Asthma in adolescents and young adults: relationship with early childhood respiratory morbidity

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SUMMARY

Aim. *This study was undertaken to examine the relationship between respiratory illness in early childhood and asthma in adolescence and young adulthood (age group 10–23 years).*

Method. *The study population comprised 277 boys and 274 girls, born between 1967 and 1978 and registered from their birth to the year of study (1989) on the practice lists of the four general practices taking part in the continuous morbidity registration project (CMR) at the University of Nijmegen in the Netherlands. Details of all episodes of respiratory morbidity presented in the first five years of life and registered in the project were collected together with data on current respiratory status determined by means of a questionnaire on respiratory symptoms, spirometry and a histamine-challenge test.*

Results. *Sixteen per cent of the study group were diagnosed as having asthma. Only asthma and acute bronchitis in early childhood were significantly associated with asthma at age 10–23 years.*

Conclusion. *Asthma in adolescence and young adulthood is related to asthma and acute bronchitis in early childhood. This study supports the view that this could be a causal relationship although an alternative explanation could be misclassification. The results provide no indication that upper respiratory tract infections are associated with the development of asthma in adolescence or young adulthood.*

Keywords: asthma; respiratory tract infections; childhood morbidity; adolescents; young adults.

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Introduction

IT has been suggested that early childhood respiratory morbidity is related to the development of asthma,[1,2] particularly lower respiratory tract infections.[3,4] The mechanism of this relationship is poorly understood, but it seems probable that severe acute lower respiratory tract infections cause irreparable damage to the epithelium of the bronchi and bronchioles and to the irritant receptors in this epithelium, resulting in a state of chronic hyperreactive airways.[5,6] Epidemiological support for this hypothesis has been provided by several studies demonstrating a relationship between lower respiratory tract infections in early childhood and subsequent bronchial hyperresponsiveness.[7-10] The anatomical changes and enhanced reactivity might make the airways more susceptible to other harmful agents, such as cigarette smoke, or to repeated infections, thus initiating a process of progressive damage and decline of respiratory function, leading to asthma or chronic obstructive pulmonary disease in later life. The finding of Hopp and colleagues that bronchial hyperresponsiveness usually precedes the onset of asthma supports this hypothesis.[11]

Epidemiological studies on this subject were comprehensively reviewed by Samet and colleagues in 1983.[12] They concluded that there were important methodological shortcomings in most of the studies which were for the greater part retrospective and/or hospital-based, resulting in recall bias[13] and limited generalizability of the results. In their view, the evidence for a relationship between childhood respiratory illness and chronic airflow obstruction in adult life was insufficient to allow firm conclusions to be drawn.

Subsequently, other studies have reported a relationship between childhood respiratory morbidity and asthma in adulthood, partly avoiding the methodological problems described by Samet and colleagues.[14-17] In all these studies the diagnosis of asthma was based on signs and/or symptoms and/or spirometry; no evidence was presented on the development of bronchial hyperresponsiveness. However, bronchial hyperresponsiveness is generally recognized as an essential diagnostic feature of asthma.[18]

The aim of this study was to examine the relationship between early childhood respiratory illness and asthma in adolescence and young adulthood. Respiratory symptoms, lung function and bronchial responsiveness were assessed in a sample of adolescents and young adults, whose morbidity had been recorded prospectively since their birth in a general practice registration project. The influence of sex, socioeconomic status, allergy and other covariates on this relationship was also investigated.

Method

Study population

The subjects of this study were recruited from the practice population of the continuous morbidity registration project (CMR) of the department of general practice at the University of Nijmegen in the Netherlands. The characteristics of this registration project have been described elsewhere.[19,20] All the patients on the practice lists of the four practices taking part in the project, who were born between 1967 (the year the project started) and 1978 (1441

patients) and who were still on the 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 years. A total of 926 patients (64.3%) met these criteria — 484 male and 442 female patients, aged 10–23 years at the time of the study. Of the 515 patients who were no longer at the practices before the start of the study 492 had moved with their families to another area and 23 had died, none as a consequence of respiratory disease.

The 926 patients and their parents (in the case of those aged less than 16 years) were given a written explanation of the study and about one month later an oral explanation by telephone. Of the group, 581 patients (62.7%) gave informed consent and participated in the study.

Data collection

The morbidity data used in this study were collected prospectively from the continuous morbidity registration project database. All respiratory diagnoses ever recorded in the study population were included. These diagnoses related to the categories of the *International classification of health problems in primary care*[21] as follows: asthma conforms to ICHPPC-2 code number 493, hay fever to code number 477, pneumonia to 486, acute bronchitis to 466, laryngitis to 464, tonsillitis to 463 (including proven streptococcal infections 034), otitis media to 3820 and the common cold to 460 (including influenza 487).

