

# The Natural History of Asthma in a Primary Care Cohort

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## ABSTRACT

**BACKGROUND** We examined the natural history of asthma in a primary care cohort of patients 10 years after the cohort was stratified for asthma risk by responses to a questionnaire and bronchial hyperresponsiveness (BHR) testing.

**METHODS** Children and young adults who were born between 1967 and 1979 within 1 of 4 affiliated family practices of the Nijmegen Department of Family Medicine, the Netherlands, were asked to participate in an asthma study in 1989. Of 926 patients available, 581 (63%) agreed to participate. Their family physicians' diagnoses of upper and lower respiratory tract disease and asthma were prospectively collected during the next 10 years and were analyzed.

**RESULTS** BHR or the presence of asthma symptoms at screening did not result in a significantly disproportionate number of physician visits during the next 10 years for 4 or more upper or lower respiratory tract infections when compared with patients who did not have these findings at the beginning of the study. The presence of asthma symptoms correlated with an increased risk of an asthma diagnosis or allergic rhinitis in the group of patients who did not have asthma diagnosed at start of the study. One half of the known asthmatic patients at the onset of the study (21 of 44) had no further visits to their physicians for treatment of asthma during the next 10 years.

**CONCLUSIONS** In primary care, BHR testing has limited value in predicting subsequent respiratory tract disease for patients who have asthma diagnosed by a physician. The use of symptom questionnaires can be of clinical use in predicting asthma.

*Ann Fam Med* 2004;2:110-115. DOI: 10.1370/afm.40.

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## INTRODUCTION

The current view of asthma is that of a chronic disease with periodic clinical exacerbations,<sup>1</sup> a considerable change from our previous view of asthma as primarily episodic in nature. The highly variable nature of the clinical course of asthma makes it difficult for physicians and patients to know at any given time how much treatment is necessary and for how long. Asthma is, in essence, still quite different from other chronic diseases, such as hypertension or hyperlipidemia, the natural histories of which we now know quite well. The only information about the natural history of asthma is based on relatively few cohort studies.<sup>2,3</sup> Information about the natural history of asthma in primary care populations remains a missing link between our biological knowledge of the disease and our clinical management of it. Insight into the natural history is complicated by the level of undiagnosed asthma.<sup>4-6</sup> Underdiagnosis of asthma is as much a problem for asthma research as it is for practitioners. Although much has been attributed to physicians' problems in interpretation of clinical information, there are growing indications that patients' reluctance to complain of symptoms or to adhere to follow-up visits also contribute to underdiagnosis.<sup>6</sup>

Longitudinal outcome studies of primary care patients with asthma should help us create this linkage and understand the developmental

Conflicts of interest: none reported

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epidemiology of asthma. Such studies require reasonable asthma definitions, stable primary care populations observed for prolonged periods, and—given the frequency of undiagnosed asthma—a population perspective. Most clinical studies of asthma have used a combination of bronchial hyperresponsiveness (BHR) testing and responses to respiratory questionnaires to assist with an asthma diagnosis. Use of these diagnostic tools is consistent with recommendations from the American Thoracic Society,<sup>7</sup> World Health Organization, and National Heart, Lung and Blood Institute.<sup>8</sup> Others have used physician diagnosis as the standard. Long-term follow-up remains a problem, partly because diagnosed asthma frequently disappears later on. Whether asthma disappears as a consequence of the natural history of asthma, adherence by the patient to treatment, or another phenomenon is not well known.

To improve our knowledge of the natural history of asthma, we observed a primary care cohort of children and adolescents that had been screened 10 years earlier for respiratory tract signs and symptoms by Kolnaar et al.<sup>9,10</sup> The objective of the current study was to clarify the natural history of respiratory tract complaints and asthma in primary care.

