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REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Half of children with recurrent or chronic wet cough before three years of age were symptom-free by age seven

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Abstract

Aim: We aimed to study the natural course of recurrent episodic and chronic wet cough in preschool children, the proportion and age of resolution, and risk factors for persistent symptoms.

Methods: Parents of children with recurrent or chronic wet cough who had attended the outpatient clinic before the age of three years during 2010-2013 at Stavanger University Hospital, Norway, answered a questionnaire regarding clinical symptoms and current medication at a follow-up in 2017-2018.

Results: We invited 840 children to participate, and parents consented for 348 (41.4%) of the children. At the first outpatient visit, 171 children (58.8%) had recurrent episodic and 120 (41.2%) had chronic wet cough. At follow-up at a median age of 82 months, 57.0% in both groups were symptom-free, and 9.4% with episodic cough and 13.3% with chronic cough had more than mild symptoms. During the last 12 months prior to the survey, 27.2% with episodic cough and 18.6% with chronic cough had used inhaled corticosteroids.

Conclusion: Half of the preschool children with recurrent episodic or chronic wet cough outgrew their symptoms by the median age of seven years, but one in four still used inhaled corticosteroids.

KEYWORDS

children, chronic cough, inhaled corticosteroids, preschool

1 | INTRODUCTION

During the first years of life, airway infections commonly involve coughing, but the cough normally ceases within two to three weeks.[1-3] Some children experience recurrent episodes with cough or chronic cough, sometimes leading to the suspicion of an underlying disease. Chronic cough is defined as a cough that persists for more than four or eight weeks,[4-10] and in preschool children, the cough is mainly wet or productive due to mucus secretion.[4] An untreated chronic cough may last for months and lead to impaired sleeping, poor feeding, sick leave and reduced quality of life for the children and families affected.[4,5,7,10,11] Most children with recurrent episodic or chronic wet cough probably have a good prognosis, but for some children, the cough represents the first sign of chronic suppurative lung disease, which is important to diagnose and treat early.[5,10,12]

Abbreviations: CPAP, continuous positive airway pressure; ICS, inhaled corticosteroid; PBB, protracted bacterial bronchitis; PEP-mask, positive expiratory pressure mask.; *t*PTEF/*t*E, peak tidal expiratory flow to total expiratory time.

Episodic or chronic wet cough is a common reason for consulting a primary care physician and referral to a specialist. Handling recurrent or chronic cough is challenging, even in a specialist unit. Children with chronic wet cough may be misdiagnosed with asthma, leading to overdiagnosis and overtreatment with potential side effects.[13-15] The few available objective tests, such as bronchoscopy and thoracic CT scan, are limited by capacity and burden of the procedure for the child. Evaluation is therefore mainly based on the medical history and the clinical examination.[16]

Studies have suggested that protracted bacterial bronchitis (PBB) with bacterial colonisation in lower airways is the most common reason for chronic wet cough in young children, with antibiotics for two to four weeks as the recommended treatment.[4,16,17] However, studies of children with chronic wet cough are largely based on selected patients recruited from tertiary centres.[4] To date, few studies have evaluated the natural course and identified risk factors for a prolonged course or an underlying chronic disease in children with recurrent episodic or chronic wet cough, including PBB.[3,4,10]

In clinical practice, separating chronic wet cough from long-lasting recurrent episodes of wet cough by history is challenging. Furthermore, concurrent bronchopulmonary obstruction or wheezing is common, leading to increased suspicion of asthma as the underlying cause. Studies on the natural history of wet cough should therefore include these issues. Our aims were to study the long-term course of young children with recurrent episodic and chronic wet cough, find the proportion and age of spontaneous resolution, and to identify possible risk factors for persistence of symptoms.

Key notes

- Episodic or chronic wet cough is common in young children, but the long-term prognosis is not known.
- We studied the persistence of symptoms and medication in outpatient children under three years of age with episodic or chronic wet cough.
- Half of the preschool children with recurrent episodic or chronic wet cough outgrew their symptoms by the median age of seven years, but one in four still used inhaled corticosteroids.

2 | METHODS

2.1 | Study site and subjects

The study subjects were recruited from the paediatric outpatient clinic at Stavanger University Hospital in Norway, which covers a population of approximately 15 000 children under three years of age and have a yearly birth rate of approximately 4500. The hospital has the only paediatric ward and outpatient clinic covering this area and all children requiring specialist consultations are therefore referred to our hospital.

