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The relationship between respiratory symptoms and bronchial hyperresponsiveness in a population-based sample of adolescents and young adults

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Objectives: to study the relationship between chronic respiratory symptoms and bronchial hyperresponsiveness (BHR) in adolescence and young adulthood and to assess the possible predictive value of these symptoms for BHR.

Methods: a cross-sectional analysis: in a population sample of 551 subjects aged 10–23 years, data collected with a standardized questionnaire on respiratory symptoms were compared with the results of a histamine challenge test.

Results: 43% of the subjects reported one or more chronic respiratory symptoms; of these subjects 54% did not show BHR. Forty-two per cent of the subjects had a $PC_{20} \leq 8{\cdot}0\ mg\ ml^{-1}$ histamine, of which 53% reported no chronic respiratory symptoms. Wheezing and breathlessness were related to the level of BHR, but only 'breathless when walking on the flat' was independently related to BHR; however, its predicted value for BHR was negligible.

Conclusions: in adolescents and young adults the relationship between chronic respiratory symptoms and BHR is incomplete. A standardized questionnaire on respiratory symptoms does not provide adequate information to discriminate between those with and without BHR.

Introduction

In estimating the prevalence of asthma it is not acceptable to rely on the general practitioner's diagnosis only, since a substantial number of patients with asthma might not be recognized in general practice (1,2). Therefore, in epidemiologic surveys standardized questionnaires on respiratory symptoms have been used to assess the prevalence of this condition. This method, however, lacks validity due to the weakness of the relation between symptoms and airways obstruction (3,4) and to differences in interpretation of the questions.

The need for a more objective marker of asthma seemed to be satisfied by the recognition of bronchial hyperresponsiveness (BHR) as a hallmark of asthma (5–8). However, BHR is not specific to asthma because it has been demonstrated in patients with chronic airflow obstruction (9), rhinitis (5) and upper respiratory tract infections (10). Moreover, this viewpoint has been questioned on the basis of the results of studies in unselected populations (11–15) which focused on the relation between respiratory symptoms and BHR. These studies showed a considerable overlap of BHR between subjects with and without symptoms.

As a consequence, the predictive values of the symptoms to BHR were unsatisfactory and, therefore, the standardized questionnaires used failed to discriminate between subjects with and without BHR (16,17).

Most studies were based on populations of children or adults, whereas the diagnosis and treatment of asthma are problematic in adolescence and young adulthood as well.

This study examines the relationship between chronic respiratory symptoms and BHR in a community-based population sample of subjects aged 10–23 years, and the usefulness of the standardized questionnaire for assessing BHR.

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Materials and Methods

This study was a cross-sectional analysis of chronic respiratory symptoms and BHR in 581 10–23-year-old subjects. The study was part of a follow-up study of the relationship between respiratory morbidity in early childhood and asthma in adolescence and young adulthood (18).

STUDY POPULATION

The subjects of this study were recruited from the practice population of the Continuous Morbidity Registration (CMR) of the Department of General Practice of the University of Nijmegen. The characteristics of this registration project have been described in detail elsewhere (19,20). Briefly, this project includes four general practices with a stable population of 12 000 persons, whose sociodemographic composition and morbidity spectrum do not differ essentially from those of the Dutch population. All subjects of the practice lists of the four CMR-practices, who were born between 1967 (the year the CMR-project started) and 1978 ($n=1441$) and who were still on these practice lists at the time of this study in 1989, were invited to participate. The study was confined to subjects born before 1979 to guarantee a follow-up period from birth of at least 10 yr for the above-mentioned follow-up study. There were 926 subjects (64% of the original birth cohorts) who met these criteria, 484 boys and 442 girls, aged 10–23 years at the time of this study (hereafter referred to as 'adolescents and young adults'). Before the start of this study 515 subjects had left the practices; 492 had moved with their families to another area; 23 children had died, none of them as a consequence of respiratory disease.

The 926 subjects (where subjects were younger than 16, also their parents) were given written and oral explanations and they were asked to complete a respiratory questionnaire and to undergo spirometry and a histamine-challenge test.

Of this group 581 subjects (63%) gave informed consent and participated in this study. Of 551 subjects all the necessary data were available (study group).

