

Original article

Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study*

Background: The western world's increase in childhood asthma is suggested to level off. We aimed to investigate asthma prevalence in 10-year-old children within the prospective birth cohort Environment and Childhood Asthma (ECA) Study in Oslo established in 1992/1993.

Subjects and methods: Six hundred and sixteen (77%) of 803 children (mean age 10.9 ± 0.9 (SD) years) with lung function measurements at birth were reinvestigated at age 10 years. At birth they corresponded to the entire birth cohort ($n = 3754$) regarding gender, socio-demographic factors, parental allergic diseases, pet keeping and maternal smoking. Results from structured parental interview, spirometry, and skin prick test for inhalant and food allergens are presented. Asthma definition required minimum two positive criteria, (i) doctor's diagnosis of asthma, (ii) wheeze and/or chest tightness, (iii) use of anti-asthmatic treatment. Current asthma required asthma definition plus either (ii) and/or (iii) in the last 12 months, and/or $\geq 10\%$ fall in forced expired volume in 1 s after treadmill running.

Results: Lifetime prevalence of asthma was 20.2%; current asthma 11.1%, doctor diagnosis of asthma 16.1% and wheezes ever 30.3%. Allergic sensitization (29.3% overall) was more common among children with current (56.3%) compared to asymptomatic (last 12 months) (26.0%) or no asthma (27.6%) ($P < 0.001$). Boys more often than girls had current asthma (14.4 vs 7.1%, $P = 0.004$), wheeze ever (36.9 vs 22.5%, $P = 0.002$) and allergic sensitization (36.2 vs 22.1%, respectively, $P < 0.001$).

Conclusion: Childhood asthma apparently continues to increase in Oslo, having affected every fifth 10-year-old child.

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Recent reports (1, 2) suggest a levelling off in childhood asthma prevalence in some European countries, after several decades with an increase of asthma observed in the Western world (3, 4), including Norway (5, 6). Some studies, on the other hand, have found continuous increases, such as for the periods from 1986 to 2001 in 7 to 17-year-old Danish children (7) and 1992–1999 among 5 to 14-year-old German children (8), respectively.

Prevalence rates of asthma vary greatly, with the highest rates reported in English speaking countries and lower levels in other Northern European countries (9). In the mid-1990s doctor diagnosed asthma was reported in approximately 20% of British children (9), compared to 8–9% of Norwegian school children (5, 6, 10, 11), 5.1% in Russian children bordering to Scandinavia (12), and as low as 4–7% in Finland (13). 'Wheeze ever' on the other

hand, was reported in 49% of children in Great Britain (14), but only in approximately 11% in Oslo, the capital of Norway (5, 6) and 13–20% in Finland (10). Thus, previously reported childhood prevalence of diagnosed asthma and asthma symptoms were substantially lower in the Scandinavian countries compared to Great Britain.

The use of standardized International Study of Asthma and Allergy in Childhood (ISAAC) questionnaires (15) in many cross-sectional studies including the Norwegian (12), Finnish (10) and British (14), has improved the comparison of prevalence rates. However, the consistently higher prevalence rates of 'wheeze' in English speaking countries has questioned the validity of translating the word 'wheeze' as a valid symptom of asthma in other countries (10). The concern has been supported by lower asthma symptom reports on ISAAC video compared to questionnaire data. Thus, objective measurements added to questionnaires are likely to reflect a more 'true' prevalence data. Combining cross-sectional surveys and prospective studies, which is possible in large birth

*The study is performed within the ORACLE (the Oslo Research Group of Asthma and Allergy in Childhood; the Lung and Environment), which is part of the Ga2len network.

cohorts may further improve the quality of the study, and may unravel possible causes of the observed increases in asthma and allergic diseases.

The primary aim of the present study was to assess the prevalence of asthma among 10-year-old children in a general urban population within the frame of a birth cohort study.

