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Temporal stability of multiple trigger and episodic viral wheeze in early childhood

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Summary of 'take home' message: Multiple trigger and episodic viral wheeze track in early childhood and likely reflect distinct disease processes.

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Key Words: asthma phenotypes; childhood asthma; cohort study; preschool children; respiratory tract infections; wheezing disorders

Abstract

The distinction between episodic viral wheeze (EVW) and multiple trigger wheeze (MTW) is used to guide management of preschool wheeze. It has been questioned whether these phenotypes are stable over time. We examined the temporal stability of MTW and EVW in two large population-based cohorts.

We classified children from the Avon Longitudinal Study on Parents and Children (N=10,970) and the Leicester Respiratory Cohorts (LRC, N=3,263) into EVW, MTW and no wheeze at ages 2, 4 and 6 years based on parent-reported symptoms. Using multinomial regression, we estimated relative risk ratios (RRRs) for EVW and MTW at follow-up (no wheeze as reference category) with and without adjusting for wheeze severity.

Although large proportions of children EVW and MTW became asymptomatic, those that continued to wheeze showed a tendency to remain in the same phenotype: Among children with MTW at 4 years in LRC the adjusted RRR was 15.6 (95% CI: 8.3, 29.2) for MTW (stable phenotype) compared to 7.0 (2.6, 18.9) for EVW (phenotype switching) at 6 years. The tendency to track was weaker for EVW and from 2-4 years. Results were similar across cohorts.

This suggests that MTW and, to a lesser extent, EVW track regardless of wheeze severity.

Introduction

There is debate whether recurrent wheezing in young children represents a single disease entity, "childhood asthma", or a heterogeneous group of disorders, referred to as asthma "phenotypes". Numerous attempts have been made to distinguish phenotypes.[1-3] A commonly used classification is the distinction between episodic viral wheeze and multiple trigger wheeze.[4, 5] *Episodic viral wheeze (EVW)*, also called exclusive viral wheeze, characterises children who wheeze only during respiratory infections. During the intervals between colds, these children are asymptomatic. EVW is frequent in infancy and preschool years, less prevalent in older children,[6] and has also been described in adults.[7] *Multitrigger wheeze (MTW)* more closely resembles classical asthma.[8] Children with MTW also wheeze between respiratory infections in response to a variety of factors, including allergens, exercise, laughing or crying, strong smells or certain foods or drinks.[9] MTW is more strongly associated with lung function abnormalities[8] and atopy.[10] While most children with EVW become asymptomatic, MTW tends to persist.[11, 12] This two-phenotype model has been used to guide management of preschool wheeze.[9, 13-16] For instance, a taskforce of the European Respiratory Society (ERS) recommended using inhaled corticosteroids for maintenance treatment of MTW, but montelukast for EVW.[9]

The distinction between EVW and MTW and its usefulness for the management of preschool wheeze has been challenged.[17, 18] Garcia Marcos and colleagues suggested that the two phenotypes merely reflect the ends of a severity spectrum with MTW representing more severe wheeze.[19] Severity of wheeze, in particular frequency of episodes, strongly predicts long-term prognosis.[12, 20, 21] It has also been questioned whether these phenotypes are sufficiently stable over time to represent clinically meaningful entities.[22, 23] In an update of their recommendations in 2014, the ERS taskforce pointed out that wheeze patterns in young children vary over time and with treatment, rendering the distinction between EVW and MTW difficult in many patients.[17] Consequently, inhaled corticosteroids remained the first-line treatment for MTW, but

were also recommended for patients with frequent or severe EVW. The taskforce concluded that future research should focus on disease severity in addition to phenotypes.[17]

The current study used longitudinal data on wheezing at ages 2, 4, and 6 years from two large population-based birth cohorts, to examine the stability of MTW and EVW over time, and the degree to which stability was explained by differences in wheeze severity.

Material and methods

Study populations

ALSPAC is a longitudinal population-based birth cohort study that recruited 14,541 pregnant women resident in Avon, UK, with expected dates of delivery between April 1991 and December 1992. There were 14,062 live born children. The study has been described in detail elsewhere.[24] Each year up to children's age of 8 years, the study mothers were sent child health questionnaires including detailed questions on respiratory symptoms. Ethical approval was obtained from the ALSPAC Ethics and Law Committee and from Local Research Ethics Committees.

