

Severe episodic viral wheeze in preschool children: High risk of asthma at age 5–10 years

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Abstract In population studies, most children with episodic viral wheeze (EVW) become symptom free by 6 years. We studied the outcome of children with severe EVW, treated and followed up in hospital. We followed up 78 children <4 years, managed by paediatricians for severe EVW, to the age of 5–10 years. We recorded respiratory symptoms, spirometry and exhaled nitric oxide (FeNO). At follow-up, 42 children (54%) had current wheeze or dyspnoea, and 52 (67%) had current asthma. There was no significant difference between children with and without current asthma in FEV1 ($p=0.420$), but FeNO was higher in children with current asthma (median (interquartile range) 14.5 (11.25–21.50) ppb) than in those without (12.0 (10.0–13.8) ppb, $p=0.020$). Positive family history of asthma was the only factor associated with current asthma (odds ratio 8.77, 95% CI 2.88–26.69, $p<0.001$). This remained significant after adjustment for duration of follow-up, gender and parental smoking. **Conclusion.** Severe EVW at preschool age has a high risk of asthma at age 5–10 years, and this is reinforced by a positive family history of asthma and to elevated FeNO levels.

Keywords Preschool wheeze · Asthma · Episodic viral wheeze · Outcome · Cohort studies

Introduction

In population studies, one in three children under the age of 3 years have at least one episode of wheezing prior to their third birthday, and 50% by the age of 6 years [6, 20, 21, 24]. Most preschool children with wheeze only do so during viral upper respiratory tract infections (episodic viral wheeze, EVW) [7]. Some young children also wheeze in response to other triggers such as cigarette smoke, fog or allergens (multiple trigger wheeze, MTW) [7]. In the majority of these wheezy preschool children, symptoms disappear between the ages of 3 and 6 years [24, 36]. Disappearance of wheeze over time is more likely in preschool children with a low level of lung function in infancy [24, 36], with maternal smoking [1, 24] and in children with EVW [9, 16].

The common perception that EVW has a high likelihood of spontaneous resolution over time is based on general population studies which examined the outcome of wheeze in children who had at least one episode of (usually mild) wheezing [7]. Preschool children with more frequent or more severe episodes of wheezing are more likely to develop asthma than children with mild or isolated episodes of wheeze in early life [4, 9, 10, 23]. Clinical studies on the outcome of more severe wheeze in early childhood are rare, however. Only a few studies have investigated the long-term prognosis of preschool children hospitalised for a severe episode of wheezing [17, 37]. To our knowledge, no follow-up studies of clinical cohorts of preschool children with EVW have been performed to date.

We hypothesised that preschool children with EVW, referred to a hospital setting for management of their

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wheezing disorder, would have more severe symptoms and would therefore be at higher risk of wheeze persisting beyond the preschool years than children with viral associated wheeze in population studies.

Methods

Study population and participant recruitment

We performed a retrospective chart review of all children who had been treated and follow-up at the Princess Amalia Children's Clinic between 2002 and 2007 for symptoms of recurrent wheeze and who were <4 years of age at time of their first visit to the clinic. In the Netherlands, children can only be seen by a paediatrician after referral by their general practitioner; Dutch guidelines for management of asthma/wheeze in primary care recommend referral to a paediatrician in case of severe or therapy-resistant signs and symptoms [5].

The hospital chart contained a standardised asthma/wheeze history questionnaire, in which the pattern of wheeze was evaluated by asking the parents “Does your child's wheeze/dyspnoea only occur during viral colds?” and “Does your child ever wheeze when (s)he is not having a viral cold?” In order to identify children with EVW [7], we included only patients with an affirmative answer to the former and a negative answer to the latter question in the hospital chart. Patients in whom the answer to either of these questions was missing or unclear were excluded. Thus, our population consisted of children with exclusive EVW, who were referred by their general practitioner because of severe or therapy-resistant symptoms (from here on referred to as “severe EVW”). Clinical management in these patients, including the decision to test for allergic sensitization (by Phadiatop screening test for atopy) [38] and treatment with anti-inflammatory maintenance medication, was at the discretion of the attending paediatrician.