Subjects and methods

Study design

The present study is a 10-year follow up of the 'Environment and Childhood Asthma' (ECA) study in Oslo, described elsewhere (16). Briefly, a cohort of 3754 children was established at birth in Oslo during 15 months from January 1, 1992. Inclusion criteria were: birth-weight > 2000 g, absence of illness likely to impair respiration (severe respiratory, cardiovascular, neuromuscular or metabolic disease) and no requirement for assisted ventilation or oxygen therapy beyond 6 h after birth. Exclusion criteria were: plans to move out of Oslo within 6 months and insufficient language skills. Written informed consent was obtained from parents of all subjects, and the study was approved by the regional medical ethics committee and the Norwegian Data Directorate.

Questionnaires including information on the child's health and diseases with specific questions related to infectious diseases, family history of disease, socio-economic factors and environmental exposures from birth up to the child's second birthday were completed by the parents every 6 months.

Lung function was measured in 803 children at birth (17) (mean age 2.7 days) by tidal flow-volume loops ($n = 802$) and respiratory mechanics (by the passive occlusion technique) ($n = 664$).

A nested case-control study was established to perform detailed examinations of children with recurrent (> 1) or persistent (> 4 weeks) doctor confirmed bronchial obstruction (rBO) ($n = 306$) and age-matched controls ($n = 306$) (the child without lower respiratory illness born closest in time to the case) (18). All children with suspected bronchial obstruction (BO) from questionnaire reports or from direct contact with parents or doctors/health care personnel in Oslo, were investigated by a study doctor, and a panel of experienced paediatricians determined if case-control study inclusion criteria were met. Two clinical investigations between 0 and 2 years were performed, with at least one investigation in 562 (91.8%) children. The attendance rate at the 2-year visit was 84% ($n = 516$), equally distributed between cases and controls.

The 10-year follow-up study between September 2001 and July 2004 included detailed parental structured interview, blood tests, skin prick tests (SPT) for allergic sensitization, spirometry, methacholine challenge test, exhaled nitric oxide, urine sampling and clinical examinations on day 1, and an exercise test by treadmill running within 1 week. Dust samples were collected by parents from the child's mattresses by vacuum-cleaner filters in a standardized manner. Of the 1215 children with lung function measured at birth ($n = 803$) and/or a clinical investigation by 2 years of age, 1019 (84%) attended the follow-up study (Fig. 1).

Results from the structured interview, spirometry, treadmill test and SPT are reported in the present study.

Subjects

The present study comprises the 616 children with lung function measurements at birth (332 boys, 284 girls), mean age ($\pm$) 10.9 (0.9) years (Table 1), who attended the 10-year examination (77%

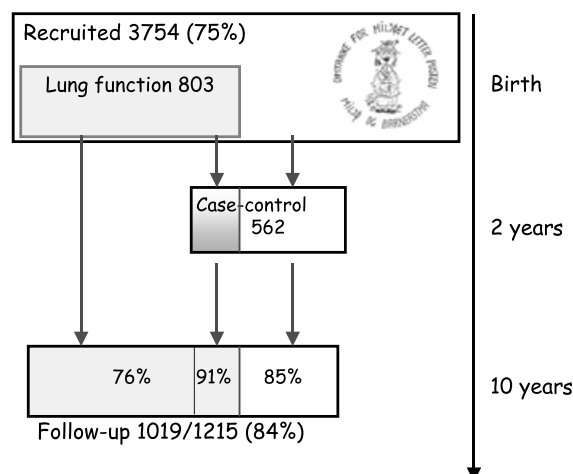


Figure 1. Flow chart of children in the birth cohort study; the 'Environment and Childhood Asthma Study in Oslo.' The overall attendance rate for the 10-year follow up was 1019/1215 (84%), with the respective rates being 76% of children with lung function at birth, 91% of children with lung function at birth who were included in the nested case-control study and 85% of children in the nested case-control study who did not have lung function measured at birth.

attendance rate) (Fig. 1). The included children were representative of the entire birth cohort ($n = 3754$) as there were no significant differences at birth with respect to gender, parental age, parental asthma, eczema or rhinoconjunctivitis, maternal smoking during pregnancy, pet keeping, parental education, paternal employment rate, family income or number of siblings (Table 2).

