

Wheezing in school children is not always asthma

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Our objective was to study whether children with reported asthma differed from children with wheeze but without asthma, and from children with neither asthma nor wheeze, regarding lung function, bronchial hyper-responsiveness (BHR) using methacholine inhalation, exercise-induced bronchoconstriction (EIB), and skin prick test (SPT) reactivity. School children ($n=2188$), enrolled in a survey of asthma, were classified into three mutually exclusive groups by parental report of: asthma, wheeze, and no asthma/no wheeze. A random sample of 80 children in each group was tested ($n=240$). Among asthmatics, 68% (95% confidence interval (CI), 57–79) had a BHR (measured as PD_{20} forced expiratory volume in 1 s (FEV_1) ≤ 8.16 μ mol using methacholine) compared to 31% (CI 20–42%) and 30% (CI 19–40%) in the wheeze and no asthma/no wheeze groups. The dose-response slope (DRS) confirmed the PD_{20} data and distinguished equally between groups. EIB ($\geq 10\%$ fall in FEV_1) was more frequent (40%, CI 29–52%) among asthmatics than among children with wheeze (12%, CI 4–19%) and no asthma/no wheeze (7%, CI 1–13%). The prevalence of at least one positive SPT was twice as high in the asthma group (58%, CI 47–69%) than in the wheeze (27%, CI 16–37%) and the no asthma/no wheeze (25%, CI 15–35%) groups. These results indicate that children with asthma differ from children with wheeze and children with no asthma/no wheeze regarding lung function, BHR, EIB, and SPT reactivity. Children with wheeze are more similar to children with no asthma/no wheeze with respect to these parameters.

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Epidemiological studies of asthma rely primarily on data from questionnaires. Prevalence estimates are based either on reported asthma or on respiratory symptoms, such as wheeze and whistling in the chest. Such symptoms are, however, not unique to asthma. Furthermore, the prevalence of asthma may reflect the doctor's readiness to use the term asthma. Considerable limitations of studies of geographic differences, time trends, and risk factors, have been the lack of knowledge of the extent that asthma and wheeze, as applied in questionnaires, include different wheezing phenotypes. Such information is sparse (1, 2). For these reasons it is important to estimate how school children, who report

respiratory symptoms and asthma, differ regarding lung function, bronchial responsiveness (BR), and skin prick test (SPT) reactivity.

Recently, the International Study of Asthma and Allergies in Childhood (ISAAC) was developed to provide a standardized approach for comparing the prevalence and severity of childhood asthma (3). Evaluations of the ISAAC questionnaire have been published (4–7). The current study presents further data on the clinical status of school children who were classified mainly by the ISAAC questionnaire.

Our objective was to study whether children with reported asthma differ from children with wheeze but without asthma, and from children

with neither asthma nor wheeze, regarding lung function, bronchial hyper-responsiveness (BHR) using methacholine inhalation, exercise-induced bronchoconstriction (EIB), and SPT reactivity.

Subjects and methods

Subjects

The parents of a random sample of school children ($n=2188$), 6–16 yr old, enrolled in a cross-sectional study of asthma and allergy in Oslo, completed the standardized ISAAC questionnaire and other questions previously used in studies of childhood asthma (3, 8–10).

The children were classified into mutually exclusive categories by parental reports of asthma and wheeze. 'Asthma' was defined by a positive response to the following question: 'Does the child still have asthma?' 'Wheeze' was defined by a positive answer to the question: 'Has the child had wheezing or whistling in the chest in the last 12 months?', and a negative answer to the asthma question: 'No asthma/no wheeze,' was defined by a negative response both to the asthma and the wheeze questions. A total of 5.5% (121/2188) of the children had current asthma, 6.3% (138/2188) had wheeze, and 87.0% (1904/2188) had no asthma/no wheeze. Children with previous asthma and wheeze (1.1%; 25/2188) were not included in any group. A random sample of 80 children in each group were investigated for: measures of lung function, BHR, EIB, and SPT reactivity ($n=240$).

