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Episodic viral wheeze and multiple-trigger wheeze in preschool children are neither distinct nor constant patterns. A prospective multicenter cohort study in secondary care

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Abstract

Objectives: To evaluate whether episodic viral wheeze (EVW) and multiple-trigger wheeze (MTW) are clinically distinguishable and stable preschool wheezing phenotypes.

Methods: Children of age 1 to 4 year with recurrent, pediatrician-confirmed wheeze were recruited from secondary care; 189 were included. Respiratory and viral upper respiratory tract infection (URTI) symptoms were recorded weekly by parents in an electronic diary during 12 months. Every 3 months, diary-based symptoms were classified as EVW or MTW and compared to phenotypes assigned by pediatricians based on clinical history. We collected nasal samples for respiratory virus PCR during URTI, respiratory symptoms and in absence of symptoms.

Results: Of 660 3-month periods, the diary-based phenotype was EVW in 11%, MTW in 54% and 35% were free from respiratory episodes. Pediatrician-based classification showed 59% EVW and 26% MTW. The Kappa measure of agreement between diary-based and pediatrician-assigned phenotypes was very low (0.12, 95%CI, 0.07-0.17). Phenotypic instability was observed in 32% of cases. PCR was positive in 71% during URTI symptoms, 66% during respiratory symptoms and 38% in the absence of symptoms.

Conclusion: This study shows that EVW and MTW are variable over time within patients. Pediatrician classification of these phenotypes based on clinical history does not correspond to prospectively recorded symptom patterns. The applicability of these phenotypes as a basis for therapeutic decisions and prognosis should be questioned.

KEYWORDS

asthma & early wheeze, episodic viral wheeze, multiple-trigger wheeze, preschool children

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1 | INTRODUCTION

Recurrent wheezing is common in preschool children. In contrast to the more persistent pattern of asthma in children over 6 years of age, recurrent preschool wheezing commonly shows a transient course over time.[1,2] Based on these observed differences in the natural course, the common perception is that preschool wheezing disorders are a heterogeneous group of syndromes with different pathophysiology and prognosis.[3] However, attempts to distinguish different clinical phenotypes have had little success, partly due to a lack of reliable data.[4] In 2008, an ERS task force recommended the use of two pragmatic clinical phenotypes based on symptom patterns: "episodic viral wheeze" (EVW) and "multiple-trigger wheeze" (MTW), although the task force acknowledged that this recommendation was based on little evidence and that it was likely to change when new evidence became available.[5] EVW was defined as wheeze in discrete episodes, associated with viral upper respiratory tract infections (URTIs), whilst children were classified as having MTW when they also wheezed in response to other triggers. Although this phenotype distinction appears straightforward, a Canadian study showed considerable variation between physicians in the phenotype assessment of the same patient vignettes.[6] In addition, considerable within-patient phenotype switching has been reported in two prospective cohort studies in primary and hospital-based pediatric care, with up to 80% of phenotype changing in children with recurrent wheeze over a period of 1 to 2 years.[7,8] Conversely, in two large population-based birth cohort studies, Spycher et al[9] recently reported a tendency of wheeze phenotypes to track in children who continued to wheeze between the ages of 2 and 7 years.

These conflicting findings underscore the limited evidence base for the concept of EVW and MTW and highlights the need for additional studies on phenotyping preschool wheezing disorders.[10]

So far, no clinical studies have investigated the actual existence and stability of EVW and MTW by the use of symptom diaries, nor have prospectively reported symptoms been compared to clinical assessments by the patient's own physician. The aim of this prospective cohort study was to evaluate whether EVW and MTW are clinically distinguishable and stable phenotypes, by the use of symptom diaries, clinical assessments by pediatricians, and viral diagnostics.