Methods

Parental structured interview included central ISAAC questions related to airways symptoms (validated in Norwegian language (12)) of the child, in addition to detailed questions regarding environmental exposure, life-style and diseases (index child and family). The two clinical examinations were performed 2–7 days apart, at least 4 weeks after any suspicion of respiratory tract infection.

Forced expiratory flow volume loops were measured according to European standard (19) (reference values of Zapletal (20)) on a SensorMedics Vmax 20c (SensorMedics Diagnostics, Yorba Linda, CA, USA) on four occasions, prior to methacholine and exercise challenge tests and after salbutamol given at the end of challenge tests, respectively (on separate days). The reported values were the best baseline values obtained before challenge testing.

A standardized exercise test (21) was performed on the second day (after withholding short and long acting β -2 agonists for at least 12 and 48 h, respectively and leukotrine antagonists for 72 h), by a 6–8 min treadmill run, of which the last 4 min at 95% maximal pulse rate on a 5% incline, with a 20 min observation time after running, followed by nebulized 0.1 ml per 10 kg bodyweight of a 5 mg/ml solution of salbutamol. FEV1 was measured 15 min thereafter. The exercise test was considered positive with a fall in FEV1 $\geq 10\%$ of baseline FEV1 3–20 min after running ceased.

Skin prick tests to common inhalant and food allergens were performed in 608 of the children with Soluprick® allergens (ALK Albellø, Denmark), and sensitization considered positive with a

Table 1. Demography at birth of the 616 children with completed structured interview and clinical examination at the 10-year follow-up study compared to the remainder of the birth cohort ($n = 3138$). There were no significant differences (all $P > 0.1$)

	Included	Nonincluded
Gender (% boys)	53.7	50.9
Parental asthma (%)	12.1	12.2
Parental rhinoconjunctivitis (%)	29.9	27.2
Parental atopic eczema (%)	28.0	31.3
Maternal smoking in pregnancy (%)		
No	75.3	75.6
Occasionally	9.5	9.2
Daily	15.2	15.2
Number of siblings (mean $\pm$ SD)	0.56 $\pm$ 0.68	0.56 $\pm$ 0.73
Dog in the house (%)	9.1	9.2
Cat in the house (%)	7.0	7.6
Paternal employment (yes)	92.3	92.0
Family gross income (category)	3.76	3.73
Maternal year of birth (median [SD])	1962 (26)	1962 (29)
Paternal year of birth (median [SD])	1960 (35)	1960 (41)
Maternal education	4.37	4.43
Paternal education	4.52	4.57
Years parents have lived together (mean $\pm$ SD)	5.3 $\pm$ 3.5	5.3 $\pm$ 3.7

Parental allergic diseases are reported as the present of disease in mother, father or both.

Family income is given in five categories; from 1; <1 00 000 NOK, to 5: >5 00 000 NOK.

Parental education is given in six categories from 1: maximum 9 years elementary school, to 6: university degree.

Table 2. Demography of children at the 10-year follow up in the Environment and Childhood Asthma Study in Oslo

	Girls	Boys	All	P-value
Age (mean $\pm$ SD)	10.9 $\pm$ 0.9	10.9 $\pm$ 0.8	10.9 $\pm$ 0.45	n.s.
Parental rhinoconjunctivitis (%)	48.8	48.0	48.4	n.s.
Parental asthma (%)	17.3	13.3	15.1	n.s.
Number of siblings	1.32 $\pm$ 1.18	1.23 $\pm$ 0.79	1.27 $\pm$ 0.99	n.s.

The P value describes statistical significance of gender related differences.

$P \geq 0.1$ is given as not significant (n.s.).

Parental refers to one or both of the parents.

wheel diameter ≥ 3 mm larger than the negative control (NaCl). The following allergens were used: Domestic mites (*Dermatophagoides* (*D.*) *pteronyssinus* and *D. farinae*), german cockroach, dog, cat and rabbit dander, birch, timothy (grass) and mugwort pollens, moulds (*Cladosporium herbarium* and *Alternaria alternata*), egg white, milk, peanut and codfish.