Methods

Each child had to attend the laboratory twice, on d 1 and d 2, with at least 1 week between each visit. Day 1 included registration of height, weight, baseline lung function, and methacholine or exercise challenge test. Day 2 included lung function measurements, skin prick testing, and methacholine or exercise challenge tests. Equal numbers of children were randomized to perform the exercise test on d 1 and methacholine on d 2, and vice versa. Children using inhaled, short-acting β_2 -agonists had to withhold medication 8 h before examination, theophylline for 12 h, depot theophylline and long-acting β_2 -agonist for 72 h, β_2 -agonist tablets or mixture for 12 h, and anti-histamines for 1 week. Participants had to be free from respiratory infections for 6 weeks before testing. Other criteria for not undergoing examination were: symptoms of bronchial obstruction, a forced expiratory volume in 1 s

(FEV₁) of less than 60% of the predicted value, vigorous physical activity prior to the test, and smoking 12 h before testing.

Lung function. Lung function was measured by maximum forced expiratory flow-volume curves (Master Lab, Erik Jaeger, GmbH & Co. KG, Wurzburg, Germany). Calibration was performed daily. The room temperature (20–24 °C) and relative humidity (40%) were kept stable during the test period. The measurements were obtained with the child seated and wearing a nose clip. Each child practiced the technique until they achieved a representative maximum forced expiratory curve. The highest value of FEV₁ was used in the analyzes. Baseline lung function was also measured by forced expiratory flow at 50% of vital capacity (VC) (FEF₅₀). Predicted values of FEV₁ and FEF₅₀ were based on reference values according to Zapletal et al. (11).

Methacholine-induced BHR. A methacholine bronchial challenge test was performed using a standard method based on that described by Yan et al. (12). Baseline lung function was measured, and a dose of isotonic saline (first nebulization) and methacholine was administered using an aerosol provocation system with a fixed output (APS Jaeger, Erik Jaeger, GmbH & Co.) in doubling doses ranging from 0.128 to 16.3 μmol . Each nebulization was triggered by inspiration, lasted 0.5 s, and yielded an output of 0.5 ml. Lung function was measured 1 min after each dose. The test was stopped if the FEV₁ fell by $\geq 20\%$ from the post-saline value, or when all methacholine dose steps to 16.3 μmol had been administered. The methacholine response was recorded as the cumulative dose that caused a 20% fall in FEV₁ (PD₂₀FEV₁), as determined by linear interpolation on a semi-logarithmic dose-response curve. Children with a PD₂₀FEV₁ $\leq 8.16 \mu\text{mol}$ were defined as being bronchial hyper-responsive.

The response to the methacholine challenge was also expressed by the dose-response slope (DRS) (13). The DRS of each child was calculated by the percentage fall in FEV₁ from the post-saline value of FEV₁ after the last methacholine dose, divided by the total cumulative dose (13). The DRS values are indicated by units of per cent fall in FEV₁/ μmol . Children with a value of ≤ 0 , which comprised a total of nine children (range – 0.13 to 0) were given the value 0.01.

EIB. The exercise challenge consisted of an 8-min standardized run on a motor-driven treadmill (Woodway GmbH, USA) with an inclination of 3° (5.2%). The heart rate (HR) was recorded electronically every minute by Sport tester (PE 3000; Polar Electro, Kempele, Finland). The exercise load was increased during the first 2 min by increasing the speed of the treadmill until a HR of 180 ± 10 beats per minute (b.p.m.) was obtained. This load was maintained or increased during at least the last 4 min of the test until the mean HR of the last 2 min was 190 ± 10 b.p.m. Speed (km/h) and running time (min) were recorded. Lung function was measured before, immediately after, and 3, 6, 10, and 15 min after running. If there was a fall in FEV₁ between 10 and 15 min, the subject was followed for 20 min. The exercise response was recorded as the largest fall in FEV₁ following exercise, expressed as percentage of the baseline FEV₁. A positive test was defined by a $\geq 10\%$ fall in FEV₁ from baseline lung function, as used previously in other population-based studies (14–16). A second, more conservative, cut-off point ($\geq 15\%$) was also used.

