ORIGINAL ARTICLE

Gender differences in asthma prevalence may depend on how asthma is defined

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Abstract *Background*: Asthma may be defined either as wheeze within the previous 12 months (current wheeze), doctor-diagnosed asthma (DDA), or current wheeze plus confirmed airway hyperresponsiveness (AHR). *Aims*: We wanted to estimate asthma prevalence in randomly selected adolescents based on different criteria for asthma diagnosis, study gender differences in reported asthma-like symptoms *vs* DDA, and relate our findings to measurements of AHR, levels of exhaled nitric oxide (ENO) and total IgE. *Methods*: As part of the health survey of North-Trøndelag (HUNT), 8571 adolescents aged 13–19 years were investigated with an interview on allergic and respiratory symptoms (phase I study). Of these, 401 subjects who reported wheeze within the previous 12 months (current wheeze) and 213 non-symptomatic controls were randomly selected and investigated with allergy screening, methacholine bronchoprovocation test and measurements of ENO (phase II study). *Results*: In the phase I study, prevalence of current wheeze was 26% (30% in girls and 23% in boys, $P < 0.01$). Prevalence of DDA was 10.8% (10.5% in girls and 11% in boys). Among subjects with current wheeze, the likelihood of having DDA was reduced in girls compared to boys, odds ratio (95% CI) 0.82 (0.68-0.98) which was partly explained by a longer history of wheeze among boys. In the phase II study, although more girls than boys with current wheeze had AHR (62% versus 50%, $P < 0.02$), more boys than girls reported DDA (44% *vs*. 32%, $P < 0.02$). Of the objective parameters, increased levels of ENO most strongly increased the risk of having DDA. *Conclusions*: When asthma is defined as DDA, there is a risk of underestimating the prevalence of asthma, especially among girls.

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Keywords gender differences; current wheeze and airway hyperresponsiveness; doctor diagnosed asthma.

INTRODUCTION

In Norway, as in most developed countries, an increase in the prevalence of asthma-like symptoms and doctor-diagnosed asthma (DDA) has been demonstrated both in children and adults (1–3). As asthma may be defined either as wheeze within the previous 12 months (current wheeze), DDA, or current wheeze plus confirmed airway hyperresponsiveness (AHR) (4,5), any calculated asthma prevalence will depend on the prevailing definition. While prevalence of DDA will be influenced by how asthma is defined and explained, prevalence of AHR is influenced by the distribution of age and sex (6–8).

In the present study, we wanted to estimate asthma prevalence in adolescents based on three different criteria for asthma diagnosis, current wheeze, current wheeze plus confirmed AHR and DDA. Secondly, we wanted to study the relationship between various asthma-like symptoms and DDA and analyse possible gender differences in the association between specific symptoms and the likelihood of having DDA. Finally, we wanted to compare girls and boys with current wheeze with and without DDA with respect to objective parameters of allergy and airway inflammation, such as AHR to methacholine and exhaled nitric oxide (ENO).

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SUBJECTS AND METHODS

Subjects

Phase I study (*Young-HUNT*): As part of the Norwegian North-Trøndelag Health Study (HUNT), all residents of the North-Trøndelag county aged 13–19 years (9917 individuals) were invited to attend the Young-HUNT Study. The attendants were investigated with a self-administered questionnaire, a structured interview containing validated questions concerning asthma-like symptoms and allergy, and a clinical investigation with flow volume spirometry (9).

Phase II study: According to their answers given during the interview, three symptom groups were defined. Subjects from each group were randomly invited for further investigation with allergy screening, measurements of ENO and a methacholine bronchoprovocation test, Group 1 (264 subjects): wheeze related to allergen exposure; group 2 (375 subjects): wheeze not related to allergen exposure; group 3 (318 subjects): non-symptomatic controls. Adolescents with wheeze (groups 1 and 2) were investigated during the non-pollen seasons of 1997 and 1998. Non-symptomatic controls (group 3) were investigated in the period from September1997 to June 1998. Those who were taking antiasthmatic drugs were asked not to take inhaled or oral β-2-agonists 12 h before the investigation, and smokers were asked to refrain from smoking 30 min before their appointments. A nurse and a physician carried out the investigations. Those with symptoms of lower respiratory tract infection or sinusitis were not investigated, but tested on a later occasion if possible.