Data on wheezing history, personal history of eczema, family history of asthma and eczema, parental smoking habits and results of tests of atopic sensitization (if performed) were obtained from the hospital chart from the time period when the child was under follow-up at our clinic. In 2009, all children with severe EVW identified in this way were invited by letter and telephone to return to the clinic for a follow-up assessment. Written parental informed consent was obtained, and the study was approved by the hospital Ethics Review Board, a certified subsidiary of the national committee of medical ethics in the Netherlands.

Measurements at follow-up in 2009

Questionnaire Respiratory symptoms were recorded by ISAAC questionnaire for children of 6–7 years [2]. In

addition, parents were asked whether their child had used any oral or inhaled medication for respiratory symptoms or asthma during the previous 12 months and whether a doctor had diagnosed asthma in their child after the age of 4 years.

Lung function A complete expiratory flow-volume curve was obtained on the Jaeger MasterScreen (Jaeger, Houston, TX, USA) at our pulmonary function laboratory according to ERS/ATS guidelines [26]. Measurements were supervised by skilled technicians encouraging the children to perform optimal measurements. We recorded forced expiratory volume in 1 s (FEV1) and the ratio of FEV1 to forced vital capacity (FEV1/FVC) and expressed obtained values as percent of predicted [34].

Exhaled nitric oxide The fractional concentration of exhaled nitric oxide (FeNO) was measured by NIOX MINO (Aerocrine, Solna, Sweden) and expressed in parts per billion [35].

Definitions

Current wheeze at follow-up was defined as an affirmative answer to the question “has your child wheezed during the last 12 months?”; current dyspnoea as an affirmative answer to the corresponding question on dyspnoea/shortness of breath during the last 12 months. Children were classified as current asthma medication users when their parents reported use of inhaled bronchodilators, inhaled corticosteroids, oral montelukast or oral corticosteroids in the last year. Current asthma was defined as current wheezing, current dyspnoea or current asthma medication use.

Statistical analyses

Statistical analyses were performed using chi-squared tests to compare proportions and by Mann–Whitney *U* test to compare medians and distributions between groups. Non-parametric testing was used throughout because of small group sizes and skewed distributions. Multiple logistic regression analysis was carried out to identify patient characteristics associated with the presence or absence of current asthma at follow-up at the age of 5–10 years. All analyses were performed with SPSS 16.0. *p* values <0.05 were considered statistically significant.

Results

Subjects

Between 2002 and 2007, 483 children <4 years were diagnosed, treated and followed up at our clinic for recurrent

severe wheeze. In the majority of cases, medical history data recorded in the hospital chart were insufficient to allow reliable classification as MTW or EVW (Fig. 1). Because we were specifically interested in children with EVW, we only included the 134 children in whom this pattern of wheeze could be reliably identified from data in the hospital chart (27.8% of the 483 children whose charts were reviewed). There were no significant differences in age, gender and rate of hospitalisation for wheeze between the 134 children with EVW and the children who were excluded because of insufficient chart data or those with MTW (all p values >0.4) (Fig. 1).

After excluding patients whose parents could not be contacted or refused participation, a total of 78 patients completed the study (58.2% of the 134 children with EVW (Fig. 1)) at the age of 5–7 years in 2009; their characteristics are presented in Table 1. There were no significant differences in clinical and demographic characteristics between our study population and non-participants, indicating that our study population was representative of the root population of 134 EVW patients.

Twenty-four patients had been admitted to hospital at least once before the age of 4 years because of severe wheeze. The median number of wheezing episodes in these patients in the year before referral to our clinic was 6 (interquartile range (IQR) 3 to 8).

