

Review

Definition of respiratory symptoms and disease in early childhood in large prospective birth cohort studies that predict the development of asthma

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We have reviewed the prospective value of early respiratory symptoms for determining the risk of development of asthma later in life by using data from studies based on the general population, hospital population, and general practices. Although 'wheezing' in infancy generally has a good prognosis, it is an important risk factor for the development of asthma later in life. The prognostic value of 'coughing' and 'shortness of breath' in infancy for the later development of asthma is less clear.

Despite the fact that no internationally accepted criteria for the definition of asthma in early childhood are available, many studies have been performed on this topic. We also investigated the outcome variables that were used to describe respiratory symptoms and disease in early childhood in the publications of nine large prospective birth cohort studies on the development of asthma. From seven of these studies, we reviewed the original questionnaires. We found that various studies used different outcome variables, but the data actually collected were similar. This is an important observation because it implies that comparisons between studies can be markedly improved by data sharing among investigators.

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Systematic international comparison of the prevalence of asthma has been made possible for school-age children by the International Study of Asthma and Allergy in Childhood (ISAAC) (1,2). Unfortunately, no valid criteria for asthma are available for infants and preschool children. Comparison of the prevalence of early respiratory symptoms in different regions of the world is clearly important for learning about the etiology of asthma in greater detail (3). The most important symptom of asthma is wheeze; other symptoms include shortness of breath and recurrent cough (4). Wheezing and cough are especially common in preschool children, in

whom they usually occur in association with respiratory infections, and asthma will develop in only a minority of children who have ever wheezed. This raises the question of which respiratory symptoms in early life are relevant for the subsequent risk of developing asthma. The first aim of this work was to assess the prognostic value of respiratory symptoms in preschool children with respect to subsequent development of asthma. The second aim was to compare the respiratory outcome variables that have been used for children of 0–3 years of age in publications of large birth cohort studies in regard to risk factors for the development of asthma in child-

hood. In addition, we collected the original questionnaires of most of these studies in order to compare the data that were actually gathered.

Prognostic value of respiratory symptoms in preschool children

Wheezing

Wheezing is the most frequently studied respiratory symptom in preschool children with regard to its prognostic value for the later development of asthma. However, wheeze is a problematic symptom. Members of non-wheezing families do not necessarily recognize a wheeze properly (5), and upper respiratory noises (such as sniffles, snoring, and stridor) are difficult to differentiate from wheeze. Furthermore, when questionnaires are used for international comparison, many languages do not have an equivalent for wheezing.

Wheezing is a relatively common symptom in infancy and early childhood and affects ≈ 25 –60% of children in the first few years of life, depending on the definition that is used and the population that is studied (6). Wheezing in early life is highly associated with viral infections (7); however, until the end of the 1980s no distinction was made between descriptive terms such as virus-associated wheezy bronchitis, recurrent bronchiolitis, and asthma. These syndromes were considered as having a common underlying disorder (8,9). To date no diagnostic tools are available to distinguish between transient and persistent wheezing at an early stage (10,11). Nevertheless, even though the majority of children who wheeze in infancy and early childhood do not develop asthma later in life, follow-up studies indicate that wheezing in infancy remains an important risk factor for wheezing later in life. In the Tucson cohort, 40% of the children who wheezed at least once in the first 3 years of life also wheezed at age 6, compared to only 22% of the children who did not wheeze in the first 3 years of life (10). Infants with wheezing lower respiratory disease in infancy are four to five times more likely to have recurrent wheezing at age 11 (11). These findings are in agreement with various other population-based studies (12–18). In highly selected hospital- or general practice-based populations, some studies showed remission of wheezing in more than 50% of the patients (19–21), while other studies showed persistence of symptoms in later life in the majority of patients (8,22,23). Most studies indicate that early-onset wheezing has a better

outcome than late-onset wheezing (15,17,20,24), but some controversy exists (8,16,23).