The Leicestershire 1998-b respiratory cohort (LRC) consists of a population-based random sample of 4300 children born between May 1996 and April 1997 in Leicestershire, UK. It is, described in detail elsewhere.[25] Perinatal routine data were obtained from Leicestershire Health Authority Child Health Database and mothers were sent questionnaires including detailed questions on respiratory symptoms in 1998, 1999, 2001, 2003, 2006 and 2010. The study was approved by the Leicestershire Health Authority Research Ethics Committee.

We include all children in both cohorts whose parents responded to a questionnaire sent at age 2, 4, or 6 years (30, 57 and 81 months' questionnaires in ALSPAC).

Definition of wheeze phenotypes

The questions used to address wheeze or whistling in the previous 12 months (current wheeze) were similar in both cohorts (**Table 1**). Children were assigned to the EVW phenotype if they reported current wheeze in the previous 12 months with infections as a trigger and no other triggers (**Table 1**). Children with current wheeze in the previous 12 months reporting a trigger category other than infections were assigned to MTW. Children with current wheeze who could not be assigned either to EVW or MTW were designated non-classifiable.

Information on wheeze severity

We defined the following indicators of wheeze severity based on symptoms in the previous 12 months: frequent wheeze attacks (≥3 in ALSPAC, ≥4 in LRC), shortness of breath during wheeze attacks, sleep disturbed due to wheezing, speech limited to 1-2 words at a time between breaths due to wheeze (ALSPAC only), wheeze interfering with child's daily activities (LRC only). The questions used to assess this information and the definitions of severity indicators are provided in the supplementary **Table S1**.

Statistical analysis

We carried out the following analysis steps:

a) We computed the prevalence of current wheeze, EVW and MTW at ages 2, 4, and 6 years.

b) At each age, we assessed the association between wheeze phenotypes and dichotomous indicators of severity (supplementary **Table S1**) by calculating odds ratios (OR) for MTW vs. EVW comparing severe with less severe wheeze using logistic regression.

c) For each age interval, 2-4, 4-6, and 2-6 years, we assessed whether wheeze phenotype at the first time point (baseline) predicted current wheeze at the later time point (follow-up). We used logistic regression to estimate odds ratios (OR) for current wheeze at follow-up, comparing children with EVW and MTW at baseline with those without wheeze.

d) For each age interval, we assessed whether children tended to have the same wheeze phenotypes at follow-up as they did at baseline. We first calculated the probability for these categories at follow-up given the category at baseline. Using multinomial logistic regression, we then estimated relative risk ratios (RRR) for EVW and MTW at follow-up respectively comparing these phenotypes with no wheeze at baseline. We adjusted regression models for symptom severity (original variables, not dichotomised) at baseline to determine whether the phenotypes at baseline predicted the phenotypes at follow-up independent of severity. In separate models we additionally adjusted for sex, ethnicity (white, other), maternal smoking during pregnancy, older siblings (yes/no), crowding (>1 person/room) and pet ownership. The RRRs compare the risk ratio for phenotypes at follow-up (probability for having the phenotype divided by probability of having no wheeze) in children of a given phenotype at baseline (EVW, or MTW) to children with no wheeze at baseline. We also tested for the equality of RRRs between EVW and MTW at baseline. Such equality implies absence of tracking. For instance, equality of RRRs for EVW at follow-up means that, after excluding children with MTW at follow-up, those with EVW and MTW at baseline are equally likely to have EVW at follow-up.

Results

Of the 14,062 live born children recruited in ALSPAC, we included 10,970 (78%) for whom information on wheeze was available for at least one time point (age 2, 4, or 6 years). Information on wheeze was provided for 9953, 9391 and 8393 children at the ages of 2, 4 and 6 years respectively (**Table 2**). Similarly, of the 4300 children in the LRC (1998-b cohort), we included 3263 (76%) and information on wheeze was reported for 2355, 2609 and 2077 at ages 2, 4, and 6 years respectively.

The cohorts differed with respect to ethnicity and socio-economic conditions (**Table 2**). In ALSPAC, 97% of the children were white. In the LRC, 85% were white and 15% of south Asian origin. Households in the LRC tended to be more crowded, and maternal smoking and pet

ownership was less common than in ALSPAC. The proportions of children whose mothers smoked during pregnancy, who had older siblings or who lived in crowded homes were lower in children who participated in only 1-2 surveys compared to those who participated in all 3 ~~surveys~~, and lower still in children excluded from analyses (**Supplementary Table S2**). Maternal smoking during pregnancy was more common among children with MTW than EVW (**Supplementary Table S3**).