The following information was collected in a survey in the winter of 1989–1990:

(a) Questionnaire on respiratory symptoms:
The questionnaire was based on the standardized questionnaire on respiratory symptoms (children's version) of the British Medical Research Council (BMRC) and the American Thoracic Society (ATS) (21). Its reproducibility and criterion-validity had been found satisfactory (22,23).

Questions on age, sex and smoking behaviour were added. The questions on chronic respiratory symptoms are listed in Appendix A, together with the questions on smoking behaviour. Asthma symptoms were considered present in case of an affirmative answer to at least one of questions numbered 1, 3, 4 or 5.

All subjects completed the questionnaire themselves.

(b) Allergy to inhalant allergens was assessed by the Phadiatop-test (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden) (24). The test was considered positive when the ratio (patient's serum/reference serum) was higher than 1.

(c) Spirometry and histamine-challenge protocol:
Spirometry was carried out with a Microspiro HI-298, a portable flow-volume meter (Chest Corporation, Tokyo, Japan) (25). Each patient had to perform three satisfactory forced vital capacity (FVC) manoeuvres (values within 10% of each other). Data were taken from the highest sum of FVC and the forced expiratory volume in one second (FEV_1).

Subjects who had a $FEV_1 \leq (FEV_1$ predicted $- 2SD)$ (26,27) were considered to have airways obstruction.

Subjects who had a baseline $FEV_1 \leq 50\%$ of their FEV_1 predicted, or less than 1 l, were excluded from the histamine-challenge test.

PC_{20}-histamine was assessed by means of the concise version of the tidal breathing procedure of Cockcroft *et al.* (28). Following an inhalation of saline, histamine concentrations from 0·03–16 mg ml^{-1} were inhaled.

Bronchodilators and anti-histamines, when used, were withheld at least 8 and 48 h respectively before the test. When a subject had had a respiratory tract infection with fever a short time before, the test was postponed for 6 weeks. Results were expressed as the concentration of histamine required to produce a 20% fall in FEV_1 (PC_{20}). Subjects with a $PC_{20} \leq 8{\cdot}0$ mg ml^{-1} were considered to have bronchial hyperresponsiveness.

ANALYSIS

In order to analyse whether the study group was a representative sample of the original birth cohorts, sociodemographic features of the 551 subjects of the study group were compared with those of the original birth cohorts who did not belong to the study group.

Univariate analyses were made to determine whether there were relations between each of the chronic respiratory symptoms separately on the one

hand and BHR on the other. The relations of age, sex and smoking status to BHR were studied as well. Age, number of chronic respiratory symptoms and smoking status were used as categorical variables; sex and each respiratory symptom separately were used as dichotomous variables. BHR was handled in both ways: as a dichotomous outcome variable and as an outcome variable categorized according to criteria previously determined in clinical studies of asthmatic subjects (8).

The chi-square test and the Wilcoxon test for trend were used to determine the significance of the relations.

Then a multiple logistic regression analysis was carried out. This analysis involved finding the 'best' mathematical model (in this case in a logistic form, since the outcome variable BHR was handled as a dichotomous variable) to describe a dependent variable as a function of several independent variables or to predict the dependent variable from these independent variables (29,30). Here it was used to identify chronic respiratory symptoms that were independently related to BHR, controlling for the other chronic respiratory symptoms, age, sex, smoking status, prechallenge FEV_1 and allergy as potentially confounding factors. In addition, to assess the predictive values of these symptoms to BHR, the best model was constructed with only these symptoms and the other factors that related significantly to BHR as independent factors. The goodness of fit of this model (concordance, discordance) was determined to judge whether it explained sufficient variance of BHR to be useful for assessing the predictive values. The predictive value in the case of the presence of a symptom was defined as the proportion of subjects with that symptom who had BHR, and the predictive value in the case of the absence of a symptom was defined as the proportion of subjects without that symptom who did not have BHR (31).

The regression analysis was repeated after stratification for prechallenge FEV_1 and allergy to examine the effect of these factors on the relations between chronic respiratory symptoms and BHR.

Finally, the regression analysis was repeated using more restrictive definitions of BHR, viz. successively BHR in case of $PC_{20} \leq 4{\cdot}0$ and in case of $\leq 2{\cdot}0$ mg ml^{-1}.

All analyses were performed using the SAS statistical package (SAS Institute Inc, Cary, NC, U.S.A.).

Permission for the study was given by the Ethics Committee of the Faculty of Medicine of the University of Nijmegen.