All subjects, as well as the parents of subjects less than 16 years of age, gave written informed consent prior to participation. The study was approved by the regional ethical committee in Trondheim, and the Data Board Inspectorate gave their consent.

Methods

Flow-volume spirometry (MasterScope spirometer, software version 4.1, Erich Jaeger), and *methacholine bronchoprovocation test* (tidal volume triggered equipment, Automatic Provocation System APS, Erich Jaeger GmbHöchberg, Germany) were performed as have previously been described in detail (10–12). AHR was defined as a reduction in $FEV_1 \geq 20\%$ on a cumulative dose of methacholine (PD_{20}) ≤ 2 mg.

Measurements of ENO were performed in accordance with the European Respiratory Society Task Force (13) with an LR 2000 nitric gas analyser (Logan Research Ltd., Rochester, U.K.). Subjects were in a seated position and exhaled from total lung capacity against a resistance of 5-cm H_2O to residual volume. The exhalation and sampling flow rates were 250 ml/s and 250 ml/min, respectively. For each subject, mean of two plateau levels from acceptable ENO curves were registered in parts per billion (ppb).

Allergy screening was performed with serological testing (Phadiatop CAP™ and RAST, Pharmacia Diagnostics, Lund, Sweden). Specific IgE concentrations were recorded in a scale from 0 to 5, and a test result equal to or above two was regarded as a positive RAST.

Questionnaire: In the phase I study, the adolescents were interviewed by specially trained nurses. The interview contained questions concerning respiratory and allergic symptoms as well as asthma medication (Appendix A). The questions were either adapted from The International Study of Asthma and Allergies in Childhood (ISAAC) (14), from The European Community Respiratory Health Survey (ECRHS) (15), or they were created for The Young Hunt Study. There was a time interval of 6–24 months (mean 12 months) between the phase I and the phase II study. The adolescents were classified as subjects with current wheeze or subjects with current wheeze plus DDA in accordance with their answers given in the phase I study interview.

Statistical analyses

Statistical analyses of the data were performed by the 1999 SPSS Inc. Windows 10.0 statistical program (SPSS Inc. 233 S. Chicago, Il, U.S.A.). Data from measurements of dose response ratio to methacholine (DRR), ENO, and total IgE were close to log-normal distributed, thus parametric tests were used with log-values, and results presented as geometric mean. Numeric data were analysed with Independent-Samples *t-t*ests or Mann–Whitney *U*-test when appropriate. Categorical data were analysed with Chi-square tests. Multivariate analyses with logistic regression were used to calculate adjusted odds ratios for DDA, and to find the model best fit to predict DDA. Missing data were excluded from analyses. A two-sided *P*-value ≤ 0.05 was regarded as statistically significant.

RESULTS

Phase I study

Asthma-like symptoms vs. doctor diagnosed asthma (Table 2)

Of the 9917 individuals invited to the phase I study, 8571 subjects (86%) attended the interview. DDA was reported by 10.8%, and 26% reported wheeze during the previous 12 months (current wheeze). Less than one-third of the subjects with current wheeze reported DDA (Table 1).

Table 1. Adolescents reporting wheeze within the previous 12 months (current wheeze)

	All	Girls	Boys
Subjects with current wheeze	2242	1278	964
Mean age (range)	15.6 (12–19)	15.6 (12–19)	15.5 (12–19)
Duration of wheeze > 5 years (%)	331 (15)	154 (12)	177 (18)***
DDA (%)	683 (31)	366 (29)	317 (33)*
Asthma med. last 12 months (%)	638 (29)	354 (28)	284 (30)
Daily cigarette smokers (%)	337 (17)	228 (18)	145 (15)

*$P = 0.03$, ***$P < 0.001$.

Table 2. Adjusted odds ratios for DDA in adolescents with current wheeze; a multivariate analysis including reported asthma-like symptoms, gender, duration of wheeze, and age