Symptoms and medication use at follow-up

The median duration of time between the last visit to the clinic for preschool wheeze, or the fourth birthday of the patient (whichever was last), and the follow-up visit in 2009 was 3.90 (IQR 2.30–4.80) years. At follow-up at the age of

5–10 years, 31 children had current wheeze, 34 had current dyspnoea and 42 had either (Fig. 2). Of these 42 children with current wheeze or dyspnoea, 23 (54.8%) only had such symptoms during viral colds (EVW), and 19 also had symptoms after exposure to other stimuli (MTW). In the MTW group, viral colds were also the most important trigger; a total of 37/42 children with current wheeze or dyspnoea at follow-up had these symptoms during viral colds. MTW was more likely in children with a positive family history of asthma (17/52) than in those without (2/20), although the difference did not quite reach statistical significance ($p=0.08$). Personal and family history of eczema, hospital admission for wheeze at young age, atopic sensitization at young age and parental smoking were not related to MTW at the age of 5–10 years ($p>0.4$).

Current asthma medication use was reported in 45 children, 9 of whom (20%) only used inhaled bronchodilators on demand; the remaining 36 were using inhaled corticosteroids as daily controller therapy. There were no children using montelukast. Ten of these 45 current asthma medication users (22.2%) had been free from dyspnoea or wheeze in the year before completion of the questionnaire (Fig. 2). Of the 52 children with current asthma symptoms or current asthma medication use, 48 (92.3%) had a doctor's diagnosis of asthma made or confirmed after the age of 4 years.

Lung function and exhaled nitric oxide at follow-up

Complete flow-volume curves were obtained in 75 children (96.2%) and successful FeNO measurements in 60 (76.9%). Results are presented in Table 2. There were no significant differences in spirometry values between children with and without current asthma, but FeNO was significantly higher

Fig. 1 Patient disposition

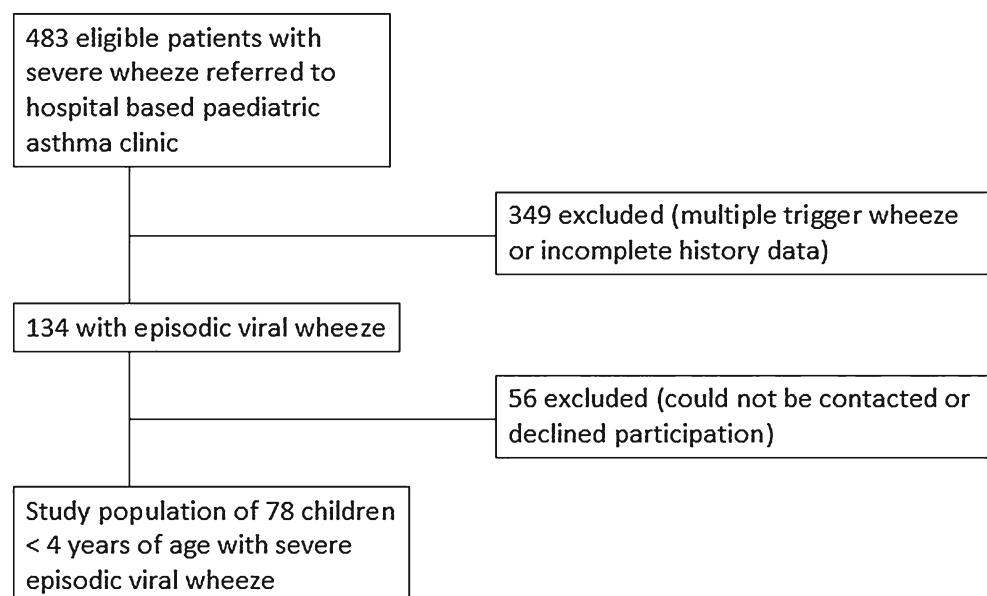


Table 1 Characteristics of study population and excluded patients

	Study population (<i>n</i> =78)	Excluded patients (<i>n</i> =56)	<i>p</i> value ^a
Median age in years at initial presentation to secondary care (interquartile range)	1.85 (1.28–3.05)	1.90 (1.30–3.10)	0.85
Male gender number (%)	54 (69.2)	34 (60.7)	0.31
Family history of asthma number (%)	36 (64.2)	30 (53.4)	0.72
Personal history of eczema number (%)	22 (28.2)	13 (23.2)	0.42
Allergic sensitization number (%) ^b	14 (33.3)	10 (34.5)	0.92
Parents smoking in the house number (%)	12 (15.4)	11 (19.6)	0.52
Ever hospitalized for asthma/wheeze number (%)	23 (31.1)	18 (32.1)	0.74