One retrospective population-based study showed that the number of wheezing episodes in the first year of life was positively associated with the persistence of wheezing episodes at 10 years of age (16). The result of this study can also be explained by recall bias. However, this finding is in agreement with the conclusions of three other studies in symptomatic children (8,22,25). We are not aware of any population-based prospective birth cohort study that has investigated the prognostic value of the frequency of wheezing attacks on the persistence of symptoms. Moreover, it is unclear whether the length of wheezing periods in preschool children has a prognostic value for the development of asthma later in life.

Chronic coughing and shortness of breath

In asthmatic schoolchildren, chronic coughing has been described as the ‘cough variant asthma’ (26). In addition, in cases of chronic coughing in infants and preschool children, a diagnosis of ‘cough variant asthma’ is frequently made (27). Minimal data exists on the relevance of chronic coughing in relation to the subsequent development of asthma later in life. The prevalence of chronic coughing in the absence of cold in preschool children, recruited from the general population, was estimated to be 10% in the United States and 20% in the UK (14,28). In one British study in preschool children, recurrent coughing, defined as a positive answer to the question ‘Does your child usually cough without a cold?’, was not associated with the development of wheezing, bronchial responsiveness, pulmonary function or peak flow variability after 3 years of follow-up (13,29). Although in this study nearly 60% of participants were lost to follow-up, these findings are in agreement with another prospective study in the USA, where no associations were found between frequent or chronic coughing in the first 2 years of life and the diagnosis of asthma at 10 years of age (14). In the same study a statistically significant association was found between reported shortness of breath at 1–2 years of age and the development of asthma at 10 years of age. This association was not significant for the 0–1-year age-group despite an odds ratio of 4.8.

Little data is available concerning the prognostic value of a combination of respiratory symptoms in early life on the subsequent development of asthma. Dodge et al. found that the risk of developing asthma was significantly higher

Table 1. Outcome variables used to describe respiratory symptoms and disease in nine prospective birth cohort studies designed to study the development of allergic disease

Author	Year	Subjects	Follow-up (months)	Definition used for the respiratory illness	Type of information	Personnel who completed/obtained the information
Croner & Kjellman Sweden (38)	1982	1701	18	Obvious bronchial asthma = recurrent wheezing, observed by the study doctor. Possible bronchial asthma = recurrent wheezing during infections or other occasions	Questionnaire Physical examination (only children with symptoms)	Parents Doctor
de Jong et al. The Netherlands (30)	1998	1482	6, 12, 24	Obvious asthma = ≥ 3 episodes of asthma or wheezing a year Possible asthma = respiratory symptoms suggesting asthma one or two times a year (asthma not defined by the authors)	Weekly symptom cart Questionnaire Physical examination	Parents Parents Doctor
Bergmann et al. Germany (31)	1994	1239	1, 3, 6, 12, 18, 24	Obvious asthma = ≥ 2 episodes of wheezing with shortness of breath in the first and second year Possible asthma = not defined by the authors	Diary for symptoms Questionnaire Structured interview Physical examination	Parents Parents From parents, by doctor Doctor
Fergusson et al. New Zealand (34)	1981	1180	12, 24	Lower respiratory symptoms = medically treated bronchitis or pneumonia or >1 episode of parental reported wheezing or chesty cold	Diary for symptoms Structured interview Hospital records	Parents From parents, by doctor Unclear
Arshad & Hide UK (36)	1992	1167	12, 24	Asthma = ≥ 3 episodes of cough and wheezing in the first year	Observation Questionnaire Physical examination	Study nurse Parents Doctor
Cushing et al. Albuquerque, USA (35)	1993	1051	0–18	Lower respiratory illness = ≥ 2 consecutive days of any upper respiratory symptoms and either wet cough or wheezing or both for at least 1 day	Diary for symptoms (only children with symptoms)	Parents
Martinez et al. Tucson, USA (10)	1992	826	0–36	Parents were instructed to contact SD when signs of respiratory illness occurred (deep or wet chest cough, wheezing, hoarseness, stridor or shortness of breath) Lower respiratory tract illness with wheezing: if wheezing was found at physical examination	Telephone interview Questionnaire Structured interview and physical examination	From parents, by nurse Parents Pediatricians of health maintenance organization
Lucas et al. UK (32)	1990	777	9, 18	Asthma or wheezing = diagnosis of asthma or ≥ 1 episode of wheezing in the first 18 months. Asthma not defined by the authors	Structured interview and physical examination	Clinical scientists and doctor
Hansen et al. Denmark (33)	1991	762	6, 12, 18	Definite asthma = Bronchial asthma (not further defined by the authors) in the first 18 months Possible asthma = ≥ 2 episodes of wheezy bronchitis	Questionnaire Telephone interview Physical examination	Parents Unclear Pediatricians