SPT. Reactivity to nine prevalent allergens was assessed by SPTs, according to the Nordic guidelines (17). The allergen extracts used were all Soluprick SQ 10 HEP (ALK A/S, Hørsholm, Denmark): hen's egg white, cow's milk, house dust mite (*Dermatophagoides pteronyssinus*), *Cladosporium herbarum*, dog and cat dander, birch and timothy pollen, and mugwort (*Artemisia vulgaris*) pollen. Saline (50:50 saline:glycerol) was used as a negative control and histamine (10mg/ml Soluprick) as a positive control. The size of the reaction was measured 15 min after testing. The histamine weal size was recorded as the sum of the longest plus the mid-point orthogonal diameters divided by two. A child was considered reactive to a specific allergen if the average diameter of the weal was at least one-half of that produced by a 10 mg/ml solution of histamine, and with an average diameter of the weal (caused by histamine) of at least 3 mm. Children with at least one positive SPT were considered to be atopic.

Statistical analyses

Age, height, weight, and baseline lung function were presented as mean values with 95% confidence interval (95% CI). One-way analysis of variance (ANOVA) with Bonferroni post-hoc test

(significance level 0.05) was used to compare the characteristics of the three groups. The prevalence of BHR, EIB, and SPT reactivity is presented as a percentage with 95% CI. Logistic regression analysis was used to estimate the association between baseline lung function (FEV₁ and FEF₅₀ in % of predicted), and BHR (PD₂₀ FEV₁ ≤ 8.16 μ mol) and EIB ($\geq 10\%$ fall in FEV₁), adjusting for group, age, and gender. The highest value of lung function was used as the reference category. All data were analyzed using the statistical package SPSS for Windows (version 6.0). BHR was also assessed using cumulative frequency distribution of the DRS. The DRS were described using a log scale. For these analysis we used the S-Plus statistical package.

All children taking part in at least one of the tests are included in the analyses. The number of children in each group thus varies. We calculated the sample size necessary for comparing two independent groups. The calculation of sample size was based on a group difference of 20%, a power of 80%, and a significance level of 95%, which yielded 60 children in each group. The prevalence (weighted mean) of BHR, EIB, and atopy in the study population (n=2188) was estimated using group size as weight, and are presented with 95% CI.

Results

The characteristics of the groups are described in Table 1. A greater number of boys than girls were included in the asthma group, whereas there were minor gender differences in the wheeze and no asthma/no wheeze groups. Age, height, and weight did not differ significantly in the three groups. Lung function – FEF₅₀ (l/s) – was lower in the asthma group than in the other groups. A similar pattern was present for FEV₁ and FEF₅₀ in % of predicted values. The risk of BHR (PD₂₀

Table 1. The characteristics of children who report asthma, wheeze without asthma (wheeze), and no asthma/no wheeze

	Asthma (n=78)	Wheeze (n=70)	No asthma/ no wheeze (n=76)
Boys (%)	67	43	45
Weight (cm)*	153 (149–156)	157 (153–160)	1544 (151–157)
Weight (kg)*	43.9 (40.8–46.9)	47.0 (43.6–50.4)	44.2 (41.4–47.1)
FEV ₁ (l/s)*	2.48 (2.29–2.68)	2.71 (2.50–2.92)	2.66 (2.48–2.84)
FEV ₁ % of predicted*	100 (98–102)	103 (100–105)	107 (105–110)
FEF ₅₀ (l/s)*	2.82 (2.58–3.07)	3.33 (3.05–3.62)	3.35 (3.11–3.58)
FEF ₅₀ % of predicted*	85 (81–89)	93 (89–98)	99 (95–104)

*Values expressed as mean (95% CI).