Outcomes

Asthma was defined by at least two of the following three criteria being fulfilled:

1. Dyspnoea, chest tightness and/or wheezing 0–3 and/or 4–10 years.
2. Doctor's diagnosis of asthma.

3. Use of asthma medication (β -2 agonists, sodium chromoglycate, corticosteroids, leukotriene antagonists and/or aminophylline) 0–3 and/or 4–10 years.

Current asthma was defined as asthma (by definition above) plus at least one of the following:

1. Dyspnoea, chest tightness and/or wheezing during the last 12 months.
2. Use of asthma medication (β -2 agonist, sodium chromoglycate, corticosteroids, leukotriene antagonists and/or aminophylline) during the last 12 months.
3. Positive exercise test.

Wheeze ever was defined by a positive response to the questions 'Has your child experienced dyspnoea, chest tightness and/or wheezing during the age periods 0–3 and/or 4–10 years?'

Statistical analyses and data validation

Statistical analyses were performed with Statistical Package for Social Sciences Version 12.0 (SPSS, Chicago, IL, USA).

Data are presented as mean with 95% confidence intervals (c.i.) for comparison of continuous data. Student's t -test or ANOVA tests were used for comparing two or multiple groups, respectively. Categorical variables were compared by Pearson's chi-square test. Statistical significance was assumed at a 5% level.

A logistic regression analysis was performed to establish possible predictors for asthma at age 10 years with results presented as OR with 95% c.i. after assessing goodness of fit. The variables included were: gender, allergic sensitization as well as parental history of allergic disease (asthma and/or rhinoconjunctivitis).

Misclassification was assessed by comparing information reported at 10 years of symptoms (wheeze/chest tightness) and use of glucocorticosteroids for 0–3 and 4–10 years with 6-monthly detailed questionnaires from birth to 2 years. We identified four children who at 10 years had reported no use of inhaled steroids 0–3 years, but with corroborative questionnaire data confirming use of inhaled steroids between 18 and 24 months of age. Two of the children had asthma by definition at 10 years and use of inhaled steroids reported for 4–10 years, the other two had no longer wheeze after 3 years of age. Thus, reported use of medication and symptoms were largely accurate.

Results

Asthma

Lifetime prevalence of asthma was 20.2%, current asthma prevalence was 11.1%, doctor diagnosis of asthma was reported in 16.1% and wheeze ever in 30.6% of the children (Fig. 2).

Boys more often than girls had current asthma (14.4 vs 7.1%, respectively, $P = 0.008$) and wheeze ever (36.9 vs 22.5%, respectively, $P = 0.002$) (Fig. 2), but with no statistically significant gender differences with respect to asthma (as defined) (22.9 vs 17.0%, respectively, $P = 0.086$) or doctor's diagnosis of asthma ($P = 0.117$).

Wheeze throughout the age strata was reported in 12.6% of children whereas similar numbers of children wheezed only during 0–3 years (8.8%) or 4–10 years (9.2%), respectively (Fig. 3). Of the 131 children (21.4%) who wheezed during 0–3 years of age, 41.2% reported no later wheeze.

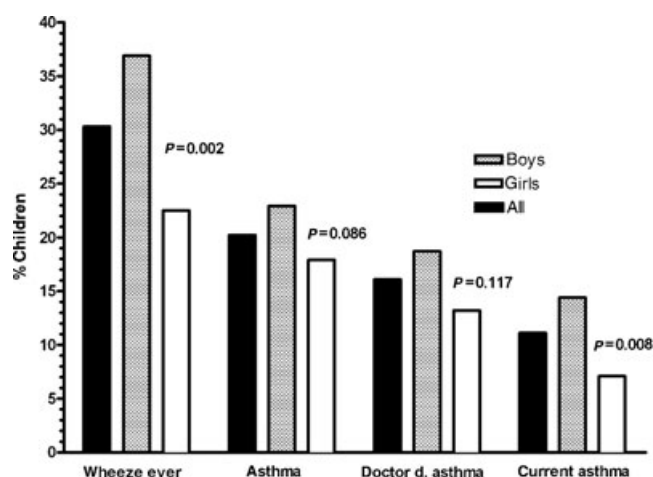


Figure 2. Prevalence of wheeze ever, asthma (minimum two of three criteria), doctor's diagnosis of asthma and current asthma (for definitions see Subjects and methods above) in 616 10-year-old children (53.7% boys) in Oslo. Doctor d. asthma refers to doctor diagnosis of asthma.