Symptom	Subjects (%) with DDA if Yes	Subjects (%) with DDA if No	Adjusted Odds Ratio (95%CI) for DDA if Yes
Cough at night in absence of colds	214 (35)	469 (29)	0.85 (0.7–1.1)
Wheeze or dyspnoea in absence of colds	563 (42)	120 (13)	2.50 (1.9–3.2)
Attacks of dyspnoea at rest	563 (45)	506 (27)	1.04 (0.8–1.4)
Attacks of dyspnoea during night	141 (61)	542 (27)	1.88 (1.3–2.7)
Allergy-induced wheeze	398 (60)	285 (18)	2.72 (2.1–3.5)
Wheeze due to exposure from smoke/irritants	273 (55)	410 (24)	1.53 (1.2–2.0)
Wheeze due to exercise	521 (47)	162 (14)	2.63 (2.1–3.4)
Duration of wheeze > 5 years	305 (61)	378 (22)	3.81 (3.0–4.9)
Cigarette smoking daily	91 (24)	592 (32)	0.84 (0.6–1.1)
Age	—	—	1.00 (0.9–1.1)
Female	366 (29)	317 (33)	0.70 (0.6–0.9)

Table 3. Univariate analyses of gender differences in the likelihood of having DDA when reporting various asthma-like symptoms

Adolescents with current wheeze	Girls% DDA	Boys% DDA	Odds ratio for DDA in girls *vs.* boys
Wheeze and dyspnoea in absence of colds	41	45	0.85 (0.7–1.1)
Allergy-induced wheeze	57	63	0.78 (0.6–1.1)
Wheeze due to exercise	43	53	0.67 (0.5–0.9)

Gender differences in current wheeze vs. DDA

There was no gender difference in the prevalence of DDA, 10.5% among girls vs. 11% among boys. However, more girls than boys had current wheeze, 30% versus 23%, $P < 0.001$. Among subjects with current wheeze, the likelihood of having DDA was reduced in girls *vs.* boys, odds ratio (95% CI) 0.82 (0.68–0.98). This was a trend in all age groups, but most significant among those aged 13–14 years, odds ratio (95% CI) 0.65 (0.47–0.88).

In a multivariate analysis including all asthma-like symptoms, duration of wheeze, cigarette smoking, age and sex, the likelihood of having DDA was significantly reduced among girls compared to boys (Table 2). Of all the reported symptoms, allergy-related wheeze (wheeze when exposed to pollen, pets or house dust), wheeze in absence of colds and exercise-induced wheeze most strongly increased the likelihood of having DDA. When stratifying for sex, wheeze in absence of colds and allergy-related wheeze were the symptoms most strongly associated to DDA in girls and boys, respectively. In an univariate analysis, girls reporting exercise-induced wheeze were less likely than boys to have DDA (Table 3).

Phase II study

Subject characteristics

Of the 957 adolescents invited to the phase II study, 622 participated. Of these, 151 subjects had wheeze related to allergen exposure, 258 had wheeze not related to allergen exposure, and 213 were non-symptomatic controls. The attendance rates were 57, 69, and 67%, respectively. Six hundred and eleven subjects completed methacholine bronchoprovocation tests, acceptable measurements of ENO were achieved from 613 subjects, and 609 subjects underwent allergy screening.

Gender differences in airway hyperresponsiveness vs. DDA among subjects with current wheeze

DDA was reported by 37% and AHR (defined as a $\geq$20% fall in FEV_1 during methacholine bronchoprovocation test) was confirmed in 58% of the adolescents with current wheeze. Moreover, 32% of the subjects with current wheeze had neither diagnosed asthma nor confirmed AHR. When defined as DDA, asthma was more prevalent in boys compared to girls, 43.9 *vs.* 32.1% ($P = 0.015$). However, when defined as current wheeze plus confirmed AHR, asthma was more prevalent in girls (62.4%) than in boys (50.3%), $P = 0.016$. When extrapolating the percentages of subjects with AHR to the larger phase I study, the estimated prevalence of current wheeze plus confirmed AHR would be 14.7% (18% in girls and 11% in boys).

Gender differences in the association between DDA and reported symptoms vs. objective parameters of lower airway inflammation and allergy

The likelihood of having DDA in girls compared to boys was reduced also when adjusting for allergy-related wheeze or AHR, but not when adjusting for a positive RAST (Table 4). Moreover, positive RAST tests were more prevalent among boys compared to girls, 65 *vs*. 44%. In a multivariate analysis of adolescents with current wheeze including allergy-related wheeze, AHR, cigarette smoking and age, the likelihood (95% CI) of having DDA in girls *vs.* boys was 0.6 (0.4–0.9).