The following aspects of the database and of the Dutch health care system are of relevance to this study. In the Netherlands every citizen is registered with a personal general practitioner; specialist care is only available through referral by this general practitioner. In the continuous morbidity registration project all episodes of disease[22] presented to the general practitioner are registered and classified (using an adapted form of the E-list[23]). Follow-up contacts for episodes already diagnosed and coded are not recorded. Diagnoses and codes are corrected when necessary. All the diagnoses made or corrected through specialist care are also included. In the case of chronic diseases[22] (in this study asthma and hay fever) only the first presentation is recorded; if the disease continues to be relevant to the patient's condition, later presentations in the following years are recorded with a prevalence code.[20]

The following information was also derived from the database: patients' age, sex and socioeconomic status (classified according to the occupation of the head of the family, using a standardized list of occupations for the Netherlands, grouped into two classes — lower and upper); whether patients had a family history (parents or siblings) of asthma (or chronic obstructive pulmonary disease), hay fever or atopic eczema; and patients' (or parents') illness behaviour, defined as the tendency to present non-serious diseases (those that do not influence the patient's functional ability) to the general practitioner.[24,25] In this study illness behaviour was assessed by counting the number of episodes of non-serious disease[20] (excluding respiratory disease) presented to the general practitioner in the five years preceding the start of the study.

Current respiratory status

The patients' current respiratory status was assessed in the winter of 1989–90 by a postal questionnaire and by spirometry and a histamine-challenge test carried out in a hospital laboratory or general practice surgery.

The questionnaire was based on the standard questionnaire on respiratory symptoms (children's version) of the British Medical Research Council and the American Thoracic Society[26] and was adapted for the age group 10–23 years and for self-administration. Questions on smoking behaviour were added. All patients completed the questionnaire themselves. In the case of at least one affirmative answer to the questions on respiratory symptoms asthma symptoms were considered to be present. The reproducibility of this questionnaire has been found to be satisfactory.[27]

Spirometry was carried out with the Microspiro HI-298® (Chest Corporation, Tokyo, Japan).[28] Each patient had to perform three satisfactory forced vital capacity (FVC) manoeuvres (values within 10% of each other). Data were recorded from the highest sum of FVC and the forced expiratory volume in one second (FEV_1). Patients who had a FEV_1 less than or equal to the predicted FEV_1 minus two standard deviations[29,30] were considered as having airways obstruction. Patients who had a baseline FEV_1 of less than or equal to 50% of their predicted FEV_1, or less than or equal to one litre, were excluded from the histamine-challenge test.

The histamine-challenge test was performed using the concise version[31] of the method described by Cockcroft and colleagues.[32] Bronchodilators and antihistamines, when used, were withheld for at least eight and 48 hours, respectively, before the test. When a patient had had a respiratory tract infection with fever in the last six weeks, the test was postponed until at least six weeks after the infection. Results were expressed as the concentration of histamine required to produce a 20% decrease in FEV_1 (PC_{20}). Patients with a PC_{20} of less than or equal to 8.0 mg ml^{-1} were considered to have bronchial hyperresponsiveness.

Allergy

Allergy to inhaled allergens was assessed by the Phadiatop test (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden).[33]

Definition of asthma

Asthma was defined as the presence of chronic and/or recurrent respiratory symptoms in combination with airways obstruction and/or bronchial hyperresponsiveness. Patients were considered to have asthma when they gave an affirmative answer to at least one of the questions on respiratory symptoms and when they had either bronchial hyperresponsiveness (as defined above) or had airways obstruction (as defined above).

All the patients who had been diagnosed as having asthma and/or who were being treated for asthma by their general practitioner in the five years preceding the start of this study were also considered to have asthma, regardless of their screening results.

Analysis

In order to determine whether the participants in this study formed a representative sample of the original birth cohorts, they were compared with those in the original birth cohorts who did not form part of the study population. Sociodemographic features and respiratory morbidity recorded in early childhood (the first five years of life) were compared using the chi square test. Therefore, children who had left the practices before the age of five years (for whom all the data for early childhood respiratory morbidity were not available) were excluded from this comparison.

In analysing the relationship between early childhood respiratory morbidity and asthma in adolescence and young adulthood the former was considered as the independent variable and the latter as the dependent variable. A simple analysis was made initially: each respiratory illness in early childhood was separately related to asthma in adolescence and young adulthood. A chi square test was used to determine the significance of the relationships.