2 | METHODS

We performed an observational 12-month prospective multicenter cohort study of 1- to 4-year-old children with recurrent wheezing, treated by hospital-based pediatricians. Recurrent wheezing was defined as a minimum of three episodes in the year before inclusion, at least one of which had been confirmed by a pediatrician. Children were recruited from pediatric departments of ten general and university hospitals in the Netherlands. To be included, the parents had to speak Dutch and have access to the internet. Children with other chronic pulmonary conditions, severe gastroesophageal reflux disease, immunodeficiencies, psychomotor delay, and hemodynamically significant cardiac defects were excluded, as well as children born at gestational age ≤35 weeks or with a birth weight ≤2000 g. The study procedures were approved by the Medical Ethics Committee of each participating hospital. Parents gave written informed consent at the start of the study period. Parents were instructed to record respiratory symptoms (cough, wheeze, and dyspnea) and symptoms of viral URTIs (rhinorrhea, ear- and/or throat pain and fever >38°C) on a weekly basis during 12 months, by using an electronic web-based secure diary (Figure S1). Before the start of the study, an educational video on the recognition of dyspnea and wheezing was presented to all participating parents.

2.1 | Definitions and data interpretation

At the start of the study period and after 3, 6, 9, and 12 months, a scheduled clinical assessment by the patient's own pediatrician took place. This interval duration was chosen because it represents a common interval for patient follow-up. At these occasions, a standardized clinical history was taken (Figure S2): data on respiratory symptoms, wheeze in relation to viral URTIs and other triggers and symptom-free periods were collected. Also, lung auscultation was performed. Medication use was continued or adjusted in accordance with current guidelines and the inhalation technique was checked and corrected when required.[11] Pediatricians were asked to classify the child's wheezing phenotype based on the (standardized) clinical history taken during the visit. Pediatricians were blinded to the content of the electronic diary registration of symptoms and did not receive specific instructions regarding phenotype assessment.

For each 3-month period ending at the date of the clinical assessment, the diary-based phenotype was assessed by the researchers (MR, AV) by evaluating the prospectively reported symptoms, using the following definitions. A respiratory episode was defined as reported cough, wheeze or dyspnea (at least 2 of these) for at least 2 consecutive days. A viral URTI episode was defined as rhinorrhea and/or ear-/throat pain and/or fever >38°C (at least 2 of these) during at least 2 consecutive days.[12] Symptom patterns were classified as EVW if respiratory episodes exclusively coincided with URTI episodes; the respiratory episode had to occur any time after the start of the URTI episode, as long as the URTI symptoms were still present. MTW was assigned when respiratory episodes also occurred outside URTI episodes. A third category was used for 3-month periods in which, according to our definition, no respiratory episodes (ie, lasting at least 2 days) occurred. Hence, periods without respiratory episodes were not necessarily free from respiratory symptoms.

We also analyzed our data using a stricter definition of a respiratory episode, in which episodes were only classified as such if the parents had reported wheeze on at least one of the days of the episode.

We first assumed that when weekly symptom registrations were missing, the children were free from symptoms during those

particular weeks. Since this may lead to underestimation of respiratory episodes, we also calculated the percentage of diary-based EVW and MTW periods after excluding the intervals with <68 reported days per period (=less than 75%), to find out whether underestimation affected our results. In the evaluation of phenotype stability, we did not take changes to and from intervals with no respiratory episodes into account.

2.2 | Virology

Parents were instructed by the electronic diary to take nasal swab samples in prespecified random periods: during URTI episodes, in periods when only respiratory symptoms were reported (and an inhaled beta-2 agonist was used for ≥5 days) and in complete absence of symptoms. Parents received an automatically generated request by email to collect a nasal swab test after filling in the weekly symptom diary. The procedure was explained by the pediatrician, an instruction video was available and instructions on paper were included in the nasal swab test set. Swabs were sent to, frozen and stored in a central hospital. When all samples were collected, semiquantitative real-time PCR was used to detect human rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus (HMPV), influenza virus A and B, parainfluenza viruses, and mycoplasma pneumonia.[13]

2.3 | Study endpoints

The clinically assessed phenotype was compared to the diary-based phenotype for each 3-month period. The primary outcome measure of our study was the agreement between these phenotypes. Our hypothesis was that the physician's clinical assessment of the phenotype agreed with the phenotype based on the prospective parental recording of their child's symptoms. Secondary outcome measures included the percentage of children in whom the phenotype changed during the study period and the occurrence and type of laboratory-confirmed URTIs both during and outside of periods with viral URTI or respiratory symptoms.