Prevalence of current wheeze and wheeze phenotypes at ages 2, 4 and 6 years

Prevalence of current wheeze in ALSPAC was 23% at age 2 years, and decreased to 13% at age 6 years (**Table 2**). In LRC, current wheeze decreased similarly from 23% at age 2 to 16% at age 6 years. The relative frequency of the two phenotypes were remarkably similar in both cohorts. At age 2, 45% of all classifiable wheezers in ALSPAC (44% in the LRC) were defined as EVW; this decreased to 36% (32%) at age 4 and 30% (24%) at age 6.

Associations between wheeze phenotypes and indicators of wheeze severity

Severity of wheezing illness as defined by the five indicators (frequency of attacks, shortness of breath, sleep disturbance, interference with activities and speech limitation) was higher for MTW than for EVW (**Table 3**). The difference between phenotypes was larger in LRC than in ALSPAC. For example, at age 2, the odds ratio (OR) for having MTW rather than EVW comparing children with frequent episodes of wheeze to those with less frequent episodes was 2.7 (95% CI: 2.2, 3.2) in ALSPAC and 6.5 (4.1, 10.4) in LRC. In the LRC, differences between the two phenotypes became more distinct (larger odds ratios) with age.

Risk of later wheeze in children with episodic viral wheeze and multiple trigger wheeze

The risk of having current wheeze two or four years later was higher for MTW than for EVW in both cohorts (**Supplementary Table S4 and S6**). In the ALSPAC cohort, the OR for wheeze at

age 4 was 7.8 (95% CI: 6.5, 9.3) for children with EVW at age 2 years, and 12.5 (10.6, 14.8) for those with MTW, compared to children who did not wheeze. Respective ORs were 3.7 (2.6, 5.3) and 9.9 (7.2, 13.5) in the LRC. Prediction of later wheeze was stronger from age 4 to 6: In ALSPAC, ORs were 26.6 (22.2, 32.1) for MTW and 11.9 (9.5, 14.8) for EVW at baseline (**Table S4**, crude OR). When the regression models were adjusted for wheeze severity, the difference in prognosis between the two phenotypes diminished somewhat, particularly in ALSPAC (**Table S4**, Adj. OR). ORs for current wheeze 4 years later (prediction from 2 to 6 years) were lower compared to the 2-year prediction intervals (**Table S6**).

Likelihood of keeping or switching wheeze phenotype

The proportion of children remaining in their phenotype or transitioning to another phenotype was similar in the two cohorts (**Supplementary Table S5** and **Figure 1**). Among ALSPAC children who had EVW at 2 years and who had a classifiable wheezing pattern 2 years later, 57% became asymptomatic, while 21% still had EVW and 22% had developed MTW. Among children with MTW at age 2, 45% became asymptomatic, 45% remained MTW and only 10% were reclassified to EVW.

Despite considerable proportions of children remitting or changing phenotype, multinomial logistic regressions showed a tendency of phenotypes to track: relative risk ratios (RRR) were consistently higher for remaining in the same phenotype than for phenotype switching (**Table 4** and s**upplementary Tables S5 and S7**). Among children with EVW at age 2 years in ALSPAC, the crude RRR was 9.4 (95% CI: 7.4, 11.9) for EVW (stable phenotype) but 7.7 (6.1, 9.7) for MTW (phenotype switching) at 4 years. Among children with MTW at 2 years the tendency for tracking was much stronger with a RRRs for later MTW and EVW of 20.5 (16.8, 24.8) and 5.9 (4.4, 7.8) respectively. Tracking was stronger for both phenotypes from age 4 to 6 years and was strongest for MTW: RRRs 44.9 (35.4, 56.9) and 27.3 (18.9, 39.6) in ALSPAC and LRC

respectively. Although the RRRs diminished after adjustment for severity, they remained considerable higher for remaining in the same phenotype than switching, particularly for MTW (**Table 4,** Adj. RRR). Despite the larger proportions of children becoming asymptomatic, RRRs for the 4 year period from age 2-6 years still reveal a tendency of phenotypes to track (Supplementary **Table S7)**. Additionally, adjusting regression models for sociodemographic variables and early environmental exposures only led to marginal changes in estimated RRRs (results not shown).