Data obtained from retrospective review of hospital chart when the child was first referred to secondary care (before the age of 4 years) and followed up for severe episodic viral wheeze

^aMann–Whitney *U* test for comparison of age; chi-squared tests for all other comparisons

^bOnly tested in 42 patients in study population and in 29 excluded patients

in children with current asthma (*n*=40) than in those without (*n*=20) (*p*=0.020, Table 2). When comparing children with and without current dyspnoea or wheeze, FVC (*p*=0.20), FEV1 (*p*=0.75) and FeNO (*p*=0.11) were not significantly different, but FEV1/FVC ratio was significantly lower in children with current wheeze or dyspnoea (median 85.2%, IQR 81.9–88.6%) than in those without (median 87.8%, IQR 81.9–91.5%, *p*=0.011). There were no significant differences in spirometry or FeNO values between children with EVW (*n*=23) or MTW (*n*=19) at follow-up (all *p* values>0.30).

Differences between children with and without current asthma at follow-up

A comparison of clinical and demographic characteristics between children with and without current asthma at follow-up is presented in Table 3. A positive family history was the only risk factor significantly associated with current asthma at age 5–10 years (odds ratio (OR) 8.77, 95% CI 2.88–26.69, *p*<0.01). This association between family history of asthma in preschool children with EVW and the risk of current asthma at the age of 5–10 years in these patients at

Fig. 2 Presence of current wheeze, dyspnoea, or asthma medication use at the age of 5–10 years in 78 children who had been referred to a hospital-based paediatric asthma clinic for severe EVW when they were 4 years of age or younger

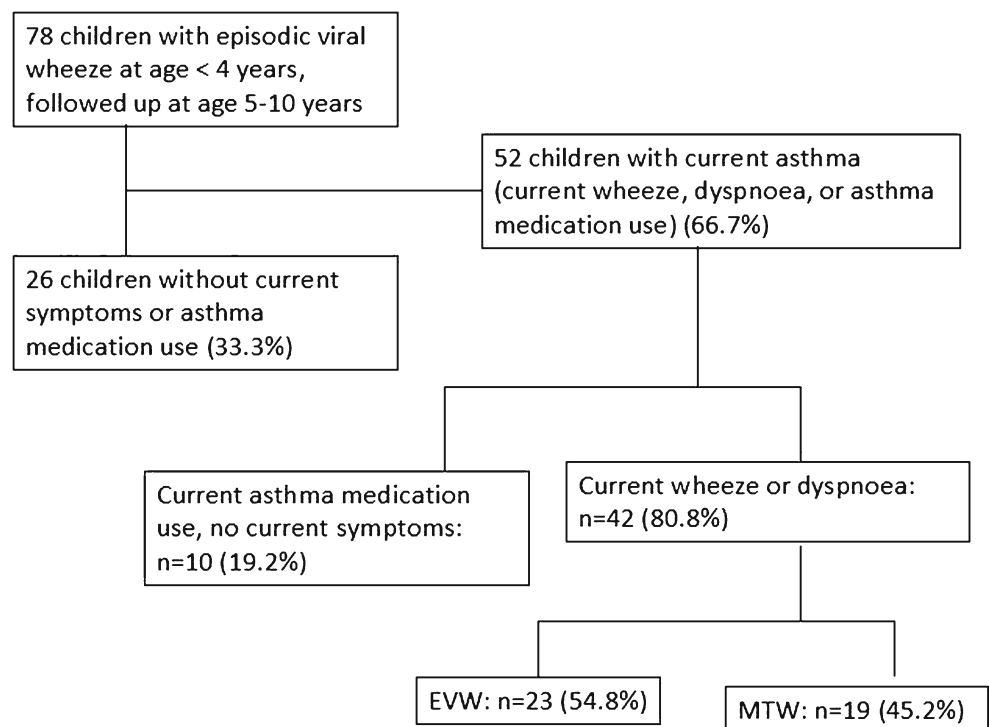


Table 2 Lung function and exhaled nitric oxide values in children with and without current asthma (current dyspnea, wheeze or asthma medication use) at follow-up