2.4 | Statistical analysis

The required sample size of 150 was based on the 95% confidence interval width around the observed agreement rate between the diagnosis EVW or MVW and clinical phenotype. A sample size of 150 corresponds with a maximum 95% confidence interval width of 0.17, which was considered sufficiently reliable. The interval width of 0.17 of the agreement rate coincides with an interval width of (1/(1−EP))×0.17 for the kappa coefficient, where EP is the expected proportion of agreement merely due to chance (ie, assuming independence between the diagnosis EVW or MVW and clinical phenotype). Setting EP at a plausible value of 0.3 results in a standard error for kappa of maximally 0.06 that was considered sufficiently reliable.

Descriptive statistics were used for the baseline characteristics and the distribution and change of phenotypes during the study period. We used mean ± standard deviation for normally distributed variables and median and interquartile range (IQR) for variables with skewed distributions.

Analysis of the agreement between the diary-based phenotype and the clinically assessed phenotype was carried out using Cohen's Kappa statistic.[14] First, Kappa was calculated for all four 3-month periods separately, after which an overall Kappa for all 3-month periods was computed as a weighted mean. The 95% confidence interval was determined by drawing 200 bootstrap samples. As a measure for phenotype stability over time, interperiod Kappas were used. For the diary-based phenotype assessments at each of the four 3-month periods, we first estimated the three interperiod Kappa coefficients. Next, weighted averages of subsets of these Kappa values were calculated.[15] The Kappa between two assessments one period apart was calculated as a weighted average of three Kappa values. In the case of assessments two periods apart, we calculated a weighted average of two Kappa values. For a time interval of three periods, only one Kappa was left. Bootstrapping (200 samples) was used to estimate standard errors of these weighted average Kappa values. The same analyses were carried out for clinical assessments. Changes to and from periods with no respiratory episodes were not taken into account by pairwise deletion.

Differences in medians and in the frequency of PCR positivity were analyzed by the Mann-Whitney *U* test. Differences in prevalence of viral pathogens were analyzed by generalized linear modeling, using a logit link function, robust covariance estimates and generalized estimating equations to account for the maximally six repeated measurements. Statistical analyses were performed with SPSS 24.0.

3 | RESULTS

A total of 189 children were included in the study and had complete baseline information (Figure 1). Characteristics of the study population are presented in Table 1. In 183 children (97%), parents started the weekly recording of their child's symptoms. The median number of completed weekly symptom reports was 48 (IQR 41-51) out of the supposed 52 weeks per patient. The median number of weekly reports per 3-month interval is displayed in Table S1. Analysis of 6.4% of these 3-month data sets was not possible as a result of missing clinical assessments. In addition, 3.4% of the data on symptoms and phenotypes was missing due to subjects being lost to follow-up.

3.1 | Phenotype assessment and stability

Of 660 3-month diary periods, in 75 periods (11%) children were classified as having EVW and in 357 (54%) as MTW. In 228 (35%) periods, no actual respiratory episodes occurred. When we restricted the analyses only to the datasets with at least 75% of daily symptom reports available, a similar distribution of phenotypes was found (12% EVW, 58% MTW, and 30% with no