Among subjects with DDA, levels of ENO and total IgE were higher in boys compared to girls (Table 5). However, among those without DDA, the dose response ratio to methacholine (DRR) was more increased in girls. Of the three objective parameters, an elevated level of

Table 4. The likelihood of having DDA in girls vs. boys with current wheeze when adjusting for allergy-related wheeze, AHR or positive RAST

	With DDA (%)		Adjusted Odds Ratios for DDA in girls vs. boys
	Girls	Boys	
Current wheeze	78 (32)	72 (44)	0.60 (0.40–0.91)
Allergy-related wheeze	44 (52)	41 (62)	0.62 (0.40–0.96)
Confirmed AHR	55 (37)	46 (58)	0.55 (0.35–0.84)
Positive RAST	42 (40)	58 (55)	0.71 (0.46–1.09)

DDA: doctor diagnosed asthma, AHR: airway hyperresponsiveness.

Table 5. Adolescents with current wheeze; the association between objective parameters of lower airway inflammation and allergy *vs.* DDA

	DDA +		DDA −	
	Girls	Boys	Girls	Boys
DRR gm (95% CI)	39 (27–57)	35 (22–54)	17 (14–21)**	9.7 (7.3–13)
ENO gm (95% CI)	7.6 (6.4–9.1)	13 (10–16)***	5.2 (4.8–5.7)	7.1 (6.1–8.2)***
IgE gm (95% CI)	77 (51–115)	154 (111–214)*	32 (24–41)	47 (31–71)

DRR: dose response ratio to methacholine, %/mg; ENO: exhaled nitric oxide; gm: geometric mean.
$^{*}P < 0.02$, $^{**}P < 0.01$, $^{***}P < 0.001$ when comparing girls and boys.

ENO ($\geq$ 8 ppb) most strongly increased the likelihood of having DDA in both sexes.

DISCUSSION

In the present study, wheeze within the preceding 12 months (current wheeze) was reported by 26%, whereas 10.8% had DDA. While the prevalence of current wheeze was increased in girls compared to boys, there was no gender difference in the prevalence of DDA. Thus, among adolescents with current wheeze the likelihood of having DDA was reduced in girls. This gender difference in DDA could not be explained by differences in reported asthma-like symptoms.

Among adolescents reporting current wheeze who attended the phase II study, 58% had confirmed AHR, whereas 37% had DDA. One-third had neither confirmed AHR nor diagnosed asthma. DDA was more frequent in boys compared to girls. However, AHR was more frequent in girls, and the likelihood of having DDA was reduced in girls irrespective of presence of AHR. In addition to the duration of wheeze, allergy-related wheeze, and increased levels of ENO, a marker of airway inflammation in atopic asthma [11] were associated with an increased likelihood of having DDA. Thus, the risk of under-diagnosing asthma seems higher among subjects reporting wheeze not related to allergy.

Our primary aim was to estimate asthma prevalence based on various criteria for asthma diagnosis. The prevalence of current wheeze and DDA were based on data from the phase I study, a huge epidemiological survey including 85% of all adolescents residing in the North-Trøndelag county. Compared to subjects reporting current wheeze in the phase I study, those who also reported current wheeze when attending the phase II study, would represent a selected group. In order to avoid any selection bias when interpreting results from the phase II study, subjects were categorised according to their answers given in the phase I study interview. Thus, changes in symptom status and diagnosing of asthma that took place during the 6–24 (mean 12) months passing between the two studies were not accounted for. As a consequence, some subjects with current wheeze who got an asthma diagnosis during this period were wrongly categorised as subjects with current wheeze without DDA. However, the yearly incidence of DDA is relatively low during adolescence(16). Considering the findings by Lars Larsson of a 1.1% yearly incidence (1.4% in females and 0.8% in males) of DDA among Swedish adolescents (17), it is unlikely that such misclassification of subjects would change our conclusions.

The 26% prevalence of current wheeze was high compared to the 10.8% prevalence of parental reported occasional wheeze among Norwegian children reported by Nystad *et al.* (2). However, there was no striking difference in the prevalence of DDA between the two studies, 10.8 and 9.3%, respectively. While parents answer most questionnaires concerning childhood asthma, from the age of 12 an increasing number of the subjects themselves answer the questionnaires (18). Therefore, when comparing differences in the prevalence of childhood, adolescent and adult asthma, results may be biased by variations in the communication between parent and child and between parents or subjects and doctors. Interestingly, our data were in line with the results from a study of 2693 adolescents living in Midwestern cities, U.S.A., where current wheeze was reported by 25% (19). Moreover, according to the ISAAC study, prevalence of current wheeze among British 12–14 year olds was 33.3% (20). In both studies, prevalence of current wheeze was increased in girls compared to boys. In contrast to our findings, in the Midwestern study, the increased prevalence of wheeze among girls was also reflected in an increased prevalence of ever diagnosed asthma in girls compared to boys.