Table 2. Crude odds ratio (cOR) and adjusted odds ratio (aOR) with 95% confidence interval (95% CI) for bronchial hyper-responsiveness using methacholine (BHR) and exercise (EIB) challenge in relation to baseline lung function (FEV₁ and FEF₅₀ in % of predicted) adjusting for group (asthma, wheeze, and no asthma/no wheeze), age, and gender

Group	BHR (PD ₂₀ FEV ₁ ≤ 8.16 μmol)		EIB (fall in FEV ₁ ≥ 10%)	
	cOR	aOR* (95% CI)	cOR	aOR* (95% CI)
No asthma/no wheeze	1.00	1.0	1.00	1.0
Wheeze	1.07	0.98 (0.47–2.07)	1.77	1.46 (0.44–4.86)
Asthma	5.67	4.52 (2.15–9.51)	8.93	6.77 (2.35–19.48)
Baseline lung function†				
FEF ₅₀ (% of predicted)	1.02	1.02 (1.01–1.04)	1.03	1.03 (1.01–1.05)
FEV ₁ (% of predicted)	1.04	1.03 (1.01–1.05)	1.06	1.05 (1.02–1.08)

*Adjusted for gender and age.

†FEV₁ and FEF₅₀ are included separately in the model and OR is given for each per cent reduction in lung function using the highest value in per cent of predicted as the reference category.

FEV₁ ≤ 8.16 μmol) and EIB (≥ 10% fall in FEV₁) increased with decreasing baseline lung function (FEV₁ and FEF₅₀ in % of predicted) in the present samples (Table 2). Sixty-five per cent (51/78) of children in the asthma group used asthma drugs. Among these, 53% (27/51) used inhaled steroids. None in the wheeze group, and two children in the no asthma/no wheeze group, used asthma drugs.

Methacholine-induced BHR

Children with asthma were more bronchial hyper-responsive to methacholine than other children. Sixty-eight per cent (95% CI 57–79) had a PD₂₀FEV₁ of ≤ 8.16 μmol, whereas the wheeze (31%, CI 20–42%) and no asthma/no wheeze (30%, CI 19–40%) groups did not differ (Table 3). The median (PD₂₀ FEV₁) was 3.4 μmol in the asthma group, whereas both the wheeze and the no asthma/no wheeze group had a median value of > 16.3 μmol. The estimated prevalence of PD₂₀FEV₁ ≤ 8.16 μmol in the study population (n=2188) was 32% (CI 31–33%).

For 80% of the children with asthma, the fall in FEV₁ was at least 20%, and a PD₂₀ FEV₁ value could be calculated. A 20% fall in FEV₁ occurred in a smaller proportion of the wheeze (38%) and no asthma/no wheeze (37%) groups.

The difference in the distribution of DRS values for the three groups are illustrated in Fig. 1. The distributions were almost identical for the wheeze and the no asthma/no wheeze groups. The distribution differed for the asthma group, where the slopes were steeper for a greater percentage of the children, compared to the others. About 25%

Table 3. The frequency (%) of methacholine-induced BHR, PD₂₀FEV₁ (μmol), and exercise-induced bronchoconstriction (EIB) % fall in FEV₁, and skin prick test (SPT) reactivity in children with reported asthma, wheeze without asthma (wheeze), and no asthma and no wheeze (no asthma/no wheeze)

	Asthma (n=78)	Wheeze (n=70)	No asthma/no wheeze (n=76)
Methacholine-induced BHR			
PD ₂₀ FEV ₁ (μmol)			
> 8.16	32	69	70
4.08–8.16	9	6	11
< 4.08	59	25	19
EIB			
Fall in FEV ₁ (%)			
<10%	60	88	93
10–14%	16	9	6
≥15%	24	3	1
Skin prick test			
≥ One positive SPT	58	27	25
Egg	1	-	-
Milk	9	1	-
House dust mite	11	1	-
(Dermatophagoides pteronyssinus)			
Cladosporium herbarum	8	1	-
Dog	40	7	1
Cat	32	10	11
Birch	32	16	13
Timothy grass	36	20	16
Mugwort (Artemisia vulgaris)	23	9	11

of the asthmatics had a DRS value of < 1.5, whereas ≈ 25% of the wheeze and no asthma/no wheeze groups had values < 0.4. In the asthma group, 95% had DRS values < 168 compared to < 27 and < 17 in the wheeze and no asthma/no wheeze groups, respectively. The median DRS was 5.54 (percentage fall in FEV₁/μmol) in the asthma group, 0.75 in the wheeze group, and 0.89 in the no asthma/no wheeze group.