SD, study doctor.

Table 2. Information available in seven prospective cohort studies based on reviewing the original questionnaires

	Croner & Kjellman Sweden (38)	De Jong et al. The Netherlands (30)	Bergmann et al. Germany (31)	Fergusson et al. New Zealand (34)	Arshad & Hide UK (36)	Martinez et al. Tucson, USA (10)	Hansen et al. Denmark (33)
Exact question on wheezing in questionnaire/interview	Did your child have wheezy or noisy breathing or serious irritating cough or shortness of breath Two categories: < 3 episodes or at least 3 episodes No Yes	Did your child have a wheezing respiration? Exact number of episodes recorded Yes Yes	Did your child have a wheezing or whistling respiration? Exact number of episodes recorded Yes Yes	Has your child visited a doctor/hospital for chesty cold or wheezy chest? Seven categories ranging from 0 to >10 episodes No No	Did the child have any wheezing episodes? Three categories ranging from 0 to > 3 episodes No No	Did your child have wheezing? Exact number of episodes recorded Yes Yes	Unknown†
Information on number of wheezing episodes*							Three categories: 0, 1–2 and 3 or more episodes No Yes
Information on duration of wheezing episodes*							
Information on symptoms of cold during wheezing episode*							
Information on cough*							
Information on shortness of breath*							
Information on other respiratory symptoms or disease*							
Information on doctor's visit for any disease							
Information on respiratory medication							

*Information collected by a standard question in a questionnaire or structured interview.

†Exact question unknown, diagnose based on interview: asthma = at least three episodes of wheezing requiring bronchodilator treatment and diagnosed by a physician. Recurrent wheezy bronchitis: at least two episodes of respiratory infections associated with wheezing, requiring bronchodilator treatment and diagnosed by a physician.

among infants with any one of three respiratory tract symptoms (frequent cough, wheezing without colds, or attacks of shortness of breath with wheeze) when they were compared with infants without any of these symptoms (14).

Respiratory outcome variables used in cohort studies

Many prospective birth cohort studies have been initiated to identify risk factors for the development of asthma. These studies can also be used to determine the prognostic values of respiratory symptoms in early childhood for the development of asthma later in life. From this perspective, it is interesting to evaluate which symptoms are used in these studies to define respiratory disease in the first 3 years of life. We performed a medline search using the following inclusion criteria: articles written in English between 1980 and 1999, prospective birth cohort study, respiratory symptoms (wheezing, cough, shortness of breath, dyspnea), and disease (asthma, obstructive disease, wheezing disorders, recurrent wheezing). Only studies containing published data on respiratory outcome after preschool age, or which stated that subjects would be followed-up for the development of asthma later in life, were included. We decided to review only studies in which the results were based on at least 750 subjects. We found nine studies that fulfilled these criteria, and the characteristics of these studies are summarized in Table 1. For each study only one article is mentioned as a reference, although most groups published more than one article. We have focussed on the outcome variables that were used to describe respiratory symptoms and disease in the first 3 years of life, the method and time interval of data collection, and relevant supplementary investigations. In addition, we asked the nine corresponding authors of these articles to send us the original questionnaire or structured interview used in their study. In response, seven sent us their questionnaires.