The recruitment of participants for this retrospective study is shown in Figure 1. In the first step, we reviewed the medical records of children under the age of three years who had at least one visit to the children's pulmonary outpatient clinic at Stavanger University Hospital from January 1, 2010, to December 31, 2014, with the following ICD-10 diagnoses; J40-J47 chronic lower respiratory diseases, Q30-Q34 congenital malformations of the respiratory system or R05 cough. Children were eligible for inclusion if they had recurrent episodic or chronic wet cough, with or without episodes of wheezing, with a total duration exceeding four weeks. Children were excluded if they were born at less than 32 weeks of gestation or had been diagnosed with a heart, lung or neuromuscular disease or any other chronic disease potentially affecting the lungs at the time of referral. Also, children with a known diagnosis of asthma or a history of mainly recurrent episodes with wheezing without wet cough were not included. If the children were found eligible for inclusion, their parents were invited by letter to participate. Parents who did not respond were sent one reminder by post, and finally one reminder with the possibility to respond electronically.

The study was approved by the Regional Committee for Medical Research Ethics in Northern Norway. Signed statements of informed consent were obtained from the parents.

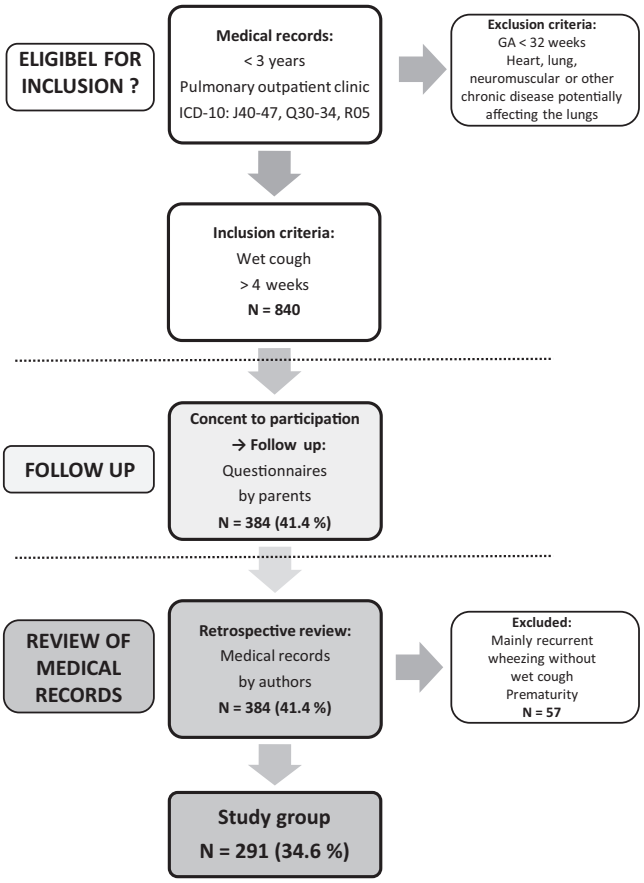

FIGURE 1 Overview of the process for inclusion and data collection

TABLE 1 Basic characteristics of 291 children under three years of age with recurrent episodic or chronic wet cough referred to a paediatric outpatient clinic

	N/Total N (%)	Recurrent episodic cough N (%)	Chronic cough N (%)	*P* values[a]
All children	291	171/291 (58.8)	120/291 (41.2)	
Boys	175/291 (60.1)	108/171 (63.2)	67/120 (55.8)	.209
Prematurity; 32-37 wk of gestation	20/203 (9.9)	15/113 (13.3)	5/90 (5.6)	.067
Parental asthma or atopy	174/248 (70.2)	108/148 (73.0)	66/100 (66.0)	.239
Siblings with asthma or atopy	75/153 (49.0)	43/86 (50.0)	32/67 (47.8)	.783
Household smoking	28/111 (25.2)	12/61 (19.7)	16/50 (32.0)	.137
Pets at home	42/94 (44.7)	26/56 (46.4)	16/38 (42.1)	.679
Atopic dermatitis ever	86/226 (38.1)	57/140 (40.7)	29/86 (33.7)	.293
Previous hospitalisation for airway infection	78/291 (26.8)	51/171 (29.8)	27/120 (22.5)	.165

Note: The denominator represents the number of participants with available data.
[a]*P* values from Pearson's chi-square test.