EIB

All children obtained a HR of at least 180 ± 10 b.p.m. during the last 4 min and 190 ± 10 b.p.m. during the last 2 min of the exercise challenge. The mean HR for the total running time was 179 (95% CI 162–196) in the asthma group, 183 (CI 168–198) in the wheeze group, and 182 (CI 165–197) in the no asthma/no wheeze group. The mean HRs for the last 2 min were 191 (CI 180–203), 192 (CI 180–204), and 194 (CI 184–204), respectively.

EIB (≥ 10% fall in FEV₁) was more frequent in the asthma group (40%, CI 29–52%) than in the wheeze (12%, CI 4–19%) and the no asthma/no wheeze (7%, CI 1–13%) groups (Table 3). The mean percentage fall in FEV₁ was higher in the asthma group (10%, CI 8–13%) compared to the wheeze (5%, CI 3–7%) and no asthma/no wheeze (3%, CI 2–4%) groups, respectively. The esti-

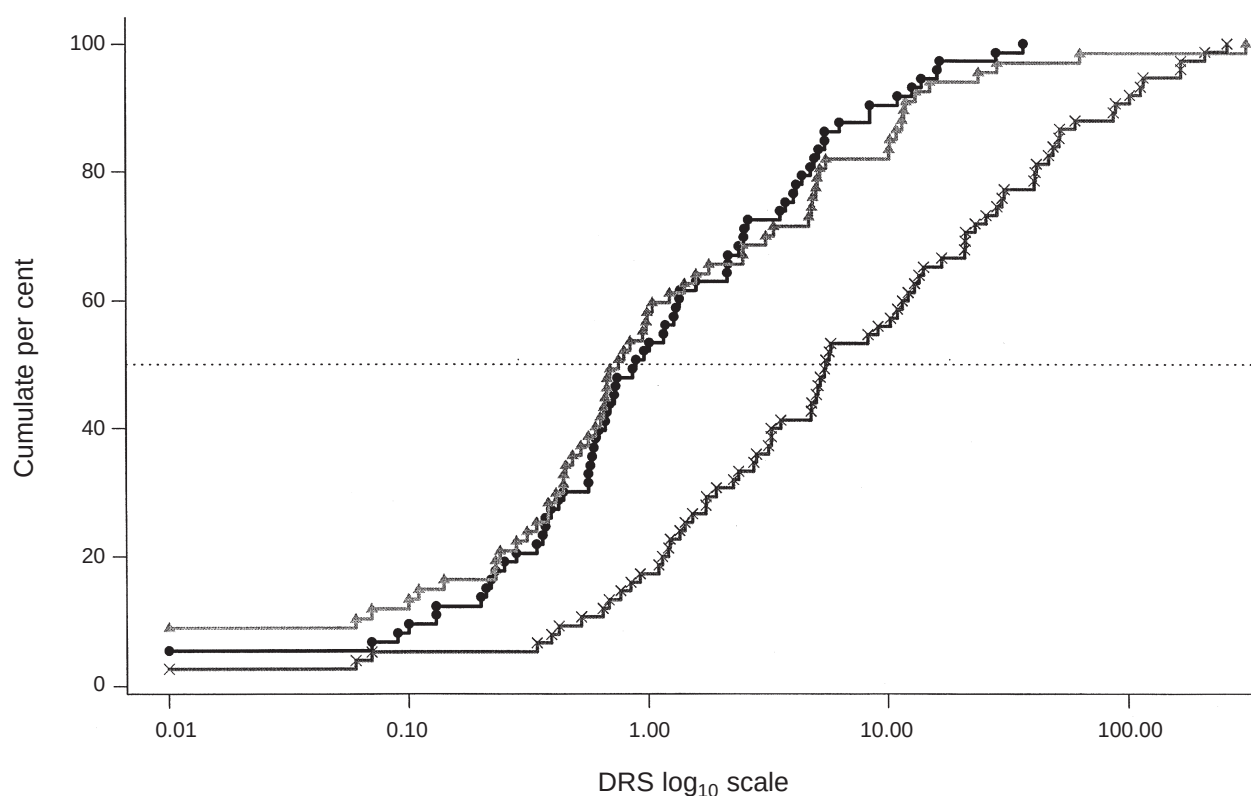


Fig. 1. Cumulative per cent of dose-response slope (DRS) (% fall in forced expiratory volume in 1 s (FEV₁)/ μ mol) in children with asthma (x), wheeze without asthma ($\blacktriangle$), and no asthma/no wheeze ($\bullet$).