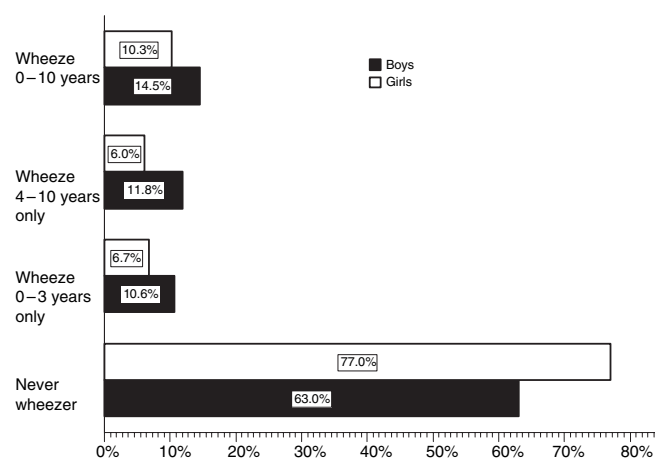


Figure 3. Reported wheeze (by structured parental interview), from 0 to 10 years at the 10-year follow-up assessment ($n = 616$) in a birth cohort population. Wheeze ever was reported significantly more often in boys ($P = 0.002$).

A family history (parents) of asthma and/or rhinoconjunctivitis was significantly more common among children with current asthma (67.2%) compared to asymptomatic (last 12 months) asthma (49.1%) and children without asthma (49.6%) ($P = 0.024$). The effect was mainly due to parental asthma (29.9% with current asthma, 12.3% with asymptomatic asthma and 13.5% with no asthma, $P = 0.002$). However among children with a negative family history of asthma/rhinoconjunctivitis, 9.7% had asthma and 7.4% had current asthma compared to 8.9 and 14.2%, respectively among children with a positive family history ($P = 0.024$).

Allergic sensitization by SPT

At least one positive SPT was found among 29.3% ($n = 178$) of the children, significantly more often among children with current asthma (56.1%) compared to asthma without current symptoms (26.8%) and no asthma (26.0%) ($P < 0.001$) (Fig. 4A). Children who wheezed during 4–10 years of age were more often sensitized than children who had never wheezed or wheezed only during 0–3 years of age ($P < 0.001$) (Fig. 4B).

Boys more often than girls were sensitized to at least one allergen (36.2 vs 26.1%), and this held true for perennial (24.6 vs 10.8%), seasonal (27.7 vs 16.5%), and food allergens (11.2 vs 3.2%), respectively (all comparisons $P \leq 0.001$).