2.2 | Data collection

After consenting to participate, the parents consecutively answered a questionnaire about the status of the child at follow-up. They reported airway symptoms during the last six months by answering the question: 'Has your child had symptoms similar to those evaluated at the outpatient clinic?' If applicable, the parents were asked if the child had had coughing or wheezing, and if they considered the severity of the symptoms to be mild or severe. Furthermore, they were asked if the child had been using antibiotics or any asthma medications specified as any inhaled corticosteroid (ICS), inhaled short-acting beta-2 agonist or oral leukotrienantagonists during the last 12 months. If the symptoms had ceased, the parents reported the year and month for resolution of symptoms.

For those who consented, further data regarding previous illnesses, family history, clinical findings and treatment prescribed were collected retrospectively by a review of the medical records (Figure 1). We included information from the first outpatient visit and all subsequent outpatient visits to our department, until the patient was no longer under follow-up. We recorded information on the children's gestational age and number of siblings, if they had pets at home or a family history of asthma and atopy and if they had ever been exposed to household smoking. We also recorded the age at debut of airway symptoms and if the main symptom at the outpatient clinic consultation was wheezing episodes and/or chronic wet cough or stridor. A history of previous hospitalisation for airway disease or atopic dermatitis was registered. The results from examinations found indicated by a physician after clinical evaluation at the first or later outpatient visits were recorded, including lung function tests, chest X-rays and tests for atopic sensitisation by skin prick test or specific IgE. Finally, we recorded information about treatment started at the outpatient clinic including use of antibiotics, short-acting beta-2 agonist, use of ICS, inhalation with isotonic saline, chest physiotherapy and use of intermittent continuous positive airway pressure (CPAP) or a positive expiratory pressure (PEP) mask. Variables were categorised as yes or no, except for the continuous variables including age, number of siblings and lung function.

Children who initially were considered eligible for inclusion were excluded if they after review of the medical records met at least one exclusion criteria or failed to meet the inclusion criteria (Figure 1).

2.3 | Definitions and measurements

Based on the history at the first outpatient visit, children were categorised into two groups. Children with recurrent episodic wet cough had more episodes with wet cough lasting more or less than four weeks each, but with a clear history of symptom-free intervals between episodes. Children with chronic wet cough had wet cough lasting for more than four weeks continuously from the start of symptoms to the first outpatient visit.

A positive chest X-ray was defined as any consolidation or atelectasis at any time. Atopic sensitisation was defined as at least one positive skin prick test or specific IgE above 0.35 KU/L ever for any tested allergen. The lung function was measured at the first outpatient visit by tidal breathing flow-volume loops with a paediatric pulmonary testing system (Exhalyzer, Ecomedics, Duernten, Switzerland) and reported as the ratio of time to reach peak tidal expiratory flow to total expiratory time (*t*PTEF/*t*E).

2.4 | Statistics

Data were expressed as proportions or medians and interquartile ranges. Group comparisons were performed with Pearson's

chi-square test for dichotomous variables or Mann-Whitney *U* test for continuous variables. *P* for trend for ordinal variables with more than two categories was analysed by the linear-by-linear association test. Logistic regression analyses were performed to explore the associations between various risk factors and persistent symptoms at follow-up.

The significance level was set to 0.05 for all tests. Analyses were carried out using SPSS version 24.0 (IBM Corp. Armonk, New York, USA).

3 | RESULTS

After the first review of medical records, 840 children were found eligible for inclusion and their parents were invited to participate in the study. Informed consent was obtained from the parents of 348 (41.4%) children. Of these, 57 children were excluded after the second review of the medical records, two children due to prematurity and 55 children due to wheezing episodes as the main symptom for referral (Figure 1). Of the remaining 291 children, 171 (58.8%) had recurrent episodic wet cough and 120 (41.2%) had chronic wet cough before the first outpatient visit.

The basic characteristics of all children are given in Table 1. No differences regarding gender, family history of asthma and atopy, household smoking, pets at home or ever atopic dermatitis were found between children with recurrent episodic cough and children with chronic wet cough.

The clinical characteristics, results of examinations and treatment started at the first or subsequent outpatient visits are given in Table 2. Children with chronic wet cough were younger than children with recurrent episodic cough, both at the debut of symptoms, at the first outpatient clinic visit and at follow-up. The median duration of wet cough before the first visit was 9 months in children with a recurrent episodic cough and 8 months in children with a chronic cough. More children with recurrent episodic than chronic wet cough also had a history of wheezing episodes. More children with chronic wet cough were given antibiotics, inhaled isotonic saline, CPAP or chest physiotherapy than children with recurrent episodic wet cough.