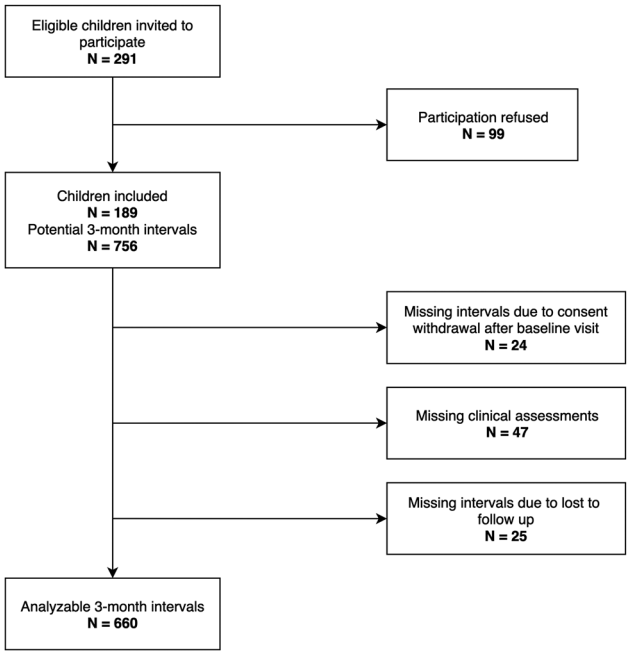

FIGURE 1 Flow chart of patient inclusion

respiratory episodes). In 3-month periods with EVW, children were completely free of respiratory symptoms (that is, no coughing, wheezing or dyspnea) on a median of 73% of days (IQR 55-83), compared with 68% (IQR 54-81) in the periods with MTW (P = .42).

During clinical assessments, the child's attending pediatrician classified 389 (59%) of all 3-month periods as EVW and 174 (26%) as MTW. An overview of the dairy-based and clinical assessments of phenotypes is presented in Table 2.

The Kappa coefficients for agreement between the diary-based phenotype and the clinically assessed phenotype were 0.09, 0.19, 0.12, and 0.09 for the first, second, third and fourth 3-month period, respectively. The overall weighted Kappa was 0.12 (95% CI, 0.07-0.17), indicating very limited agreement between the two modes of phenotype assessment.[14] Physicians more often assigned the EVW phenotype, whilst diary-based symptom patterns more often showed the MTW phenotype or no respiratory episodes at all. This observation applied to every 3-month interval (Figure 2).

In 142 children (78%), 4 evaluable 3-month periods were available for analysis of within-patient stability of wheeze phenotype. In 8 of these, the diary-based phenotype was always "no respiratory episodes." In 45 of the other 134 children (32%), the diary-based wheeze phenotype changed from EVW to MTW or vice-versa during the study period. The phenotype changed twice in 14 patients (10%). On the basis of diary data, only 4% of all children showed a stable EVW phenotype, whereas 63% had stable MTW.

The pediatrician-assessed clinical phenotype showed changes from EVW to MTW or vice-versa in 54 of 142 patients (38%), and in 13% the clinical phenotype changed twice. Stable EVW was found in 46% and stable MTW in 15%. The diary-based phenotype nor the clinically assessed phenotype changed more than twice.

TABLE 1 Patient characteristics at baseline (n = 189 children); numbers (%), mean (±SD) or median (IQR)

Gender	
Male	120 (64)
Female	67 (36)
Age at the start of the study, y	2.4 (0.9)
Preterm birth (35-37 wk)	7 (4)
Birth weight, g	3,466 (477)
Maternal smoking during pregnancy	17 (9)
Hospitalization for RS-viral infections	24 (13)
Eczema	92 (49)
Chronic rhinitis	22 (12)
Food allergies	18 (10)
Family history of atopy	170 (90)
Sensitization to one or more aero-allergens	103 (55)
Exposure to smoking	26 (14)
Age at first wheezing episode (months)	11 (8)
Number of wheezing episodes in the year before inclusion in the study	6 (IQR 4-8)
Prior hospitalizations for wheezing/dyspnea	139 (74)
Prior treatment with prednisone	113 (60)
1 course	69
2 courses	21
3 courses	10
>3 courses	13
Current daily controller medication	
Salbutamol as needed	177 (94)
Inhaled corticosteroids	146 (77)
Montelukast	6 (3)