Results

The data of 30 of the 581 subjects who participated in this study were excluded from the analysis: three subjects were not able to perform reproducible forced expiratory manoeuvres, seven could not finish the challenge test due to coughing, although FEV_1 was not significantly decreased, and 20 subjects did not complete the questionnaire satisfactorily. None of the subjects had an initial $FEV_1 \leq 50\%$ of FEV_1 predicted, or ≤ 1 l, so all 551 participants underwent the histamine challenge test.

The comparison between the study group and those of the original birth cohorts who did not belong to the study group showed that of the study group (statistically) significantly fewer subjects belonged to the higher social class and were men than of the latter group. No differences were found with respect to age.

Of the subjects, 43% reported one or more chronic respiratory symptom and 26% one or more asthma symptom. BHR was found in 40% of those without asthma symptoms, increasing to 51% in those who reported two or more asthma symptoms ($P=0{\cdot}14$).

The overall prevalence of BHR was 42%. Neither sex nor age were related to it.

Of the study group 18% smoked, 5% had stopped smoking and 77% had never smoked. BHR was found in 34, 40 and 44% respectively ($P=0{\cdot}17$).

Table 1 shows the prevalence of the chronic respiratory symptoms and their relation to the prevalence of BHR. Only the symptoms of 'quicker breathless than people of the same age' and 'breathless when walking on the flat' had a statistically significantly higher prevalence in the group with BHR.

Of those who reported one or more asthma symptom, 51% did not show BHR (54% for chronic respiratory symptoms). Of those with BHR 70% did not report asthma symptoms (53% had no chronic respiratory symptoms).

The prevalence of chronic respiratory symptoms in relation to the degree of BHR is shown in Table 2. In general the higher the degree of BHR, the higher the prevalence of each respiratory symptom. However, the differences between those with mild BHR and those without BHR were small.

The relationship between the likelihood of a positive histamine challenge test and chronic respiratory symptoms was examined in a multiple logistic regression model, which included sex, age, smoking status, prechallenge FEV_1 and allergy. Of the symptoms only 'breathless when walking on the flat' (Odds Ratio [OR]=3·9; 95% confidence intervals [CI]=1·5–10·7; P-value=0·007) turned out to be independently related to BHR. Also prechallenge FEV_1 (OR=1·9;

Table 1 Prevalence of chronic respiratory symptoms in the total study group and by histamine challenge test (HCT) response*

Respiratory symptoms	Whole study group $n=551$	Positive[a] HCT $n=232$	Negative HCT $n=319$	OR	95% CI	*P*-value
Chronic cough	28 (5)	14 (6)	14 (4)	1·4	0·7–3·0	0·4
Chronic phlegm	22 (4)	9 (4)	13 (4)	1·0	0·4–2·3	0·9
Chronic cough/phlegm	37 (7)	19 (8)	18 (6)	1·5	0·8–2·9	0·3
Wheezing	106 (19)	52 (22)	54 (17)	1·4	0·9–2·2	0·1
Tightness/wheezing	60 (11)	30 (13)	30 (9)	1·4	0·8–2·5	0·2
Breathless/age	72 (13)	42 (18)	30 (9)	2·1	1·3–3·5	0·003
Breathless/upstairs	150 (27)	68 (29)	82 (26)	1·2	0·8–1·8	0·3
Breathless/flat	24 (4)	16 (7)	8 (3)	2·9	1·2–6·9	0·01
Any asthma symptom[b]	143 (26)	70 (30)	73 (23)	1·5	1·0–2·1	0·05

*Results are presented as numbers of subjects (column percentages in parentheses).
CI, confidence interval.
[a], Positive if $PC_{20} \leq 8{\cdot}0$ mg ml^{-1}.
[b], in case of an affirmative answer to at least one of the questions on 'chronic cough', 'chronic cough with phlegm', 'wheezing' and 'tightness with wheezing'.