mated prevalence of EIB ($\geq 10\%$ fall in FEV₁) in the study population (n=2188) was 9% (CI 8.5–9.5%) and, for a $\geq 15\%$ fall in FEV₁, 2%.

SPT

The mean weal diameter (4.8 mm) of the SPT to histamine, the control value, was similar in all three groups. The prevalence of at least one positive SPT was twice as high among asthmatics (58%, CI 47–69%) than in the wheeze (27%, CI 16–37%) and the no asthma/no wheeze (25%, CI 15–35%) groups (Table 3). Cat and dog dander, timothy grass, and birch pollen reactivity were those most common among asthmatics. In the wheeze group, reactivity to timothy grass and birch pollen was most prevalent. House dust mite reactivity was rare. The estimated prevalence of more than one positive SPT in the total study population (n=2188) was 27% (CI 26–28%).

Discussion

The results of the present study demonstrate that children with asthma differ from children with wheeze but without asthma, and from children with no asthma/no wheeze, regarding lung function, BHR, EIB, and SPT reactivity.

Children with wheeze were more similar to children with no asthma/no wheeze with respect to these parameters.

One limitation of the present study is that the questionnaire data may be biased. One source is information bias. The ISAAC questionnaire relies on parental recall of asthma and wheeze in children 6–7 yr of age, and self-report in children of 13–14 yr (3). We used parental report in all ages of children in order to compare the prevalence of asthma and wheeze. Classifying children by a report of asthma, symptoms, and neither asthma nor symptoms can, however, introduce misclassification. It is not likely that parents with children without asthma would report asthma. Among children with wheeze, however, there may be children with asthma who have not been diagnosed. This type of misclassification diminishes the differences between groups.

Other sources of bias may be associated with the measures of BHR and EIB. A report of respiratory symptoms in the last 12 months reflects a period prevalence, whereas BHR and EIB reflect point prevalence. Children with a negative response to an objective measure of increased bronchial responsiveness (BR) may have seasonal variations in BR. They may have experienced wheeze during a period of increased

BR, and thus report wheeze in the last 12 months. Furthermore, the use of inhaled steroids can reduce the increased BR in children with asthma. The difference between children in the asthma group and those in the other groups may thus be greater than shown in the present study because only children with asthma used inhaled steroids.

Selection bias would arise if the participation rates differed among children with and without asthma. We obtained data from 97% in the asthma group, 87% in the wheeze group, and 95% in the no asthma/no wheeze group. If a negative test was more common among the non-attenders in the wheeze group than among the attenders, our estimate would be biased downwards. In contrast, if all non-attenders in the wheeze group had BHR ($PD_{20} FEV_1 \leq 8.16 \mu\text{mol}$), a 9% increase in BHR (from 31 to 40%) would occur in this group. Similar results would be obtained for EIB and atopy. However, this is unlikely, and in both situations the wheeze group would differ from the asthma group. Finally, it is unlikely that the few children from the group with past asthma and wheeze (25/2188), who were not included in the study, would have affected our results substantially.

It is noticeable that there were no major differences between the wheeze and the no asthma/no wheeze groups regarding the results of the objective measures. The finding that children with wheeze only may be similar to normal children is consistent with an Australian study of 7–12-yr-old school children (1). This study showed that there was no difference between children reporting wheeze only and normal children with respect to BHR measured by methacholine and SPT positivity (1). Based on these findings, the authors suggested a definition of asthma for epidemiology by the presence of recent wheeze and BHR (1). The findings of the present study suggest that wheeze and BHR may not sufficiently characterize those with the most severe disease. The findings of the present study and the Australian study are, nevertheless, consistent with the hypothesis that not all recurrent wheeze in school children is asthma. As previously found for early childhood wheeze (18), wheezing in school children also appears to be caused by different conditions. This hypothesis is supported by previous studies suggesting that we need further information to decide whether a report of wheeze reflects asthma (19). Possible sources of bias in questioning school children about wheezing may be that children's perception of wheeze may differ (20), and that lifestyle factors, such as physical activity level, may influence the report of wheeze (9).