The Kappa coefficients as a measure of period-to-period phenotype variability for the diary-based phenotypes were 0.06, 0.14 and −0.09 for the first, second and third time interval respectively, which reflects poor stability over time. For the pediatrician-assessed phenotypes, the Kappa coefficients were

TABLE 2 The overall distribution of phenotypes according to the two modes of assessment in numbers.

	Clinical assessment			
Diary-based assessment	**EVW**	**MTW**	**No respiratory episodes**	**Total, %**
EVW	51	20	4	75 (11.4)
MTW	236	102	16	354 (53.6)
No respiratory episodes	103	52	76	231 (35.0)
Total (%)	390 (59.0)	174 (26.4)	96 (14.5)	660 (100)

Abbreviations: EVW, episodic viral wheeze; MTW, multiple-trigger wheeze.

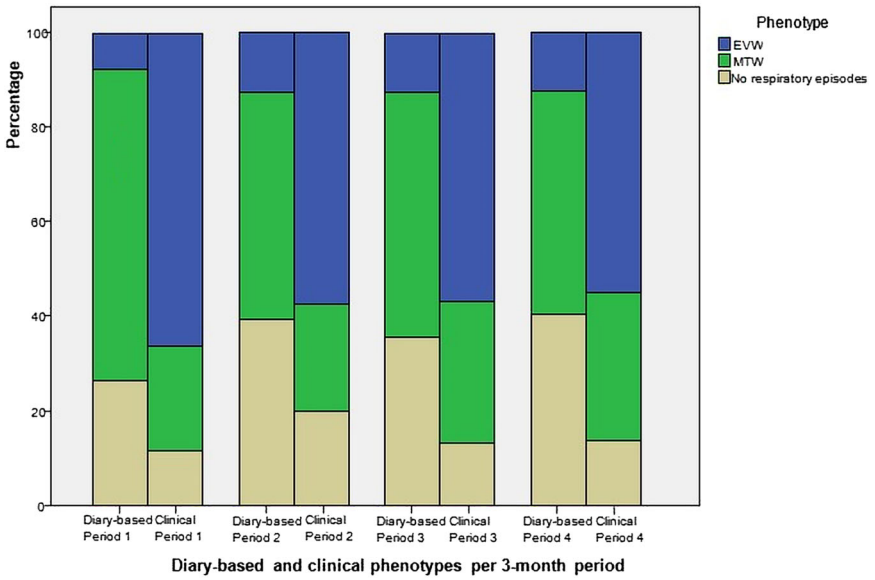

FIGURE 2 The proportion of phenotypes per 3-month period according to the two modes of assessment [Color figure can be viewed at wileyonlinelibrary.com]

0.58, 0.37, and 0.38, indicating fair to moderate stability[14] (Figure 3). The change of phenotypes over time is detailed in Figure S3.

Using the more stringent definition of a respiratory episode, in which reported wheeze had to be present on one or more days of the episode, 8% of the 3-month diary time periods were classified as EVW, 43% as MTW, whilst no respiratory episodes occurred in 49% of these time periods. Both the EVW: MTW ratio and the Kappa coefficient for agreement between the diary-based phenotype and the clinically assessed phenotype remained unchanged using the more strict definition (1:5 and 0.12 [95% CI, 0.08-0.16], respectively).