Statistical tests also support phenotype tracking. The p-values for equality of RRRs between EVW and MTW at baseline are all <0.01 except in LRC for EVW at follow-up (**Table 4**). These p-values remain low after adjusting for symptom severity.

Discussion

Using prospectively collected data from two independent population-based cohorts, our study found that children with MTW and EVW whose wheeze persisted over two year periods (from ages 2-4 and 4-6 years) showed a tendency to remain in the same phenotype. This tracking was stronger for MTW than for EVW and was only partially explained by reported symptom severity. This supports the hypothesis that EVW and MTW represent distinct disease entities rather than different ends of a severity spectrum. Our study also confirms that a high proportion of early wheeze remits (approximately 60-70% of EVW and 40-45% of MTW). Despite differences in study design and methodology, results from the two cohorts were closely similar.

Strengths and weaknesses of the study

Our study was based on two large, population-based cohort studies that assessed wheezing prospectively. This provided large representative samples and enabled us to use phenotype definitions that are consistent over time. Both cohorts have information on frequency and severity of wheeze, which allowed us to assess whether differences in severity explained the

tendency for phenotypes to track. Although the two cohorts use different measures of severity, the relationships between these markers and phenotypes are similar in both cohorts.

Phenotype definitions were based entirely on parent reports of symptoms during the previous 12 months. Parental assessment may be unreliable not only for the presence of wheeze, but also for wheeze severity and the presence of viral infections. In both cohorts, we defined phenotypes indirectly based on individual triggers of wheeze reported. Non-viral triggers may have been underreported because not all possible triggers were specifically addressed. However, in LRC, parents' direct assessment of children's wheezing pattern shows good agreement with our phenotype definitions and does not suggest under reporting of non-viral triggers (supplementary **Table S8**). EVW may have been underreported in ALSPAC, as wheeze with colds was not an explicit response option (**Table 1**). This may explain the larger proportion of non-classifiable wheeze in ALSPAC. Although both cohorts were large and population-based, not all children participated in each survey. The samples with information available at baseline and follow-up were thus somewhat reduced and not fully representative of the entire cohorts.

How do the results compare to other studies?

Our study is the largest study investigating the temporal stability of MTW and EVW and the only one to statistically test whether these phenotypes track. Furthermore, it is the only study to investigate whether this tracking is explained by symptom severity, a known risk factor for the persistence of wheeze. To our knowledge, only four studies have assessed the stability of EVW and MTW over time.[22, 23, 29, 30] Study populations were smaller than either of our two cohorts. The results of these studies are summarised in the supplementary **Table S9**. Despite differences in study population and design, the proportions of children becoming asymptomatic or changing phenotype were broadly comparable to those in our study. Two of the four studies investigated both EVW and MTW and one showed, in agreement with ours, that the proportion of children remaining in the same phenotype was larger for MTV than for EVW,[22] while the other study

showed greater stability for EVW.[23] However, none of these studies used regression modelling to investigate the tendency of phenotypes to track or the extent to which such a tendency might be explained by symptom severity.

Our observation that the proportion of children with MTW increases with age while EVW decreases with age is in line with other studies.[3, 6, 11, 26, 27] An early cross-sectional study showed a positive correlation of age with allergy and exercise as triggers of asthma and a negative correlation with respiratory infections.[26] Using partly overlapping data from the LRC, we have previously shown a decrease in the proportion of infections as an exclusive trigger among children with current wheeze from 57% at age 1 to 21% at age 9 years, while the proportion of children also reporting other triggers increased correspondingly.[27]

Similarly, our findings that MTW is associated with more severe wheeze than EVW confirms findings from other studies.[6, 28]. Cross-sectional surveys in Aberdeen reported less frequent episodes, and less night cough, shortness of breath and chest tightness in children with EVW compared to those with MTW.[6, 28]

Interpretation

In both cohorts, we found that, RRRs for EVW at follow-up were higher for children with EVW than for those with MTW at baseline, while RRRs for MTW at follow-up were higher for children with MTW at baseline. In the absence of any phenotype stability, we would have expected these RRRs to be equal. Instead, we found that children tend to remain in the same phenotype. We then explored if this was explained by differences in severity. If children with MTW on average had more severe disease, children classified as MTW at baseline would tend to be reclassified as MTW at follow-up. This did in fact explain part of the difference, however the direction of our findings (higher RRRs for the same phenotype) remained the same after

adjusting for severity. It is possible that results are still residually confounded by unmeasured severity. Although we corrected for a wide range of measures including frequency of episodes, shortness of breath, sleep and activity disturbance, these measures were based on parental report and may be inaccurate. We also cannot exclude that the observed stability of phenotypes was partially due to parent's tendency to give the same, possibly inaccurate, answers to the same questions on symptoms over time.