It is of interest that cat- and dog-dander reactivity were most prevalent in the present study, whereas house dust mite allergy was rare. This finding supports previously published data from Scandinavia, suggesting that the house dust mite levels may be low, and that dog and cat dander and other aero-allergens are more important (21, 22). The Australian study showed that there was no statistically significant difference between the three groups (normals, wheeze only, BHR only and asthma) regarding pollen sensitivity, whereas the difference was large with respect to house dust mite sensitivity (1). A similar pattern is present in our study. Within the wheeze and no asthma/no wheeze group, reactivity to pollen was more frequent than reactivity to perennial allergens. However, in the asthma group, reactivity to perennials was as frequent as to seasonal allergens, and reactivity to both perennials and seasonal allergens was common. In Norway, owing to the climate, seasonal allergens are outdoor allergens, whereas indoor allergens are mainly perennial. Perennial allergens may be a stimulus to continuous inflammation and thus increased BR. The presence of recent wheeze and SPT reactivity to perennial allergens may characterize a sub-group with severe disease.

A similar pattern was present in the 1969 study of Williams & McNicol (2). They compared children with mild wheezy bronchitis, wheezy bronchitis, and asthma, with a group of controls, regarding a history of wheezing and hay fever, SPT reactivity, and nasal eosinophilia (2). The asthma group differed from the other wheezing groups with a much higher prevalence of SPT reactivity (2). Furthermore, a differential ratio between boys and girls occurred in the three groups. In the mildest wheezing group there were predominantly girls, with the ratio of boys to girls increasing to 7:3 in the asthma group (2). A similar pattern is present in our study with a greater number of boys than girls in the group with the highest prevalence of SPT reactivity. The Australian study does not present the gender distribution of the different sub-groups (1). Another finding of Williams & McNicol was that if a clinical feature or distribution of a measurement in any of the three wheezing groups differed significantly from the control group, then this significant difference usually occurred in all the three wheezing groups. Our findings do not confirm these results, and a change in the diagnosis of asthma from the 1960s to the 1980s may have influenced our results.

In agreement with previous studies, we have shown that asthmatic children are more likely to have increased BR and atopy compared with

non-asthmatic children (1, 23–26). The present study adds to this information by using several measures, associated with asthma, in a population-based study of a wide age-range of school children using the standardized ISAAC questionnaire. Interestingly, a smaller proportion of children had EIB, which is specific for asthma, compared to BHR, which is a more non-specific measure (27). Furthermore, baseline lung function was associated with BHR and EIB in the present samples. The DRS data, which included all children in the analyzes, confirmed the PD₂₀ data and distinguished equally well between children with asthma, wheeze, and no asthma/no wheeze. The difference between the asthma group and the wheeze group suggested that asthma with wheeze and wheeze without asthma constituted two sub-groups.

The results revealed that primary-care physicians in Norway are able to distinguish between wheezy children with and without asthma. However, to use wheeze as the only asthma outcome in epidemiological studies of childhood asthma may result in misclassification, and overestimate the prevalence of asthma. Recently, the results of the ISAAC study indicated a worldwide variation in the prevalence of asthma symptoms in children (28). The item of morbidity was: 'wheezing or whistling in the chest in the last 12 months'. To what extent the worldwide variation in reported symptoms reflects a variation in morbidity, and/or a variation in possible sources of bias, may be unclear. We suggest that one should pay attention to factors that may influence the report of wheezing when studying the occurrence of asthma symptoms among school children. Objective measures of asthma ought to be included in epidemiological studies of childhood asthma.

In conclusion, the present study demonstrates that a report of asthma and wheeze without asthma appears to discriminate, to some extent, between different wheezing phenotypes.

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