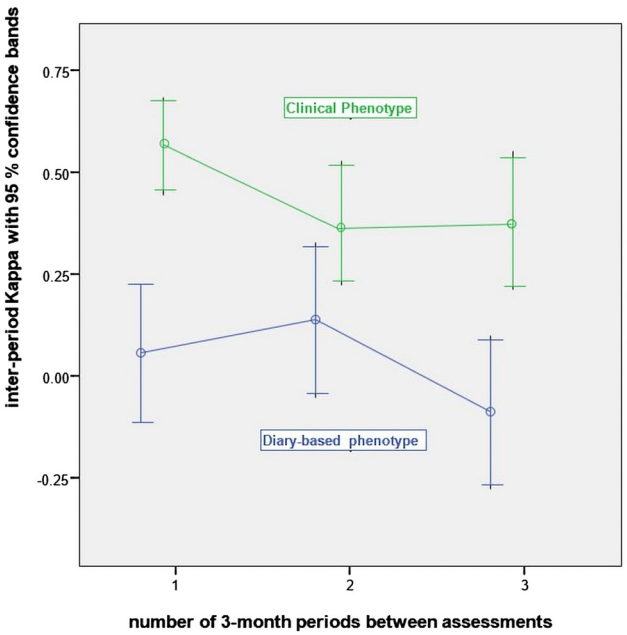

FIGURE 3 Interperiod Kappa coefficients for phenotype stability over time [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Nasal samples

During the study period, 503 nasal samples were taken from 154 children: 290 samples were taken during URTI episodes (covering 56% of all URTI episodes recorded), 108 during only respiratory symptoms, and 105 in the complete absence of symptoms. A positive PCR result was found in 71%, 66%, and 38%, respectively. These frequencies of a detected virus differed significantly between URTI episodes and no symptoms, and between respiratory symptoms and no symptoms (both $P < .001$), but there was no significant difference between URTI episodes and only respiratory symptoms ($P = .41$). The frequency and odds ratios of detected pathogens in relation to these different symptoms are displayed in Table 3 of this article and in Table S2. HMPV and RSV were significantly more prevalent during URTI episodes compared with episodes with only respiratory symptoms (OR, 4.46 (CI, 1.04-19.1) and 1.71 (CI, 0.67-4.34),

TABLE 3 Detected pathogens in nasal samples

	Symptoms during sample taking			
Positive PCR result	Viral symptoms N (%)	Respiratory symptoms N (%)	No symptoms N (%)	Total N (%)
HMPV	23 (8)	2 (2)	1 (1)	26 (5)
Rhinovirus	111 (38)	59 (55)	34 (32)	204 (41)
Influenza A	24 (8)	0	2 (2)	26 (5)
Influenza B	11 (4)	0	1 (1)	12 (2)
Parainfluenza	27 (9)	8 (7)	6 (6)	41 (8)
RSV	36 (12)	8 (7)	4 (4)	48 (10)
M. pneumoniae	3 (1)	1 (1)	1 (1)	5 (1)
Total number of samples	290	108	105	503

Abbreviations: HMPV, human metapneumovirus; RSV, respiratory syncytial virus.

respectively) or no symptoms (OR, 8.84 (CI, 1.30-60.3) and 3.50 (CI, 1.31-9.32), respectively). By contrast, rhinovirus was detected significantly more often during respiratory symptoms (OR, 0.53 (CI, 0.34-0.84) for URTI episodes as compared to respiratory symptoms, OR, 2.51 (CI, 1.38-4.55) for respiratory symptoms as compared with no symptoms). The presence of influenza A and B, parainfluenza and M. pneumoniae did not differ significantly between URTI episodes, respiratory symptoms or in absence of symptoms.

4 | DISCUSSION

4.1 | Main findings

Our study shows a very weak agreement between phenotypes derived from prospectively recorded symptoms by parents at home, and phenotype classification by hospital-based pediatricians based on parental history taken over the same 3-month periods. This poor agreement was present whether or not wheeze was included as a mandatory symptom in the definition of an episode of lower respiratory symptoms. Prospective symptom diaries showed phenotype switching between periods in 32% of the study subjects. Presence of viral DNA or RNA was found in 71% of episodes with symptoms of viral infection and in 66% of episodes with only respiratory symptoms, compared to 38% in completely symptom-free episodes.