## METHODS

In 1989, a cohort of children and young adults from 4 affiliated family practices in the Netherlands was identified for an asthma study based on date of birth.<sup>9,10</sup> Given the structure of the Dutch health care system, this cohort reflects the characteristics of the population.<sup>11</sup> The study of Kolnaar et al<sup>9,10</sup> assessed the relation of early childhood respiratory tract morbidity and asthma in adolescence. For that reason, the study was confined to the 926 patients drawn from all the children born in Continuous Morbidity Registration practices (addressed below) between 1967 and 1979, and who were still registered with the practices in 1989. The study cohort did not differ from the original birth cohort in terms of respiratory tract morbidity, but patients were more often of lower social class.<sup>9</sup> From this group, 581 agreed to participate, and 551 (60%) were able to complete the testing and questionnaire satisfactorily for interpretation. Again, there were no essential differences between participants and nonparticipants with regard to respiratory tract morbidity. All participants were

screened for asthma by a symptom questionnaire and BHR testing.<sup>4,9,10</sup> The respiratory symptom questions used in this study are displayed in Table 1. This questionnaire was based on the children's version of the respiratory symptom surveys of the British Medical Research Council and American Thoracic Society.<sup>12</sup> Patients were considered symptomatic if they answered "yes" to the questions 1, 3, 4, or 5 (Table 1).

Histamine challenge testing was assessed by the concise version of the European Respiratory Society standardized testing procedure.<sup>13</sup> If the provocative concentration of histamine causing a 20% decline in forced expiratory volume (FEV<sub>1</sub>) was  $\leq 8.0$  mg/mL (PC<sub>20</sub>), the study participants were considered to have a positive BHR test. Details of this study have been previously described.<sup>10</sup> At the conclusion of this 1989–1990 study, all participants and their families were informed of their results, and those with symptoms or evidence of BHR were advised to visit their family physician.

No relation could be found between early childhood respiratory tract morbidity (mainly infections) and asthma, respiratory symptoms, or BHR testing results in 1989.<sup>9</sup> There was a substantial undiagnosed frequency of asthma (10%),<sup>4</sup> however, and we were intrigued by the high frequency of BHR (39%) in otherwise healthy adolescents without symptoms.<sup>10</sup>

Since 1967, 4 family practices associated with the University of Nijmegen in the southeast of The Netherlands have been continuously collecting outpatient morbidity data from all the patients they serve, a process now called the Nijmegen academic family practice research network Continuous Morbidity Registration (CMR).<sup>11,14</sup> The CMR was the source of the population and morbidity data for this study. The CMR provides a database in which the physician diagnoses (morbidity) for each episode of outpatient care are coded and recorded. Each patient has a unique identifier number

**Table 1. Respiratory Questionnaire Items**

| Symptom                   | Questions  |
|---------------------------|--|
| Chronic cough             | 1. Did you usually, at least 5 days per week, cough (when getting up or during the day or night) during a period of at least 3 consecutive months? |
| Chronic phlegm            | 2. Did you usually, at least 5 days a week, bring up phlegm (when getting up, or during the day, or at night) for at least 3 consecutive months?   |
| Chronic cough with phlegm | 3. Have you coughed up phlegm, more than usually, for at least 3 consecutive weeks in the last 12 months?  |
| Wheezing                  | 4. Have you had wheezing in your chest in the last 12 months?  |
| Tightness with wheezing   | 5. Have you had attacks of tightness with wheezing in your chest (attacks of asthma) in the last 12 months?  |
| Breathless, age           | 6. Do you think that you get breathless more quickly than friends of your own age?   |
| Breathless, upstairs      | 7. Have you been breathless going upstairs or riding a bike at a normal pace at least once in the last 12 months?                                  |
| Breathless, flat          | 8. If yes, have you been breathless when you walked on the flat at a normal pace at least once in the last 12 months?                              |
| Smoking behavior          | 9. Do you smoke? Have you ever smoked, and did you stop smoking?   |

**Table 2. Hazard Ratio for Getting an Asthma Diagnosis (N = 500)**

| Variable                      | Hazard Ratio | 95% Hazard Ratio Confidence Limits | P Value |
|-------------------------------|--------------|------------------------------------|---------|
| Symptomatic*                  | 3.414        | 1.386, 8.410                       | .008    |
| Bronchial hyperresponsiveness | 1.278        | 0.519, 3.148                       | .59     |
| Age                           | 0.816        | 0.687, 0.969                       | .02     |
| Male                          | 1.230        | 0.499, 3.031                       | .65     |