In any study, the estimated asthma prevalence will depend on how asthma is defined. Questionnaires and tests used in epidemiological studies have been compared with clinically diagnosed asthma (21, 22), but no consensus of a "gold standard" for defining asthma has been reached (23). In epidemiological studies, the prevalence of reported DDA is often used as a parameter of asthma prevalence. However, before getting an asthma diagnosis, symptoms must be perceived and presented to a doctor (24) and the doctor must recognise the symptoms as asthma-like (25). Thus, asthma prevalence may be under-estimated. On the other hand, when using current wheeze as an indicator for asthma, the result may be an over-estimated prevalence of asthma. We found that one-third of those reporting current wheeze did not have asthma either when defined as DDA or as current wheeze plus confirmed AHR.

In the present study, AHR was increased in girls compared to boys. The relationship between airway calibre, lung volume and AHR has been discussed in several papers (6–8). In the longitudinal study of Paoletti and colleagues, AHR was increased in subjects $<$13 years in both sexes compared to older age groups (8). With increasing age, reduction in AHR tended to be more profound in males compared to females, and after childhood AHR appeared higher in females than in males unrelated to airway calibre and lung volume. It has also been shown that more girls than boys develop asthma during adolescence (26). This is in line with our findings of an increased frequency of confirmed AHR in girls in spite of a shorter history of wheeze compared to boys. One can speculate whether these girls are under-diagnosed asthmatics who will become diagnosed asthmatics during early adulthood.

Some authors have pointed out that only when female patients behave "just like a man", i.e. presents

their symptoms the way men do, they are treated equally as male patients, Yentl Syndrome (24, 27). The increased likelihood of having diagnosed asthma in subjects with allergy-related wheeze may reflect an attitude among doctors that asthma is primarily an atopic disease. When compared to boys, fewer girls were atopic and their asthma symptoms were less often related to allergen exposure. Thus, asthma might more easily be under-diagnosed in girls.

In summary, among adolescents reporting current wheeze, one-third had DDA, whereas about 55% had confirmed AHR. When current wheeze or current wheeze plus confirmed AHR were used as gold standards for asthma, asthma prevalence was increased in girls compared to boys. This gender difference was not reflected in DDA, having the same prevalence in both sexes. Moreover, current wheeze was more strongly associated to markers of allergy in boys compared to girls and there was a significant association between DDA and allergy-related symptoms as well as markers of allergy.

We conclude that gender differences in asthma prevalence depend on what is chosen as prevalence indicator for asthma. The reduced likelihood of diagnosing asthma in girls compared to boys was partly explained by a stronger association between current wheeze and allergy and a longer history of wheeze among boys. However, some under-diagnosing of asthma due to female gender could not be excluded.

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APPENDIX A

Key questions and alternative answers used in the study

Questions	*Possible answers*	
Have you ever had wheezing or whistling in the chest at any time in the past?[a]	Yes	No
Have you ever had wheezing or whistling in the chest in the last 12 months?[a]	Yes	No
Have you ever had asthma?	Yes	No
If yes, has a doctor said you have asthma?[b]	Yes	No
In the last 12 months, have you had a dry cough at night, apart from cough associated with a cold or a chest infection?[a]	Yes	No
Has the wheezing or whistling in the chest been triggered by pollen or grass[b]	Yes	No
Has the wheezing or whistling in the chest been triggered by furred animals or birds[b]	Yes	No
Has the wheezing or whistling in the chest been triggered by house dust[b]	Yes	No
In the last 12 months, has your chest sounded wheezy during or after exercise?[a]	Yes	No
Have you ever had attacks of dyspnoea at rest[b]	Yes	No
Have you been woken by an attack of shortness of breath at any time in the last 12 months[c]	Yes	No

[a] International Study of Asthma and Allergies in Childhood (ISAAC).
[b] Young Hunt Study
[c] European Community Respiratory Health Survey (ECRHS).

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