The poor agreement between symptom patterns proving from symptom diaries and the pattern that the pediatrician apparently deduces from the clinical history, as well as the phenotype instability over time, challenge current paradigms on phenotype classification of preschool wheeze.

4.2 | Results in relation to other studies

Over the past decade, three studies evaluated the prevalence and stability of EVW and MTW. Schultz et al[7] reported a 54% change in phenotype during a 1 year period using a standardized questionnaire in preschool children with pediatrician-diagnosed recurrent wheezing, who had all been prescribed daily inhaled corticosteroids and followed up by hospital-based pediatricians. Two-thirds of the study subjects who were classified as EVW and half of the subjects classified as MTW at the screening visit were re-classified as no wheeze, EVW or MTW at the end of the study. Van Wonderen et al[8] investigated children from general practices known with recurrent cough, wheeze or shortness of breath, and found that approximately 50% of phenotypes changed over 1 year and 80% after 2 years. In 2 years of follow-up, 28% received a prescription for inhaled corticosteroids. In children with stable MTW, the risk of asthma at the age of 6 was considerably higher than in children with stable EVW with odds ratios of 14.4 and 3.6 respectively, compared to children free of wheeze. In contrast to the previously mentioned studies, Spycher et al recently reported data from two large prospective birth cohort studies using questionnaires at ages 2, 4 and 6 years, and showed that MTW, and to a lesser extent, EVW, tended to persist in children who continued to wheeze. Among 4-year old children with the MTW phenotype, they described a risk ratio adjusted for symptom severity of 15.6 for MTW (stable phenotype) compared to 7.0 for EVW (phenotype switching) at 6 years.[9]

In comparison to Schultz et al's original and our current study, Van Wonderen and Spycher likely investigated a population with less severe symptoms, since children were recruited from general practices and general population samples. Our study is the first to use a prospectively collected weekly symptom diary and to reassign the phenotype every 3 months. In our cohort, the phenotype changed once or twice in a smaller (compared to the other prospective cohort studies) yet considerable proportion of patients, a finding that suggests that phenotypes may not be stable, nor evolving in one particular direction. Since children with the MTW phenotype also respond to viral infections, overlapping may, however, have played a role in the observed phenotype switching.

Wesolowska-Andersen et al recently detected a respiratory virus in 13% of symptom-free asthmatic children and healthy controls using quantitative PCR,[16] which is considerably lower than the percentage we found in symptom-free children. This difference is likely explained by the age difference between the studies: 1-to-4-year-olds in our study, compared to 10-to-21-year-olds in the previous study. In symptom-free children under the age of 6, Jansen et al reported a positive PCR in 28%.[17] From a study investigating the occurrence of viral infections in children hospitalized for wheezing, a virus was identified in 71%. RSV was most frequently detected, followed by rhinovirus, adenovirus and human bocavirus.[18] Lopez-Perez et al[19] studied viral pathogens using direct immunofluorescence in children with a history of wheezing or asthma, presenting with symptoms of rhinopharyngitis. A virus was identified in 75% of children with a history of asthma and 44% of children known for preschool wheezing. RSV and influenza A dominated in the preschool age group, whereas influenza A, adenovirus and parainfluenza were more frequent in older children.

4.3 | Strengths and limitations

The main strength of our study is the careful prospective recording of not only the temporal pattern of respiratory symptoms but also the frequency and associated symptoms of viral infections that allowed for an accurate distinction between EVW and MTW. The educational video that was offered to parents on the standardized recognition of dyspnea and wheezing before enrollment may also have contributed to the reliability of our results, since it may help parents to distinguish wheeze from upper airway noises.[20,21] The lack of a difference between the results based on respiratory episodes with or without wheeze included in the definition also supports the validity of our findings. Another strength is the recruitment of the study population from hospital populations, with at least one episode that was confirmed by a pediatrician. This population is likely to have more severe symptoms than patients from primary care populations and general population samples. Also, children with doctor-confirmed wheeze exhibit

greater airway resistance than with only reported wheeze.[5] Indeed, only 35% of all 3-month observation periods were free of respiratory episodes.