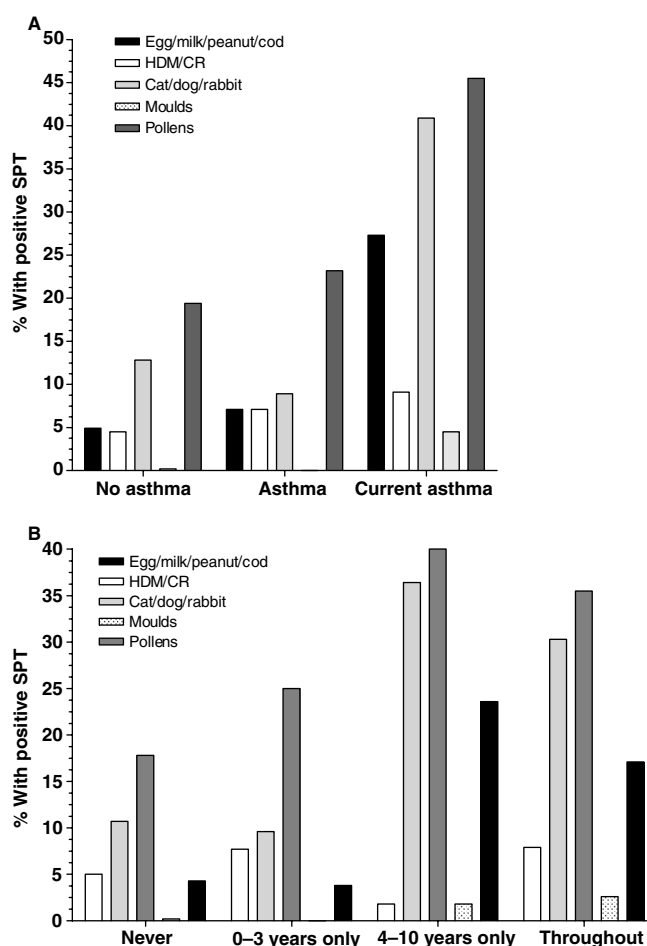


Figure 4. Differences ($P < 0.001$) in allergic sensitization assessed by positive SPT (by allergen categories) according to the presence or absence of asthma (A) (top) and reported wheeze (B) (bottom) at 10 years. HDM/CR, House dust mites (*pteronyssinus* and/or *farinae*) and/or German cockroach; Moulds, *Cladosporium Herbarum* and/or *Alternaria Alternata*; Pollens, Birch, timothy grass and/or mugwort.

Risk of current asthma

Compared to nonsensitized girls, the risk of current asthma increased significantly with allergic sensitization (OR 5.0 (1.9–12.9) (95% c.i.) ($P = 0.001$) in girls and OR 6.5 (3.0–14.5) in sensitized boys ($P < 0.001$)) as well as with male gender (OR 2.4 (1.0–5.4) in nonsensitized ($P = 0.03$) boys).

A positive family history of asthma and rhinoconjunctivitis increased the risk of current asthma in all children (OR. 2.1, 1.2–3.5 (95% c.i.)), but the effect was significant in boys only (OR 3.1, 1.6–6.2) (and OR 1.0, 0.4–2.4 in girls).

Lung function as FEV1% predicted (mean, 95% c.i.) was significantly reduced among children with current asthma (95.8, 93.3–98.3) compared to asthma without current symptoms (100.3, 97.7–102.8) and no asthma (99.1, 98.3–100.0), ($P = 0.021$), whereas the corresponding values for FEF50% predicted were 79.0, 73.8–84.0 (current asthma), 86.7, 82.1–92.1 (asthma without current symptoms) and 91.0, 89.4–92.7 (no asthma), respectively, ($P < 0.001$ for trend).

A positive exercise test was found among 8.6% ($n = 40/466$) of all children who completed the test, significantly more often among children with (current) asthma (36.7%) compared to no asthma (5.9%) ($P < 0.001$). Among the never-wheezers 4.3% of children had a positive exercise test.

Discussion

In 10-year-old children in the ECA a birth cohort study in Oslo, the prevalence of asthma (ever) was 20.2%, reported doctor's diagnosis of asthma 16.1%, current asthma 11.1% and wheeze ever (30.3%) in 2004. More than one third of boys and almost one quarter of girls had wheezed at sometime.

Allergic sensitization by SPT was found in 29.3% of all children. More than 50% of children with current asthma were sensitized. Boys more often than girls were sensitized to perennial, food and seasonal allergens.

Asthma prevalence has continuously increased among children in Norway since the first report of 0.4% in 1948 (22). Published reports from cross-sectional studies in Norway demonstrates lifetime asthma prevalence of 1.77% in 1954 (23), 2.5% in 1978 (24), 3.1% in 1981 (25) to 8% in 1993 (5) and 9.3% in 1994 (6), respectively. Whereas earlier studies employed different questionnaires, the three last studies (5, 6, 25) used identical questionnaires within Oslo, and should thus be comparable. Similar results among school children were found during the first part of the 1990s with asthma prevalence in Northern Norway of 12.3% (26) and in Mid-Norway of 10.2% (27), but lower in West Norway (5.4%) (28). The present study indicates an almost exponential increase in childhood asthma in Oslo since 1948, the

prevalence more than doubling over the last 10 years up to the present finding of 20.2%.