In order to determine the influence of potentially interacting factors (sociodemographic characteristics, family history of

asthma, hay fever or atopic eczema, allergy to inhaled allergens, illness behaviour and active and passive smoking) on the relationships found in the simple analysis, the Breslow–Day test was used.[34] When studying a relationship in which a potentially interacting factor comprises different categories, this test enables determination of whether the odds ratios or relative risks of the categories differ significantly. If a significant difference is found, it can be concluded that the strength of the relationship depends on the category or level of the interacting factor.

A multiple logistic regression analysis was then carried out. This analysis involves finding the best mathematical model (in this case in a logistic form) to describe a dependent variable as a function of several independent variables, or to predict the dependent variable from these independent variables.[35,36] Here it was used to identify early childhood respiratory illnesses that were independently related to asthma in adolescence and young adulthood, controlling for the potentially interacting factors mentioned above. In addition, the goodness of fit of the model with only these illnesses as independent variables was determined to judge whether it could be used to assess the predictive values of these illnesses for asthma in adolescence and young adulthood. The regression analysis was repeated for respiratory morbidity recorded during the remaining years between five years of age and the start of the study. Finally, the regression analysis was carried out using stricter criteria for the diagnosis of asthma in adolescence and young adulthood.

All analyses were performed using the *SAS* statistical package.

The study was approved by the ethics committee of the Faculty of Medicine of the University of Nijmegen.

Results

The data from 30 of the 581 patients who participated in this study were excluded from analyses: three patients were not able to perform reproducible forced expiratory manoeuvres, seven could not finish the histamine-challenge test owing to cough although FEV_1 was not significantly decreased and 20 did not complete the questionnaire satisfactorily. None of the participants had an initial FEV_1 of less than or equal to 50% of their predicted FEV_1, or less than or equal to one litre. All the necessary data were therefore available for 551 patients and they formed the study population.

The comparison between the study population (n = 551) and those from the original birth cohorts who did not form part of the study population (excluding those who had left the practices before the age of five years) (n = 589) showed that significantly fewer patients in the study population were in the upper social class and were male than of those who did not participate. Significantly fewer non-participants had presented episodes of most respiratory diseases in the first five years of life than had participants. There were no differences with respect to age.

Table 1 shows the prevalence of the asthma symptoms among the 551 patients. One or more asthma symptoms were present in 143 patients (26.0%). Airways obstruction was demonstrated in 93 patients (16.9%) and bronchial hyperresponsiveness in 232 (42.1%). On the basis of the screening criteria asthma was diagnosed in 82 patients (14.9%). In addition, 25 patients (4.5%) had been diagnosed as having asthma and/or had received asthma treatment from the general practitioner in the five years preceding the study. Overall, asthma was diagnosed in 89 patients (16.2%).

Table 2 shows the relationship between respiratory illnesses in the first five years of life and asthma when aged 10–23 years. Only asthma and acute bronchitis in early childhood were significantly related to asthma when aged 10–23 years. Pneumonia, hay fever and the upper respiratory tract infections (common cold, laryngitis, tonsillitis and otitis media) were not related to asthma when aged 10–23 years.

Table 1. Patients' responses to questions on asthma symptoms and smoking behaviour.

Question	% of patients responding positively (n = 551)
Chronic cough: Have you had a cough (when getting up, during the day or at night) for at least 5 days a week for a period of at least 3 months in the last 12 months?	*5.1*
Chronic cough with phlegm: Have you coughed up more than normal amounts of phlegm, for at least 3 consecutive weeks in the last 12 months?	*6.7*
Wheezing: Have you had wheezing in your chest in the last 12 months?	*19.2*
Chest tightness with wheezing: Have you had attacks of tightness with wheezing in your chest (attacks of asthma) in the last 12 months?	*10.9*
Smoking behaviour:	
Do you smoke?	*18.1*
Have you ever smoked, but have now stopped?	*5.4*
Parental smoking: Did your parents smoke during the first 5 years of your life?	*72.2*

n = total number of patients.

Table 2. Relationship between respiratory illness in the first five years of life and asthma when aged 10–23 years.