Published outcome variables used to describe respiratory symptoms and disease

All nine studies used wheezing as the most important symptom of respiratory disease and six used the term 'asthma' to describe these symptoms. Four studies provided an incomplete definition in their method section (30–33). Three studies considered a single wheezing episode per year as a case (10,32,34), while in other studies this required more than two (31,33,35) or more than three episodes (30,36). In one study, the frequency of wheezing episodes was not men-

tioned (37). In the same study, obvious asthma was only diagnosed when symptoms were confirmed by a physical examination. Only one study defined the minimal duration of a wheezing episode (35). Although most studies used wheezing as the only relevant symptom, one also included shortness of breath (31) and another study used coughing (36) as a criterion to be considered as a case. In a study from New Zealand, medically documented bronchitis or pneumonia was incorporated in the definition of lower respiratory illness (34). In three studies, the presence or absence of signs of rhinitis or infection in relation to wheezing were considered as criteria (10,35,37).

Method of data collection

Follow-up intervals varied from four times a year (31) to once in 18 months (37). In one study, the follow-up period was a continuum, and subjects were seen during episodes of respiratory disease (10). Eight out of nine studies used questionnaires completed by the parents, and four studies used weekly or monthly symptom cards (30,31,34,35). In seven out of nine studies, the subjects were seen and interviewed by a study doctor or nurse (10,30–33,36,38); the other three studies relied on questionnaires or medical records only. In two of the seven studies in which a physical examination was performed, the children were examined only when they had signs and symptoms of atopic disease (36,37), while in the remaining five studies all were examined.

Relevant supplementary investigations

Lung function measurements were performed in only one of the nine studies (10). Viral cultures were taken in two studies (10,35).

Information collected on respiratory symptoms and disease, based on review of the original questionnaires or structured interviews

Table 2 summarizes the data on respiratory symptoms or disease in early childhood that were actually collected by questionnaire or structured interview in seven prospective cohort studies on the development of asthma. All studies collected data on the number of wheezing episodes, and the categories are generally comparable. Data on coughing were available in five out of seven studies. Information on shortness of breath and symptoms of cold during wheezing episodes was less extensively collected. All studies collected data on symptoms of cold or rhinitis independently of wheezing episodes and most

studies also gathered information about lower respiratory tract infections. Six out of seven studies collected data on respiratory medication. Finally, in all seven studies the study doctor or nurse recorded additional information about the respiratory health of the child in a non-structured fashion.

Conclusions

Recent birth cohort studies have contributed greatly to our understanding of the natural history and prognosis of respiratory symptoms and disease in early childhood, but many issues are still unresolved. It is now well established that early wheezing is associated with asthma later in life, but the majority of wheezing infants will not develop asthma. The relative prognostic value of the frequency or duration of wheezing episodes, and the significance of the presence or absence of signs of the common cold during wheezing episodes in preschool children for the development of asthma later in life, needs further study. Chronic or persistent cough in preschool children seems to be a poor predictor for the development of asthma later in life. The definitions and terminology that have been used in publications to describe lower respiratory symptoms and disease in early childhood differed widely between large prospective birth cohort studies. In addition, the methods used to collect data differed between studies. This may contribute, to a large extent, to the considerable variation reported in the prevalence and incidence rates for respiratory symptoms and disease in infancy and early childhood. Only a limited part of the large data sets of recent studies has been published. However, based on review of the original questionnaires, the various studies are considerably more comparable than can be concluded from the published literature. Pooling data from different cohort studies could therefore be attempted to investigate the prospective value of different respiratory symptoms in early life that might determine the risk of later asthma. This would be useful for defining the criteria for respiratory symptoms in early life that can be used for future birth cohort studies.

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