table 3), and was only reported in roughly 25% of the nonsevere current asthmatic children; suggesting that minor criterion 4 provided relevant information about exercise limitations and discriminated between children with severe and nonsevere symptoms. Minor criterion 5 did not alone include any patient as severe asthma in this study.

Reduction in pulmonary function (FEV₁ $<80\%$ predicted) has been included as a criterion for severe asthma in both adult and paediatric studies (24, 26), but was intentionally omitted in the present study to be able to assess the independent association between different pulmonary function measures and severe asthma in these children. It has previously been argued that episodic decline in lung function precedes chronic airflow limitations in asthmatic children (27), and studies have shown that decline in FEV₁ (or FEV₁/FVC ratio) is more pronounced in adolescents with severe asthma than in younger children (25, 28). We therefore considered that FEV₁ was a less relevant inclusion criterion for severe asthma in the current age group than in adult or adolescent asthma populations.

Defining severity of asthma according to ICS treatment presumes that ICS-dose has been adequately increased in patients with insufficient asthma control. Several studies

show, however, that ICS treatment is often inadequate (7, 29), and consequently the true prevalence of severe asthma in the present population may be underestimated.

Only three children were defined as having severe asthma within the population-based cohort in ECA; implying that the estimated true prevalence of severe asthma in the general population is uncertain. One would need clinical studies on significantly larger population-based cohorts than ours to address this question with a higher level of certainty.

Children defined as having severe asthma in the current study had significantly reduced FEV₁/FVC ratios compared to nonsevere current asthmatics, and were more likely to demonstrate severe BHR. Similar results have been reported from other severe asthma studies in children (25, 30); indicating that despite the differences in inclusion criteria, similar subpopulations of asthmatic children are identified. In correspondence with previous paediatric reports (25), we also found a pronounced reduction in mid-expiratory flow rate (FEF₅₀) among severe asthmatic children. We propose that this pulmonary function parameter may be interesting to assess in future studies of severe asthma in children.

We found significantly higher BMI in the severe asthmatic children as compared to nonsevere asthmatics; the increase in BMI was particularly pronounced in females. This agrees with the reported association of severe asthma to increased BMI, especially in adult females (1). A recent review concluded that obesity plays a role in the persistence of childhood asthma (31), and more information is needed to illuminate the relationship between gender, weight and asthma severity in the pediatric population.

In the present study, we found no significant difference in rate of allergic sensitization between severe and nonsevere asthmatics (Table 4). This is in line with findings previously reported in both children (32) and adults (1, 33); whereas other studies have indicated increased rates of allergic sensitization with increasing asthma severity in children (34, 35). Larger severe asthma populations than ours would be needed to explore this question further.

Too few severe asthmatic children have been identified at age 10 years to make good use of the ample longitudinal data present within the ECA study. Using the severity score previously described by our group (21) we did, however, find that children with severe asthma at age 10 years appeared to present with more severe symptoms already at age 2 years than their nonsevere counterparts.

Conclusions

The prevalence of severe asthma was 0.5% within a population-based cohort of children examined at age 10 years and 4.5% among current asthmatic children. Children identified by the definition of severe asthma applied in the present study had significantly more often severe BHR, lower FEV₁/FVC ratio and lower FEF₅₀.

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