3.1 | Follow-up—resolution of symptoms

At follow-up, parents reported by questionnaire that 57.0% of the included children had no symptoms, 32.0% had mild symptoms and

TABLE 2 Clinical characteristics for 291 children under three years of age with recurrent episodic or chronic wet cough referred to a paediatric outpatient clinic

	N/Total N (%)	Recurrent episodic cough N (%)	Chronic wet cough N (%)	*P* values[a]
All children	291	171/291 (58.8)	120/291 (41.2)	
Age at debut of symptoms; *months; median (quartiles)*	291	10 (4,13)	6 (3,12)	**.015**
Age at first visit; *months; median (quartiles)*	291	22 (15,28)	16 (9,26)	**<.001**
Duration of symptoms from debut to first visit; *months; median (quartiles)*	291	9 (5,16)	8 (4,12)	**.005**
History of wheezing episodes	173/291 (59.5)	120/171 (70.2)	53/120 (44.2)	**<.001**
Consolidation/atelectasis on chest X-ray	88/239 (36.8)	49/134 (36.6)	39/105 (37.1)	.927
Lung function, *t*PTEF/*t*E-ratio[b]; *%;median (quartiles)*	232/291 (79.7)	36 (27, 45)	37 (27, 44)	.683
Atopy	42/62 (67.7)	32/46 (69.6)	10/16 (62.5)	.603
Treatment prescribed or continued at outpatient visits				
No treatment	64/291 (22.0)	41/171 (24.0)	23/120 (19.2)	.329
Antibiotics	61/282 (21.6)	22/165 (13.3)	39/117 (33.3)	**<.001**
Beta-2 agonist	172/283 (60.8)	107/168 (63.7)	65/115 (56.5)	.225
ICS	136/286 (47.6)	88/170 (51.8)	48/116 (41.4)	.084
Inhalation of isotonic saline	49/287 (17.1)	22/169 (13.0)	27/118 (22.9)	**.029**
Chest physiotherapy	16/287 (5.6)	5/170 (2.9)	11/117 (9.4)	**.019**
CPAP	9/287 (3.1)	1/170 (0.6)	8/117 (6.8)	**.003**

Note: Continuous variables were reported as medians and quartiles, dichotomous variables were reported as number and %.The denominator represents the number with available data.

Abbreviations: Beta-2 agonist, inhaled short-acting beta-2 agonist; CPAP, continuous positive airway pressure; ICS, inhaled corticosteroids in any combination.

[a]P values from Pearson's chi-square test for dichotomous variables or Mann-Whitney *U* test for continuous variables. Bold values represent *P* values under the significance level set to 0.05.

[b]Lung function was measured by tidal breathing and was reported as the ratio of time to reach peak tidal expiratory flow to total expiratory time (*t*PTEF/*t*E).

TABLE 3 Symptoms during the last six months and treatment during the last 12 months before follow-up in 291 children initially referred to a pulmonary outpatient clinic for recurrent episodic or chronic wet cough. All children were under three years of age at the first visit to the paediatric outpatient clinic

	N/Total N (%)	Recurrent episodic cough N (%)	Chronic wet cough N (%)	*P* values [a]
All children	291	171/291 (58.8)	120/291 (41.2)	
Age at follow-up; *months; median (quartiles)*	291	84 (71, 99)	81 (61, 92)	.021
No symptoms the last six months before follow-up	166/291 (57.0)	98/171 (57.3)	68/120 (56.7)	.571[b]
Mild symptoms the last six months before follow-up	93/291 (32.0)	57/171 (33.3)	36/120 (30.0)	.571[b]
Wheeze	68/290 (23.4)	43/171 (25.1)	25/119 (21.0)	.413
Cough	69/290 (23.8)	42/171 (24.6)	27/119 (22.7)	.713
Severe symptoms the last six months before follow-up	32/291 (11.0)	16/171 (9.4)	16/120 (13.3)	.571[b]
Wheeze	30/290 (10.3)	15/171 (8.8)	15/119 (12.6)	.292
Cough	30/290 (10.3)	15/171 (8.8)	15/119 (12.6)	.292
Treatment the last 12 mo before follow-up				
No treatment	179/291 (61.5)	98/171 (57.3)	81/120 (67.5)	.079
Any treatment	112/291 (38.5)	73/171 (42.7)	39/120 (32.5)	.079
Beta-2 agonist	89/283 (31.4)	62/168 (36.9)	27/115 (23.5)	**.017**
ICS	64/271 (23.6)	43/158 (27.2)	21/113 (18.6)	.099
Leukotrienantagonist	7/250 (2.8)	7/145 (4.8)	0/105 (0)	**.022**
Antibiotics	26/268 (9.7)	15/157 (9.6)	11/111 (9.9)	.923
Duration of symptoms in the symptom-free group; *months; median (quartiles)*	159/291 (54.6)	36 (20, 54)	33 (17, 48)	.208
Age of resolution in the symptom-free group; *months; median (quartiles)*	159/291 (54.6)	44 (30, 63)	39 (23, 54)	.133