It should be noted that the stability of MTW observed in our study is not an artefact of its definition: It might for instance be objected that a child by definition becomes (and remains) a multiple trigger wheezer from the first time they wheeze in response to a non-viral trigger. However in our study children were assigned to phenotypes based only on triggers of wheeze in the previous 12 months. Thus children wheezing only with colds during this period were classified as EVW regardless of whether they previously had MTW. This 12-month period of observation makes sense because interval symptoms may be seasonal and a classification based on shorter periods might be strongly affected by season.

We suspect that the explanation of our finding is that differences in the underlying diseases processes other than severity cause some children to wheeze only during respiratory tract infections and other to be sensitive to other triggers. This reopens the possibility that certain therapies might indeed be more effective in certain phenotypes.[9, 14, 16, 17] More research is needed to understand the underlying differences between EVW and MTW. Epidemiological studies should continue to distinguish between these phenotypes and better characterise them regarding risk factors and prognosis. While translating such knowledge to clinical management will take time, our study suggests that we should not prematurely discard these phenotypes.

Conclusions

Using data from two large population based birth cohorts, we found that MTW and, to a lesser extent, EVW show a tendency to track from preschool to early-school age. While many children in both phenotypes become asymptomatic, those that continue to wheeze tend to remain in the same phenotype, though some phenotype switching does occur. The tendency to remain in the same phenotype was only partially explained by wheeze severity suggesting that there are other differences in the underlying disease processes of children with MTW and EVW.

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References

1. Henderson J, Granell R, Sterne J. The search for new asthma phenotypes. Arch Dis Child 2009; 94:333-6.
2. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: are they real? Clin Exp Allergy 2010; 40:1130-41.
3. Just J, Saint Pierre P, Amat F, Gouvis-Echraghi R, Lambert-Guillemot N, Guiddir T, et al. What lessons can be learned about asthma phenotypes in children from cohort studies? Pediatr Allergy Immunol 2015; 26:300-5.
4. Silverman M. Out of the mouths of babes and sucklings: lessons from early childhood asthma. Thorax 1993; 48:1200-4.
5. Silverman M, Grigg J, Mc Kean M. Virus-induced wheeze in young children - A separate disease? In: Johnston S, Papadopoulos N, editors. Respiratory infections in allergy and asthma. New York: Marcel Dekker; 2002. p. 427-71.
6. Wassall HJ, Devenny AM, Daud Khan S, Ninan TK, Russell G. A comparison of virus-associated and multi-trigger wheeze in school children. J Asthma 2005; 42:737-44.
7. McKean MC, Leech M, Lambert PC, Hewitt C, Myint S, Silverman M. A model of viral wheeze in nonasthmatic adults: symptoms and physiology. Eur Respir J 2001; 18:23-32.
8. Sonnappa S, Bastardo CM, Wade A, Saglani S, McKenzie SA, Bush A, et al. Symptom-pattern phenotype and pulmonary function in preschool wheezers. J Allergy Clin Immunol 2010; 126:519-26 e1-7.
9. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J 2008; 32:1096-110.
10. Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehni CE. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. Eur Respir J 2008; 31:974-81.
11. Depner M, Fuchs O, Genuneit J, Karvonen AM, Hyvarinen A, Kaulek V, et al. Clinical and epidemiologic phenotypes of childhood asthma. Am J Respir Crit Care Med 2014; 189:129-38.

12. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964-1999. J Allergy Clin Immunol 2002; 109:189-94.

13. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Edinburgh, Scotland: Heatlh Improvement Scottland; 2016.

14. Kuehni CE. Phenotype specific treatment of obstructive airways disease in infancy and childhood: new recommendations of the Swiss Paediatric Pulmonology Group. Swiss Med Wkly 2005; 135:95-100.

15. Roth S, Barrazzone C, Barben J, Casaulta C, Aebischer C, Eigenmann P, et al. Empfehlungen zur Behandlung der obstruktiven Atemwegserkrankungen im Kindesalter (SGPP/PIA-CH 2009). Paediatrica 2009; 20:44-51.