The fact that we used a population from secondary care is, however, also a limitation to our study. Relatively many children were sensitized to aero-allergens, used inhaled corticosteroids and had been hospitalized for wheeze. Some of our findings may, therefore, not be applicable to other wheezing populations.

We are aware that the two modes of phenotype assessment differ substantially. The diary-based classification was based on prospectively recorded symptoms while the pediatrician classification was retrospective. The weak agreement we found may partly be explained by these differences. However, the comparison is still relevant, since the retrospective classification based on clinical history reflects clinical practice, and is being used as a basis for treatment decisions. Based on our results, misclassification in clinical practice is common when clinical phenotype assessment is compared to weekly recorded symptom patterns.

The weekly recording of symptoms by parents required commitment and has been a potential burden to parents. This may explain incompleteness of symptom diaries. The median of 48 completed weekly diaries was, however, not far from the intended 52 reports per patient. When weekly symptom reports were missing, we assumed that children were free of symptoms during those particular weeks. This may have resulted in an underestimation of respiratory episodes. However, our sensitivity analysis indicated that the incompleteness of data was unlikely to have caused bias.

We found a remarkably small proportion of 3-month intervals meeting the criterium for EVW while commonly the prevalence of EVW is considered higher than that of MTW.[5] This finding may partly be explained by our selected population from secondary care. Also in contrast to what is expected from the definitions, the median percentage of symptom-free days in EVW and MTW quarters was similar.

Our literature-based definition of URTI episodes may have been relatively strict, which is also supported by the detection of viruses in a substantial part of other episodes and may have resulted in the underestimation of EVW. However, the mean number of URTI episodes per patient in our cohort was 2.83 (SD 2.92), which is in line with other observations.[22]

Due to the use of the criterium "two consecutive days" for symptom duration in the definition of a respiratory episode, short-lasting but real symptoms may have been missed. The reported episodes are therefore more than trivial, which again points out that our results may not be generalized to the whole spectrum of wheezing preschool children.

Another limitation to our study is the fact that by PCR, some viruses can be detected for a longer time when symptoms are no longer present. Previous studies showed ongoing shedding of RSV, rhinovirus and hMPV 7 to 30 days after onset of symptoms.[23,24] This may explain some of our positive PCR results detected in the absence of viral symptoms. Also, we did not collect viral samples during all wheezing or URTI episodes and nasal samples were taken randomly.

4.4 | Clinical implications

Our results suggest that, based on parental history reports, pediatricians are not able to acquire an accurate view on the patient's wheezing pattern. A reliable distinction between EVW and MTW, deduced from the clinical history, appears to be impossible. The fact that viral pathogens were equally often detected during symptoms of viral infections and during only respiratory symptoms indicates that the EVW criterium of wheezing always coinciding with respiratory tract infections is not useful in clinical practice. Moreover, EVW and MTW are unstable over time. These findings all challenge the current paradigms on the classification of preschool wheeze. The use of EVW and MTW in the classification and treatment of preschool wheeze in pediatric practice should be questioned. Based on progressive insight, the severity and frequency of symptoms might be a better basis for prescribing daily controller therapy.[10]

5 | CONCLUSION

The results of this study suggest that EVW and MTW are not stable and cannot be accurately distinguished in clinical practice. As yet, there is however no evidence for consequent therapeutic or prognostic implications, which is why this classification might better be abandoned. A most striking finding from this study is the lack of concordance between the parental reported patterns of wheeze through weekly symptom reports and the clinical assessment of the pediatricians during outpatient clinic visits. To improve insight into the patient's wheezing pattern, a prospective symptom diary could be used.

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CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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