Note: Continuous variables were reported as medians and quartiles, dichotomous variables were reported as number and %.The denominator represents the number with available data.

Abbreviations: Beta-2 agonist, inhaled short-acting beta-2 agonist; ICS: inhaled corticosteroids in any combination.

[a]*P* values from Pearson's chi-square test for dichotomous variables or Mann-Whitney *U* test for continuous variables, except those marked b.

Bold values represent p values under the significance level set to 0.05.

[b]*P* values from linear-by-linear association test.

11.0% had severe symptoms during the last six months before filling out the questionnaire (Table 3). In children without symptoms at follow-up, children with recurrent episodic and chronic wet cough at baseline were free of symptoms after a total duration of 36 months (20-54) (median, (quartiles)) and 33 months (17-48), respectively (Table 3).

At follow-up, more children with initially recurrent episodic wet cough used beta-2 agonists than children with chronic cough, and a similar weak tendency was seen for ICS (Table 3). During the last 12 months before follow-up, 31.4% and 23.6% of all children reported use of beta-2 agonists or ICS, respectively, whereas only 9.7% of all children had been given antibiotics during the last 12 months.

In children who were considered as possible PBB and prescribed antibiotics at the outpatient visits, 41 (67.2%) were symptom-free at follow-up, 15 (24.6%) had mild symptoms, 5 (8.2%) had severe symptoms, and 11 (18.0%) had been using ICS during the last 12 months before follow-up.

In children who were considered as possible asthma and prescribed ICS at the outpatient visits, 62 (45.6%) were symptom-free at follow-up, 58 (42.6%) had mild symptoms, 16 (11.8%) had severe symptoms, and 50 (36.8%) had been using ICS during the last 12 months before follow-up.

3.2 | Risk factors for persistence of symptoms

Table 4 shows the results of regression analyses of possible risk factors for persistent airway symptoms at follow-up. None of the risk factors included in the analyses were associated with persistent symptoms.

4 | DISCUSSION

The main result of this study was the long-term outcome for children under three years of age with recurrent episodic or chronic wet cough. At around seven years of age, slightly more than half of

TABLE 4 Risk factors for persistent symptoms at follow-up, results from unadjusted logistic regression analyses in children referred to a paediatric outpatient clinic under three years of age for recurrent episodic or chronic wet cough

	Unadjusted models			
Risk factors	**N**	**OR**	**95% CI**	***P* values**
Male gender	291	0.88	0.55,1.41	.599
Prematurity (32-37 wk of gestation)	203	2.31	0.90,5.94	.081
Parental asthma or atopy	248	1.25	0.72,2.17	.431
Siblings with asthma or atopy	153	1.56	0.83,2.96	.170
Household smoking	111	1.37	0.58,3.24	.471
Pets at home	94	0.64	0.28,1.46	.290
Age at start of symptoms (months)	291	1.00	0.97,1.04	.814
Atopic dermatitis	226	1.48	0.86,2.54	.154
Previous hospitalisation for airway infection	291	1.28	0.76,2.16	.351
Positive chest X-ray	239	0.92	0.54,1.56	.747
*t*PTEF/*t*E ratio[a]	232	0.99	0.97,1.01	.481
Atopy	62	0.49	0.16,1.47	.203
Episodic cough	291	0.97	0.61,1.56	.913
History of wheezing episodes	291	1.10	0.69,1.77	.684

Note: As no variables were significant risk factors, a fully adjusted model was not included.

Abbreviations: OR: odds ratio, CI: confidence interval.