Table 2 Prevalence rates of chronic respiratory symptoms in each grade of bronchial responsiveness (BR)*

	Degree of BR; PC_{20} grouping (mg ml^{-1})				
Respiratory symptoms	Severe 0–0·5 $n=35$ 6%	Moderate 1–2 $n=41$ 7%	Mild 4–8 $n=156$ 28%	No BHR ≥ 16 $n=319$ 58%	*P*-value[b]
Chronic cough	6	7	6	4	0·37
Chronic phlegm	6	2	4	4	0·95
Chronic cough/phlegm	20	5	6	6	0·10
Wheezing	54	29	14	17	0·003
Tightness/wheezing	31	22	6	9	0·01
Breathless/age	51	22	10	9	<0·001
Breathless/upstairs	49	32	24	26	0·11
Breathless/flat	11	0	8	3	0·02
Any asthma symptom[a]	57	39	22	23	0·004

$n=551$.
*Data are percentages of total in each column.
[a], in case of an affirmative answer to at least one of the questions on 'chronic cough', 'chronic cough with phlegm', 'wheezing' and 'tightness with wheezing'.
[b], Wilcoxon test for trend.

CI=1·1–3·1; $P=0{\cdot}02$) and allergy (OR=1·7; CI=1·2–2·4; $P=0{\cdot}007$) were independently related to BHR. However, the goodness of fit of the model including only the variables independently related to BHR had limited value (concordance 51%, discordance 26%). Therefore, there was no use assessing the predictive values of these factors for BHR. Both after stratification for FEV_1 and for allergy the odds ratios of the variables did not change significantly. However, in the case of airways obstruction [$FEV_1 \leq (FEV_1$ predicted $- 2SD)$] all six subjects who had reported getting breathless when walking on the flat were hyperresponsive.

When the PC_{20}-values 4·0 and 2·0 mg ml^{-1} were chosen as cutoff points (BHR considered present in case of $PC_{20} \leq 4{\cdot}0$ or in case of $\leq 2{\cdot}0$ mg ml^{-1}), the overall prevalence of BHR was 24% and 14%, respectively. Repetition of the multiple logistic regression

analysis with use of these lower PC_{20}-values as cutoff points showed that 'breathless when walking on the flat' was no longer significantly related to BHR (OR=2·4; CI=0·8–6·5; P=0·08, and OR=0·4; CI=0·1–1·8; P=0·23, respectively). At these cutoff points 'quicker breathless than people of the same age' became significantly related to BHR (OR=3·4; CI=1·9–6·1; P<0·001, and OR=3·5; CI=1·8–6·6; P<0·001, respectively). Again, in both cases the goodness of fit of the models was not sufficient to allow a useful assessment of predictive values, and stratification did not show a significant effect of prechallenge FEV_1 or allergy on the relation found.

Discussion

This study reports the results of an analysis of the relation between chronic respiratory symptoms and BHR in adolescents and young adults. Most chronic respiratory symptoms were related to (the severity of) BHR. However, after controlling several interacting factors, only 'breathless when walking on the flat' and 'quicker breathless than people of the same age' were statistically significantly related to BHR. Which of these symptoms was related to BHR depended on the definition of BHR (i.e. on the PC_{20}-value used as cutoff point beyond which subjects are considered hyperresponsive). These results were not dependent on the presence of allergy to inhalant allergens nor on the presence of airways obstruction. The predictive values of the symptoms for BHR were negligible. A substantial number of those with asthma symptoms did not show BHR, and a substantial number of those with BHR did not report asthma symptoms.

It was demonstrated that it is possible to determine the prevalence and severity of BHR in a large population of adolescents and young adults by means of a concise version of Cockcroft's histamine challenge test. No serious side-effects of the test were observed.

The prevalence of 'any asthma symptom' found in this study was higher than most of those reported in other studies, in which the highest estimates approximate to 34% (13). However, it is difficult to compare the findings because in almost every study the symptoms considered as asthma symptoms differ, the age groups differ, and other questionnaires are used.

For each symptom the prevalence figures were two to five times higher than those assessed with the same questionnaire in a survey of schoolchildren aged 6–12 (23). This may be due to differences in age category and to the fact that in that study the parents completed the questionnaire whereas in the present study the questionnaire was completed by the adolescents and young adults themselves (32).

The prevalence of BHR found in this study was higher than that reported in other population-based studies of children and adolescents, ranging from 16–23% (11–13,33), but also values of 4% in adolescents aged 11–17 years (34) and 64% in students aged 20–29 years (35) are reported. The differences in age distribution and in methods of measuring and defining BHR (other cutoff points) may partly explain these discrepancies. In this respect the present study can best be compared with that of Cockcroft and colleagues (35) (64% of subjects with PC_{20} $\leq 8{\cdot}0$ mg ml^{-1}) and that of Backer and colleagues (36) (16% of subjects aged 7–16 years with PC_{20} $\leq 8{\cdot}0$ mg ml^{-1}).