Respiratory illness in early childhood		No. of patients	% of patients with asthma aged 10–23 years	Relative risk of asthma (95% CI)
Asthma	Yes	22	*45.4*	3.0 (1.8 to 5.0)***
	No	529	*14.9*	
Acute bronchitis	Yes	200	*23.0*	1.9 (1.3 to 2.7)**
	No	351	*12.3*	
Pneumonia	Yes	46	*21.7*	1.4 (0.8 to 2.5)
	No	505	*15.6*	
Hay fever	Yes	15	*13.3*	0.8 (0.2 to 3.0)
	No	536	*16.2*	
Common cold[a]	Yes	286	*16.8*	1.1 (0.7 to 1.6)
	No	265	*15.5*	
Laryngitis	Yes	48	*18.8*	1.2 (0.6 to 2.2)
	No	503	*15.9*	
Tonsillitis	Yes	301	*14.3*	0.8 (0.5 to 1.1)
	No	250	*18.4*	
Otitis media	Yes	319	*17.9*	1.3 (0.9 to 1.9)
	No	232	*13.8*	

CI = confidence interval. [a]Four times or more. **P<0.01, ***P<0.001.

Table 3 shows the influence of possible confounding or effect modifying factors on the relationship between acute bronchitis in the first five years of life and asthma when aged 10–23 years. This relationship was only dependent on passive smoking in the first five years of life — for those who had acute bronchitis in the first five years of life the risk of having asthma when aged 10–23 years was higher when there was no history of passive smoking in early childhood.

Multiple logistic regression analysis showed that only early childhood asthma and acute bronchitis were independently related to asthma in adolescence and young adulthood. However, the goodness of fit of the model with only these two conditions as independent variables had limited value (concordance 63%, discordance 37%). There was, therefore, no point in assessing the predictive values of these illnesses for asthma in adolescence and

Table 3. Relative risk estimates for asthma when aged 10–23 years in relation to acute bronchitis in the first five years of life, controlling for interacting variables.

Controlling for:		No. of patients	Relative risk of asthma (95% CI)
Age (years)	<16	306	2.37 (1.47 to 3.80)
	⩾16	245	1.36 (0.73 to 2.53)
Sex	Male	277	1.71 (1.02 to 2.87)
	Female	274	2.06 (1.18 to 3.59)
Social class	Lower	272	2.27 (1.28 to 4.01)
	Upper	279	1.63 (0.96 to 2.77)
Practice	1	215	2.22 (1.16 to 4.25)
	2	38	3.25 (0.62 to 16.98)
	3	155	1.50 (0.81 to 2.77)
	4	143	1.90 (0.86 to 4.21)
Family history			
Asthma	No	442	2.12 (1.38 to 3.24)
	Yes	109	1.19 (0.53 to 2.69)
Hay fever	No	396	2.17 (1.39 to 3.38)
	Yes	155	1.31 (0.64 to 2.69)
Atopic eczema	No	444	1.98 (1.28 to 3.07)
	Yes	107	1.55 (0.74 to 3.24)
Allergy[a]	No	329	2.08 (1.12 to 3.87)
	Yes	163	1.50 (0.91 to 2.46)
Illness behaviour[b]	Lower	270	2.54 (1.39 to 4.66)
	Higher	272	1.48 (0.91 to 2.43)
Personal smoking	Never	421	1.95 (1.22 to 3.12)
	Ever	130	1.54 (0.73 to 3.22)
Passive smoking*	No	153	3.78 (1.81 to 7.88)
	Yes	398	1.43 (0.91 to 2.24)

CI = confidence interval. [a]To inhaled allergens; data missing for 59 patients. [b]Frequency distribution of non-serious illnesses presented divided into 50% with lower and 50% higher level of presentation; data missing for 9 patients. *Difference between relative risks: $P<0.05$.

young adulthood. Multiple logistic regression analysis using respiratory morbidity presented between the age of five years and the start of the study as the independent variable showed the same results.

Logistic regression analysis was repeated using stricter criteria for the diagnosis of asthma — affirmative answers to all the questions on respiratory symptoms were required rather than at least one. The results of this analysis again showed that only asthma and acute bronchitis in early childhood were independently related to asthma in adolescence and young adulthood.

Discussion

In this study the relationship between respiratory morbidity in early childhood and asthma in adolescents and young adults was investigated. It was essential that the patients studied were a stable group and in the four practices in this study about two thirds of the adolescents and young adults could be followed up for at least 10 years from birth. The study required extensive testing inevitably leading to dropout, but again nearly two thirds of the patients meeting the study criteria agreed to take part. On the basis of the comparisons of the study participants with those in the original birth cohorts who did not form part of the study population it appeared that the patients studied formed a group in which a slightly greater proportion had presented episodes of respiratory morbidity to general practice in early childhood. However, this selection is unlikely to have influenced the results of the analysis of the relationship between early childhood respiratory morbidity and asthma when aged 10–23 years, since the non-participants neither consisted of the children with only low nor with only high levels of respiratory morbidity in early childhood.