	Current asthma (n=51)		No current asthma (n=24)		p value ^a
	Median	IQR	Median	IQR	
FEV1 % predictive	104.0	97.0–114.0	106.5	91.0–111.0	0.420
FVC % predictive	106.0	95.0–114.0	103.5	96.5–107.0	0.189
FEV1/FVC (%)	85.2	81.8–89.0	88.0	83.7–92.4	0.101
FeNO (ppb)	14.5	11.25–21.50	12.0	10.0–13.8	0.020

IQR interquartile range

^aMann–Whitney U test

follow-up remained significant after adjustment for age, gender and the duration of time between initial management of EVW during preschool age and the follow-up visit in 2009 (adjusted OR 9.30, 95% CI 2.68–32.13, $p < 0.01$).

Discussion

In contrast to population studies, in which the large majority of preschool children with EVW become symptom free between the ages of 3 and 6 years [9, 24, 36], we found that two thirds of preschool children with severe EVW referred to a hospital-based paediatric asthma clinic had current asthma at the age of 5–10 years (Fig. 2). Children with current asthma at age 5–10 years had elevated FeNO levels (Table 2). The only risk factor significantly associated to current asthma at the age of 5–10 years in these preschool children with EVW was a positive family history of asthma (Table 3), independent of age, gender and duration of follow-up. Our results suggest that EVW, when severe enough to warrant referral to secondary care, is not an innocuous disease which may be expected to disappear once children reach primary school age but carries a high likelihood of developing into bronchial asthma.

To our knowledge, ours is the first study to follow up a hospital-based cohort of preschool children with EVW to the age when the presence of asthma can be reliably assessed. Until now, all data on the risk of persistence of wheeze in preschool children has come from population

studies. Although such studies may be useful and informative to unravel the different clinical phenotypes of preschool wheezing and their outcome at population level, these data cannot be used to predict the outcome of children with more severe recurrent wheeze managed and followed up in secondary or tertiary care. Our results are in line with results from two Scandinavian cohorts of young children (<2 years of age) admitted to hospital for severe wheezing, where 40–49% of patients had asthma at the age of 5–7 years [17, 37]. Further follow-up showed that the high risk of asthma persisted into adulthood [15]. Taken together, these data may be used in paediatric hospitals and departments to counsel parents of preschool children with EVW on the expected outcome of wheeze in these patients.

The factors associated with current asthma in our study (positive family history of asthma and elevated FeNO levels at age 5–10 years) are in accordance with results from population studies on the outcome of preschool wheeze [1, 9, 11, 24]. Although there was a clear trend for atopic sensitization at preschool age to be more common in children with current asthma at follow-up, the low number of patients tested for atopic sensitization in our study reduced the power to demonstrate the statistical significance of this difference (Table 3). Children seen in a hospital setting with severe EVW and a positive family history of asthma or evidence of atopy may therefore be considered at high risk of asthma at 5–10 years of age.

Almost half of the preschool children with EVW whose symptoms persisted to or recurred before the age of 5–

Table 3 Demographic and clinical characteristics of children with and without current asthma at follow-up

	Current asthma (n=52)	No current asthma (n=26)	p value ^a
Median age in years at follow-up (IQR)	6.72 (6.24–8.00)	6.88 (5.94–7.99)	0.73
Median duration in years of follow-up (IQR)	3.80 (3.24–4.67)	3.97 (3.43–4.85)	0.76
Male gender number (%)	31 (59.6%)	20 (76.9%)	0.13
Family history of asthma number (%)	45 (86.5%)	11 (42.3%)	<0.01
Personal history of eczema number (%)	26 (50%)	15 (57.7%)	0.51
Allergic sensitization number (%)	13/34 tested (38.2%)	1/8 tested (12.5%)	0.17
Parents smoking in the house number (%)	6 (11.5%)	6 (23.1%)	0.18

IQR interquartile range

^aMann–Whitney U test for age and duration comparisons; chi-squared tests for all other comparisons

10 years not only had symptoms during viral colds at school age but also responded to other triggers (Fig. 2). This confirms earlier observations that EVW may develop over time into MTW and vice versa [30]. Although there was a trend for family history of asthma to be associated with MTW, our study was underpowered to identify risk factors for MTW. In the other half of EVW preschool children, the pattern of wheezing only during viral colds persisted into school age. This is in agreement with earlier studies showing that EVW is not confined to the preschool age range but may also be observed in school-aged children and adults [13, 25].