Our study group originated from birth cohorts of four general practices. The comparison of this group with those of the original birth cohorts who did not participate in the study showed that there was a small but statistically significant selection tending towards lower social class and female sex. Since morbidity figures are higher in lower social classes (37), the prevalence of symptoms and BHR may be overestimated. As these differences between the study group and those of the original birth cohorts who did not participate in the study were small, their influence on the results will have been limited. Selection bias will not have influenced the results of the analysis of the relationship between symptoms and BHR either. These high figures were probably not the result of recent respiratory infections either, since in that case the histamine challenge test was postponed for 6 weeks. Most tests were performed in December and January, thus avoiding the influence of the grass pollen season (38). Method failure seems to be an unlikely explanation as a standardized method was used (28) with regular calibration of the meters and nebulizers. Poor motivation in performing spirometry may have influenced the results, though the data of inadequately performed forced expiratory manoeuvres were excluded from the analysis.

The severity of BHR was closely related to wheezing and breathlessness, but not to cough. Most other studies found wheezing to be related to BHR as well (12–15,17,39). In a few studies, coughing has also been shown to be related to BHR (12,39). No relationship was found between BHR and sex, which is consistent with other investigations (11,14), but in contrast to other studies (11) BHR was not related to age either.

Since the predictive value of symptoms to BHR was negligible, it can be concluded that the standardized questionnaire was unable to discriminate between adolescents and young adults with and without BHR. These results are consistent with those of

studies with other standardized questionnaires in other age groups (16,17).

The finding that a substantial number of those with asthma symptoms did not show BHR has been found in other studies as well (12–14,33). The significance of asthma symptoms without BHR is not clear. Recently evidence has been provided that children with wheezing but without BHR show similar characteristics to asymptomatic non-hyperresponsive children (40), and this was confirmed after a 1-yr follow-up (41). This points to the fact that studies on the prevalence of asthma which only rely on data from questionnaires on these symptoms, are likely to overestimate its prevalence.

Of all subjects with BHR, 70% did not report asthma symptoms. Asymptomatic BHR has been found in other studies as well (11–14,33). Those with asymptomatic BHR may run a higher risk of developing asthma in later life (42). Hopp and colleagues found that BHR usually precedes the onset of asthma (43).

Long term follow-up studies on the course and prognosis of asymptomatic BHR and asthma symptoms without BHR may clarify the significance of these phenomena. The results of these studies may contribute to answering the question on the basis of which criteria the diagnosis of asthma should be established in screening surveys. The presence of both wheezing and BHR has recently been recommended as criteria in this respect (40). This is consistent with the recently published International Consensus Report on Diagnosis and Treatment of Asthma (44). Therefore, further research is needed to develop standardized questionnaires, which are more valid for BHR, e.g. by adding questions more specific to BHR, dealing with the symptomatic response to different stimuli (cold air, dust, exercise, chemical irritants).

In summary, there were two main findings in this study of a community based sample of subjects aged 10–23 years; firstly, of several chronic respiratory symptoms only 'breathless when walking on the flat' was independently related to BHR, but its predictive value for BHR was negligible; and secondly, of the subjects who showed BHR 70% did not report any asthma symptom, whereas 51% of those with one or more asthma symptoms did not show BHR.

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Appendix A

QUESTIONNAIRE

1. Chronic cough: did you usually – at least 5 days a week – cough (e.g. when getting up, or during the day or at night) for at least three consecutive months?
2. Chronic phlegm: did you usually – at least 5 days a week – bring up phlegm (e.g. when getting up, or during the day, or at night) for at least three consecutive months?
3. Chronic cough with phlegm: have you coughed up phlegm, more than usual, for at least three consecutive weeks in the last 12 months?
4. Wheezing: have you had wheezing in your chest in the last 12 months?
5. Tightness with wheezing: have you had attacks of tightness with wheezing in your chest (attacks of asthma) in the last 12 months?
6. Breathless/age: do you think that you get breathless more quickly than friends of your own age?

7a. Breathless/upstairs: have you been breathless going upstairs or riding a bike at a normal pace at least once in the last 12 months?

7b. Breathless/flat: if yes, have you been breathless when you walked on the flat at a normal pace at least once in the last 12 months?

8. Smoking behaviour: do you smoke? Have you ever smoked, but did you stop smoking?