[a]Lung function was measured by tidal breathing and was reported as the ratio of time to reach peak tidal expiratory flow to total expiratory time (*t*PTEF/*t*E).

the children were symptom-free, and only 11% had more than mild symptoms.

Few other studies have evaluated the long-term outcome in children with wet cough.[18] Wurzel et al followed 106 children with PBB for two years and found that almost one half had ongoing recurrent episodes with PBB and one in ten were diagnosed with bronchiectasis.[19] However, these were highly selected patients from a tertiary centre with a definite diagnosis of PBB. Two other small retrospective studies of children diagnosed with PBB showed that a substantial proportion of these had recurrent symptoms during the next years.[20,21] We are not aware of other studies evaluating the long-term outcome of an unselected population of children with wet cough.

Short episodes of wet cough are common during airway infections in early childhood. The children included in this study were referred to a paediatric department after a long period of several months with recurrent episodic or chronic wet cough, thus probably representing the severe end of the spectrum of young children with wet cough. The proportion of children with symptoms at follow-up was similar for those with initially chronic wet cough and for those with recurrent episodic wet cough. More children with recurrent episodic wet cough used asthma medication at follow-up. Approximately one in three children had used some asthma medication, and one in four children had been prescribed ICS during the last 12 months.

Chronic or recurrent episodes with cough or wheeze during early childhood are commonly considered as asthma, and beta-2 agonists and/or ICS are often prescribed.[15] A high proportion of the children in our study had been prescribed ICS before the first outpatient visit or had been referred for an evaluation for possible asthma (data not shown). Approximately 50% of the children continued with or were prescribed ICS at the initial visit. This is a high number, considering that asthma guidelines for young children underline that wheezing episodes are the dominating symptom of asthma, and cough without wheezing episodes should normally not be considered as asthma.[22] A substantial proportion of the children included in the study were examined by young residents at our department and not paediatric pulmonologists, which could influence the adherence to asthma guidelines. More children with episodic cough had additional wheeze, which may explain why more of these children had been prescribed beta-2 agonists and the tendency for more prescription of ICS the last 12 months before follow-up. The use of ICS may be considered as an indicator of asthma, but studies have shown that in preschool children, the use of ICS as a marker of asthma may be questionable.[13] Moreover, both children with tracheobronchomalacia and PBB may have wheezing as one of the symptoms.[23,24] To estimate the true proportion of children with asthma at follow-up, one would need a thorough clinical examination including objective testing according to current guidelines.[22]

Guidelines and reviews from the last few years suggest that PBB is the most common cause of chronic wet cough in preschool children.[18] This diagnosis is based on wet cough lasting for more than four or eight weeks and a clear response to appropriate antibiotics. A third of the children with chronic wet cough in our study were given antibiotics at the first consultation. Our department has been increasingly aware of the diagnosis of PBB during the study period and after, and probably, a higher proportion of children with chronic wet cough are now given antibiotics. Therefore, we do not know how many of the children with chronic cough actually had PBB, but overall, the group with chronic wet cough had a rather favourable prognosis, with only 11% having more than mild symptoms at follow-up, and more than half of the children had no symptoms. Moreover, only one in ten children had been given antibiotics during the last six months. Therefore, the results suggest that for children with long standing chronic wet cough in early childhood, with or without PBB, the long-term prognosis is fairly good.

The regression analyses did not reveal any significant risk factor for the persistence of symptoms at follow-up. One possible implication from this could be that a more thorough diagnostic work up may be necessary at the initial visit to identify children with a higher risk for persistent symptoms.

The major strengths of this study were the population-based design and the follow-up over a long period of time. The major

weakness was the retrospective design with the probability of recall bias, especially in children who have been symptom-free for a long time, and that symptom registration was only based on parental recall. Children were not systematically followed at the outpatient clinic until resolution of symptoms or a final diagnosis was given. Moreover, the rather low participation rate may have given a selection bias, with non-responders being different from responders. It is possible that more parents of symptomatic children have responded, and consequently, the outcome for the whole group may be more favourable than we have shown.

5 | CONCLUSION

In conclusion, we have shown that approximately half of the children presenting with severe chronic or recurrent episodic wet cough during early childhood have a good prognosis, but for some children, these symptoms may be early signs of persistent symptoms or disease. Improved care for these children may include regular follow-ups until resolution of symptoms or until a specific diagnosis is found, and appropriate treatment is established.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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