\* Symptomatic means  $\geq 1$  positive answer to the respiratory tract symptom questionnaire in 1989.

assigned at the point of care to which the coded morbidity is assigned, and this information is attached to other demographic data available for the patient. The physicians within the 4 practices meet regularly to discuss classification and coding issues to assure accuracy. Confidentiality is assured by having the identifier codes available only at the physician offices.

The Dutch health care system is ideally suited for this type of morbidity study because all patients are registered with a family physician, and all access to care must come through this physician. Family physicians' records include information of diagnosis and treatment by any other physician to whom the patient may have been referred. The CMR database includes, therefore, all diagnoses made through specialist care; for this study, respiratory tract diagnoses were made by chest physicians, internists, and pediatricians in addition to family physicians. Nearly everyone is insured by a single payer source, and the population is relatively stable. These factors allow excellent patient tracking and outstanding opportunities for studying disease longitudinally.

For this study, patient records were reviewed up to 2000. All but 7 patients could be found for follow-up, and data were available for 323 (59%) patients for the full 10-year period.

At the end of the 10 years of follow-up care, we reviewed the records of cohort patient visits to their

family physicians, looking for respiratory tract problems diagnosed by the physicians. The outcomes of the 1989–1990 screening period (symptomatic vs asymptomatic, BHR positive vs BHR negative, and the combination of symptomatic and BHR positive vs asymptomatic and/or BHR negative) were related to CMR-recorded respiratory tract morbidity from 1990 to 2000. Patients who had asthma diagnosed by their family physician before the 1989–1990 screening period were dealt with separately in the analysis. The analysis used the 1989 respiratory tract status of the patients (respiratory symptoms and BHR) as the independent variables, and the 1990–2000 respiratory tract morbidity diagnosed by their family physicians as the dependent variable. We used the Cox proportional hazard analysis to calculate the hazard ratio for getting an asthma diagnosis.

## RESULTS

Almost all 544 participants had at least 1 physician visit during the 10 years of the study. Fifty percent (272) of the population were women. The average age of the cohort at follow-up was 25 years for women and 24 years for men. Asthma was diagnosed at one time or another in 63 of the 544 patients (11.6%), of which 44 had asthma diagnosed at the onset of the study and 19 had asthma diagnosed after 1989.

From Table 2 it is apparent that the chance of having asthma diagnosed is significantly increased if patients are symptomatic or are of younger age. Remarkably, the chance is not significantly increased if patients have BHR, and there is no difference by patient sex.

Table 3 relates the baseline symptoms and BHR findings to subsequent upper and lower respiratory

**Table 3. Respiratory Tract Symptoms of 298 Active Patients Still in Practice Without an Asthma Diagnosis at Start of Study**

| Symptoms                                | BHR No. (%) | Non-BHR No. (%) | RR (95% CI)   | P Value | Symptomatic* No. (%) | Asymptomatic No. (%) | RR (95% CI)    | P Value |
|---|-------------|-----------------|---------------|---------|----------------------|----------------------|----------------|---------|
| > 4 upper respiratory tract infections† | 16 (13)     | 21 (12)         | 1.1 (0.6–2.3) | .70     | 10 (16)              | 27 (11)              | 1.5 (0.7–3.2)  | .34     |
| Lower respiratory tract infections‡     | 18 (15)     | 16 (9)          | 1.8 (0.9–3.6) | .10     | 6 (10)               | 28 (12)              | 0.8 (0.3–2.0)  | .46     |
| Allergic rhinitis                       | 18 (15)     | 21 (12)         | 1.3 (0.7–2.6) | .45     | 16 (25)              | 23 (10)              | 3.1 (1.5–6.4)  | .001    |
| Asthma                                  | 8 (7)       | 8 (5)           | 1.5 (0.5–4.1) | .40     | 8 (13)               | 8 (3)                | 4.1 (1.5–11.5) | .01     |
| Total                                   | 121 (100)   | 177 (100)       |               |         | 63 (100)             | 235 (100)            |                |         |

BHR = bronchial hyperresponsiveness; RR = relative risk; CI = confidence interval.