The relationship of lung function and FeNO at school age to wheezing disorders in preschool children is unclear. In the Tucson study, both reduced lung function during infancy and EVW were associated with wheeze resolving before the sixth birthday [9, 24]. Because lung function tends to track throughout childhood [31], children with EVW may therefore be expected to have reduced lung function at school age. However, no clear relationship between lung function and preschool wheezing phenotypes were observed in other birth cohort studies [19, 21]. Similarly, EVW in preschool children has been associated with elevated, normal and reduced FeNO levels in different studies [8, 11, 12, 28]. This suggests that EVW may not be a well-defined clinical entity and may comprise different inflammatory and functional phenotypes [29]. The normal level of lung function in the children with current asthma in our study is in accordance with a range of previous studies [3, 27, 33]. The elevated FeNO levels in the patients with current asthma supports the notion that these children did indeed have atopic asthma and were not overdiagnosed or incorrectly treated as such because of nonspecific respiratory symptoms.

We acknowledge the following limitations of our study. First, our study sample was relatively small, limiting our ability to identify risk factors for asthma at the age of 5–10 years. We deliberately chose to be very strict in including only children with exclusive EVW and to exclude patients in whom the hospital chart records either suggested MTW or were insufficient to confirm that wheeze only occurred during viral colds. Sadly, many hospital chart records contained missing data on the pattern of wheeze in early childhood (Fig. 1). Our study population was representative of the root population of 134 children positively identified as having EVW (Table 1) and of the original population seen in our hospital in terms of age and gender. Other studies in larger prospective hospital-based cohorts of EVW patients are needed to confirm our results.

A second disadvantage is that we had no data to confirm the presence of respiratory viruses in the airways during episodes of wheezing in early childhood. Studies that did look at respiratory viruses in preschool wheeze have suggested that rhinovirus and respiratory syncytial virus may be

of particular importance in increasing the likelihood of persistent asthma [14, 16, 18, 22, 32]. Most clinicians, however, refrain from testing for respiratory viruses in wheezy preschool children, and viral testing is not recommended in clinical guidelines for preschool wheeze [7]. Thus, our results reflect current clinical practice in which the pattern of wheeze in early childhood (EVW versus MTW) is only assessed through parental history.

Thirdly, the duration of follow-up was variable in our study, ranging from 3.7 to 8.8 years. Given the favourable natural history of EVW in population studies [9, 24], we considered the possibility that children with a longer time period between initial symptoms at preschool age and follow-up at the age of 5–10 years would be more likely to have outgrown their symptoms. This, however, was not the case (Table 3), and the relationship of positive family history of asthma to current asthma at the age of 5–10 years remained significant after adjustment for the duration of follow-up.

A final limitation is that our study was performed in a single centre, which may limit the generalizability of our findings. Because our paediatric asthma clinic is situated in the only district general hospital in a catchment area of 400,000 inhabitants, we believe that our study sample is representative of the preschool children with EVW in secondary care.

In conclusion, our study shows that preschool children with EVW, who have been referred to a hospital-based paediatric asthma clinic because of severe symptoms, have a high risk of persistent asthma at the age of 5–10 years. This is in agreement with earlier follow-up studies of preschool children admitted to hospital for severe virus-associated wheeze. Episodic viral wheeze in preschool children should therefore not be regarded as a transient and innocuous disease, in particular when symptoms are severe enough to warrant referral to secondary care. We recommend to evaluate, manage and follow up preschool children with severe EVW as seriously as one would in school-aged children with asthma.

Conflicts of interest The authors declare no conflict of interest.

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