When the diagnosis of asthma was based on both the general practitioner's recognition and screening results, the prevalence of asthma in this study population was 16%. Other studies have found a prevalence of between 3% and 31%.[37-41] It is difficult to compare these figures, however, since the methods applied to assess this prevalence vary widely.

Most studies of the relationship between respiratory morbidity in early childhood and asthma in adolescence have been retrospective and/or hospital-based.[12] In this study prospectively collected data on respiratory morbidity were used, so the problems of lack of recall and recall bias have been avoided. Moreover, the data on respiratory morbidity were based on the diagnostic opinion of general practitioners. However, only episodes of diseases presented to the general practitioner were included. A previous study of the population of the continuous morbidity registration project showed that patients present only a small part (10%) of the illnesses they experience.[42] Illness behaviour will influence the presentation of less serious illnesses such as upper respiratory tract infections; it will influence the presentation of more serious morbidity such as asthma, acute bronchitis and pneumonia to a lesser extent.

It has been suggested that asthma is underdiagnosed in general practice.[43-45] The diagnosis of asthma used in this study could not, therefore, be based solely on the registration of asthmatic patients by the general practitioner — screening was also necessary. However, there is still no consensus about the criteria for identification of asthma in epidemiological studies and any choice of criteria remains arbitrary. In this study it was considered important that asthma in adolescence and young adulthood, the dependent or outcome variable, should be defined in such a way that we were reasonably certain that all the patients labelled as having asthma had the disease, that is, with an emphasis on specificity. The symptoms of asthma can be present in and/or can be reported by patients who do not have asthma. In the population studied here the prevalence of asthma symptoms was high: more than a quarter of all patients reported at least one asthma symptom. If the diagnosis of asthma had only been based on these symptoms, the prevalence might have been overestimated. Bronchial hyperresponsiveness has been considered by many researchers[46-48] and the American Thoracic Society[18] as an essential diagnostic feature of asthma. However, both its specificity[49-51] and its sensitivity[52-54] to asthma have been questioned. Therefore, the diagnosis of asthma used here was not based on bronchial hyperresponsiveness alone but on bronchial hyperresponsiveness and/or airways obstruction in the presence of asthma symptoms. Recently, symptomatic bronchial hyperresponsiveness has been shown to be the most useful definition to date for measuring the prevalence of clinically important asthma in populations.[55] Adopting stricter criteria, thus making the diagnosis of asthma less sensitive and more specific, did not change the results of the present study. Therefore, it can be concluded that the weak relationship found in this study cannot be attributed to the choice of the criteria for asthma.

The results showed only a relationship between asthma and acute bronchitis in early childhood and asthma in adolescence and young adulthood. This confirms the view that asthma in early childhood is usually of a lasting character. A relationship between pneumonia and asthma could not be excluded on the basis of this study because of the small number of children that had had pneumonia in their first five years of life. These relationships have been found in other studies,[2,14,16,17] and are compatible with an increased bronchial responsiveness as a pathophysiological pathway to asthma.[11] Another explanation for these relationships could be a classification problem: symptoms attributed to acute bronchitis and, less probably, pneumonia in early child-

hood could have been the first manifestation of asthma. The eventual diagnosis of asthma requires recurring episodes of this disease, initially diagnosed as acute bronchitis or pneumonia.

Other investigators have found a relationship between tonsillitis, sinusitis and hay fever in childhood and asthma in later life. [2-17] The results of the present study did not confirm these findings (only three episodes of sinusitis were registered in the first five years of life in the study group).

The relationship between acute bronchitis in early childhood and asthma in adolescence and young adulthood was dependent on passive smoking in early childhood. For those who had acute bronchitis in their first five years of life the risk of having asthma when aged 10–23 years was higher when they did not have a history of passive smoking in the first five years of life. This surprising finding could be due to a 'healthy passive smokers effect', resulting from selective non-smoking in high risk families. This might give an indication of the role of acute bronchitis in the pathogenesis of asthma. However, the fact that the relationship between acute bronchitis and asthma was particularly strong in children from non-smoking households could indicate that acute bronchitis is more a marker of children at risk than a causal factor in itself.

In conclusion, only early childhood asthma and acute bronchitis are weakly related to asthma in adolescence and young adulthood and appear to be relevant factors. No indications were found that upper respiratory tract infections are related to the development of asthma. The relation to acute bronchitis is compatible with the assumed influence of lower respiratory tract infections on bronchial hyperresponsiveness. Further research in this area is needed. The alternative explanation is misclassification of early childhood asthma. Patients with asthma and with (apparent) acute bronchitis in early childhood should be closely observed and followed up.

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