\*  $\geq 1$  positive answer to the respiratory tract symptom questionnaire in 1989.

† Includes otitis media, influenza, acute sinusitis, and laryngitis diagnoses.

‡ Includes pneumonia and acute bronchitis.

tract infections, allergic rhinitis, and asthma for the 298 patients who were still active in the practices and did not have a diagnosis of asthma at the start of the study. It is apparent that those patients with BHR differed little from those with no BHR in the likelihood of having their physician diagnose upper or lower respiratory tract infections, allergic rhinitis, or asthma. Those who answered affirmatively to 1 or more of the asthma questions in 1989 also did not differ greatly in their likelihood of subsequently visiting their physicians with respiratory tract infections. They did, however, have a significantly higher chance of having asthma diagnosed ( $P = .01$ , relative risk [RR] = 4.1, 95% confidence interval [CI], 1.5–11.5) or an allergic rhinitis diagnosis ( $P = .001$ , RR = 3.1, 95% CI, 1.5–6.4).

We compared the outcomes of those members of the cohort thought to be most at risk for respiratory tract problems, ie, those who had a positive BHR test and were symptomatic, with those who had a negative BHR test and were asymptomatic. The 2 groups did not appear to differ in the diagnoses of upper and lower respiratory tract infections. The absolute risk of an asthma diagnosis in this subgroup of symptomatic hyperresponders ( $n = 50$ ), however, was 10% compared with 2.6% for those who did not have these characteristics ( $P = .04$ ).

## DISCUSSION

This study shows that in this cohort of children and young adults, a single positive test for BHR has limited prognostic importance for subsequent respiratory tract illness, including asthma. Because this cohort contains a specific age-group, these results are not generalizable to a different age-group. Nevertheless, the prevalence of asthma of 20 in 1,000 in the study population is in the high-normal range of the Dutch adolescent primary care population,<sup>15,16</sup> so the a priori likelihood of asthma is representative of the family practice setting. More than 50% of patients with asthma did not have asthma diagnosed by their family physician,<sup>4</sup> which highlights the relevance of case finding.

The results of this study may mean that BHR testing has limited ability to capture the disease accurately. We showed, however, that more than 1 positive answer to questions 1, 3, 4, or 5 on the respiratory symptom questionnaire does correlate with an increased diagnosis of asthma in the future.

This study was aimed at all children and adolescents in the (practice) population and consequently included those with mild and moderate respiratory symptoms. It therefore describes the natural history of asthma as an episodic disease for which most patients will have no major difficulties into adulthood.

Despite the relatively nonspecific symptoms that characterize asthma, various asthma symptom questionnaires have been developed with validation studies to support their use.<sup>17–19</sup> These studies found that questionnaires were better than BHR testing as screening tools for asthma. This study confirmed these outcomes. The studies also found that the positive predictive value of symptoms for an asthma diagnosis or for subsequent problems was limited. On the basis of our findings, we calculated a predictive value of 13%, which is in line with the low prognostic value reported by others. We also found that those who had no symptoms gained little prognostic information from BHR testing. It appears that in the epidemiologic study of respiratory tract disease, BHR testing is most useful after respiratory symptoms have been assessed.

Respiratory tract infections, in particular viral infections, increase airway inflammation and thus may provoke or increase symptoms in patients with asthma.<sup>20,21</sup> For that reason, it might be expected that patients with asthma would visit their physician more often than nonasthmatic patients for respiratory tract infections. Our data, however, did not confirm this expectation. BHR is a marker of airway inflammation; for that reason, we were particularly interested in the patients who were asymptomatic in 1989 for BHR. The lack of respiratory tract episodes in the 10 years of follow-up make it improbable that in our cohort BHR heralded an early state of airway inflammation, which might be an important difference from the other studies.