The previous Norwegian studies were all cross-sectional and retrospective. The present study is a 10-year follow up of a prospective birth cohort study, with detailed information during the first 2 years and a structured interview and clinical follow-up 8 years later. The study design increases the level of evidence as described by Harbour and Miller (29), and reduces the risk of preferential recall bias and misclassification.

In the present study we chose to define asthma more strictly than doctor's diagnosis alone, or by questionnaire-reported wheeze. Thus, a detailed structured interview and the requirement of at least two out of three commonly used criteria reduces the risk for both over- and under-diagnosis of asthma and improves the quality of asthma diagnosis. A positive exercise test suggests ongoing inflammation in the airways of children with asthma, and this measure of bronchial hyper-responsiveness further strengthens the diagnosis of current asthma. Furthermore, the presence of reduced lung function in children with current asthma as well as asthma without current symptoms compared to children without asthma, increases the likelihood that our asthma definition reflects a clinical disease state.

Increased asthma prevalence has been reported from many different countries throughout the world, as exemplified by the ISAAC studies (15). The present findings from Oslo in 2004 of wheeze ever among 30.3% among 10-year-old children brings the prevalence rate almost up to the English level from the 1990s (15). Our findings are supported by a recent report of repeated cross sectional studies of asthma 15 years apart of asthma in Danish school children, which concluded that more than a doubling in asthma prevalence had taken place from 1983 to 2001 (7). Both ours and the referred Danish study, however, contrast with recent reports indicating a levelling off in childhood asthma prevalence (1, 2, 30). A possible explanation (31) for this discrepancy is that populations may approach 'saturation' level of asthma prevalence, rendering populations with a (relatively) low prevalence (such as those of the Scandinavian countries) amenable to increases until such a 'saturation' level is reached.

In our cohort, 12.6% of children had wheezed persistently throughout childhood, whereas a similar percentage (around 8–9%) of children wheezed during the periods 0–3 or 4–10 years only. This corresponds roughly to the groups with persistent wheeze, early transient wheeze and late onset wheeze described by Martinez et al. (32).

Allergic sensitization as demonstrated by a positive SPT to at least one prevalent allergen was found in 29.3% of all children. This corresponds to previous Scandinavian reports, where Hasselmar et al. (33) found an asthma prevalence of 12.2% and positive SPT's in 31.7% 12 to 13-year-old Swedish children in 1996. Hence, our results compared to the Swedish study

suggest that the increase in asthma prevalence in Oslo has not been accompanied by a parallel increase in allergic sensitization. This is in line with the Danish findings 15 years apart (7). Only half of the Oslo children with current asthma were sensitized to allergens, which is similar to the 2001 results in the Danish child population (7). Furthermore, similar to the findings in the present study, Martinez et al. (32) reported increased allergic sensitization only among children who wheezed later in childhood.

Boys had significantly more often reported wheeze and current asthma as well as allergic sensitization in the present study. This is in line with other studies demonstrating more frequent allergic sensitization (34) and asthma (35) in boys than in girls, whereas the gender difference for asthma started to reverse at approximately 10 years in the recent Danish study (7).

The relatively high proportion of parents reporting asthma and/or rhinoconjunctivitis in the 10-year follow up (almost 50%) is mainly due to increased reports of rhinoconjunctivitis at the time of enrolment of the child in the study (from 29.9 to 48.4%). However, the sensitization rate of 29.3% among the studied children, as well as the representativity (of the entire cohort) demonstrated by a large number of factors at birth, renders it unlikely that the included children are skewed towards highly atopic families. On the other hand, the increase in reported parental atopic disease may either reflect a high 10-year incidence, or may in part be explained by increased awareness of disease due to participation in

the follow-up study. The study design does not allow a full explanation of our observed increase in parentally reported allergic disease.

Conclusion

Asthma among school children in Norway has increased during the last decade. Our finding of 20.2% lifetime prevalence of asthma among 10-year-old children represents the highest number ever reported in Scandinavia. It raises the question of why asthma, more than allergic sensitization apparently continues to increase among children. We urgently need answers that enable prevention of a further increase of asthma in the generations to come, and the present study will provide an opportunity to address these matters.

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