In 1962, BHR was included in the already established definition of asthma as a disease characterized by reversible airflow obstruction.<sup>22</sup> A single BHR reading seems insufficient, however, to yield much useful information. When we applied more stringent criteria to the definition of BHR by reducing the PC<sub>20</sub> cutoffs for FEV<sub>1</sub> to  $\leq 4$  mg/mL,  $\leq 2$  mg/mL, and  $\leq 1$  mg/mL, we obtained fewer hyperresponsive patients, but a larger percentage of those had physician-diagnosed asthma. Because severity of BHR appears to correlate with asthma and a poorer outcome,<sup>23</sup> this finding is not surprising. In changing the diagnostic criteria, we improved the specificity of these tests for an asthma diagnosis, but in exchange, we diminished the sensitivity of the test to detect asthma. Josephs et al<sup>24</sup> found that PC<sub>20</sub> measurements did not consistently correlate with exacerbations of asthma. Pattemore et al<sup>25</sup> believed that BHR testing could "not reliably or precisely separate asthmatics from nonasthmatics in the general community." Salome et al<sup>26</sup> studied BHR, respiratory tract symptoms, and asthma in 2,363 Australian children and noted that the association between these parameters and asthma is significant but incomplete. Britton and Tattersfield<sup>27</sup> suggested that the validity of a

positive BHR test in the clinical diagnosis of asthma is limited. Rasmussen et al<sup>28</sup> in their Odense Schoolchild Study showed that in 10 years of follow-up, those with asymptomatic BHR on exercise testing had a weakly associated increase in coughing and wheezing. Many other community studies have confirmed the weak association between asymptomatic BHR and the subsequent development of asthma.<sup>29,30</sup> Laprise and Boulet,<sup>31</sup> however, showed that patients with asymptomatic airway hyperresponsiveness had a greater increase in airway responsiveness and frequency of development of asthma symptoms than did normoresponsive patients. Zhong et al<sup>32</sup> reported that 45% of asymptomatic students with positive BHR tests developed asthma in the following 2 years.

The strength of the CMR database is its completeness and the reliability of its recorded morbidity data.<sup>33</sup> This study does not elucidate the qualitative experiences of the cohort in regard to respiratory disease and has selected only to look at the morbidity of this group recorded by their physicians in the 10 years after testing. The number of cases of asthma in the community, however, is not well known to the family physician.<sup>4</sup> Van den Boom et al<sup>34</sup> showed in his primary care DIMCA study that a great many adults have considerable respiratory tract difficulties that they have not made known to their physician. This finding remains fascinating, because effective treatment of asthma is possible and from a physicians' perspective desirable. By not telling physicians about their symptoms of asthma, patients hamper the implementation of such treatment. A qualitative study to explore the patient's perspective is planned in a later phase of this study.

We have found BHR testing does not help us a great deal with determining who will have problems and who will require an intervention. We did find, however, that a positive answer to the asthma symptom questionnaire was associated with an increased risk of an asthma diagnosis in the future, which suggests that the use of an asthma symptom questionnaire does have clinical significance. Until we better understand the natural history of asthma in primary care and find better ways of looking for and treating patients at most risk, we will need to continue to be cautious about its diagnosis and management.

## CONCLUSIONS

The majority of those with diagnosed asthma or asthma symptoms in primary care do not have continuous problems with the disease.

A single test for BHR has a relatively low predictive value for adverse respiratory tract outcome.

More than 1 positive answer to an asthma symptom

questionnaire increases the chance for patients having asthma diagnosed in the future.

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**Key words:** Registries/epidemiology; bronchial hyperreactivity; asthma, symptoms; diagnosis

Submitted December 20, 2002; submitted, revised, April 4, 2003; accepted April 18, 2003.

**Funding support:** This study received financial support from the Dutch Asthma Foundation.

**Acknowledgments:** The authors acknowledge the help of John Hickner, MD, for his editorial assistance, and Henry Barry, MD, for his statistical acumen.

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