16. Bush A. Phenotype specific treatment of asthma in childhood. Paediatr Respir Rev 2004; 5:S93-101.

17. Brand PL, Caudri D, Eber E, Gaillard EA, Garcia-Marcos L, Hedlin G, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. Eur Respir J 2014; 43:1172-7.

18. Schultz A, Brand PL. Episodic viral wheeze and multiple trigger wheeze in preschool children: a useful distinction for clinicians? Paediatr Respir Rev 2011; 12:160-4.

19. Garcia-Marcos L, Martinez FD. Multitrigger versus episodic wheeze in toddlers: new phenotypes or severity markers? J Allergy Clin Immunol 2010; 126:489-90.

20. Leonardi NA, Spycher BD, Strippoli MP, Frey U, Silverman M, Kuehni CE. Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. J Allergy Clin Immunol 2011; 127:1466-72 e6.

21. Pescatore AM, Dogaru CM, Duembgen L, Silverman M, Gaillard EA, Spycher BD, et al. A simple asthma prediction tool for preschool children with wheeze or cough. J Allergy Clin Immunol 2014; 133:111-8 e13.

22. Schultz A, Devadason SG, Savenije OE, Sly PD, Le Souef PN, Brand PL. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. Acta Paediatr 2010; 99:56-60.

23. van Wonderen KE, Geskus RB, van Aalderen WM, Mohrs J, Bindels PJ, van der Mark LB, et al. Stability and predictiveness of multiple trigger and episodic viral wheeze in preschoolers. Clin Exp Allergy 2016; 46:837-47.

24. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: The 'Children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. Int J Epidemiol. 2013; 42:111-27.

25. Kuehni CE, Brooke AM, Strippoli M-PF, Spycher BD, Davis A, Silverman M. Cohort profile: the Leicester respiratory cohorts. Int J Epidemiol 2007; 36:977-85.

26. Sarafino EP, Paterson ME, Murphy EL. Age and the impacts of triggers in childhood asthma. Journal of Asthma 1998; 35:213-7.

27. Strippoli MP, Spycher BD, Pescatore AM, Beardsmore CS, Silverman M, Kuehni CE. Exclusive viral wheeze and allergic wheeze: evidence for discrete phenotypes. Eur Respir J 2011; 38:472-4.

28. Tagiyeva N, McNeill G, Russell G, Helms P. Two main subtypes of wheezing illness? Evidence from the 2004 Aberdeen schools asthma survey. Pediatr Allergy Immunol 2008; 19:7-12.

29. Topal E, Bakirtas A, Yilmaz O, Ertoy Karagol IH, Arga M, Demirsoy MS, et al. Short-term follow-up of episodic wheeze and predictive factors for persistent wheeze. Allergy Asthma Proc 2013; 34:e42-6.

30. Kappelle L, Brand PL. Severe episodic viral wheeze in preschool children: High risk of asthma at age 5-10 years. Eur J Pediatr 2012; 171:947-54.

Table 1: Questionnaire items and definitions of wheeze phenotypes in the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Leicester Respiratory Cohort Study (LRC; cohort 1998-b)

ALSPAC	**LRC**
Current wheeze: 1) "Since your child was (age at previous questionnaire) old has he/she had any periods when there was wheezing with whistling on his chest when he breathed?" (Yes/No) 2) Has he/she had 'wheezing' in the last 12 months? (Yes/No) *Definition current wheeze*: positive response to 1 or 2	***Current wheeze:*** 1) "Has your child had wheezing or whistling in the chest in the last 12 months?" (yes/no) *Definition current wheeze*: positive response to 1
Triggers of wheeze: 3) "What do you think brings on the wheezing attacks? a) chest infection or bronchitis b) being in a smoky room c) cold weather d) I don't know e) other (please describe)" Responses to 2e) were coded into following categories: f) infections (upper or lower RTI) g) allergic triggers (airborne allergens, foods and beverages)	***Triggers of wheeze:*** 2) "In the last 12 months, has your child had wheezing or whistling in the chest during or soon after a cold or flu?" (yes/no) 3) "In the last 12 months, has your child had wheezing or whistling in the chest even without having a cold or flu? (yes/no) 4) "In the last 12 months did the following things cause wheezing in your child? a) exercise (playing or running) b) laughing, crying or excitement c) contact with pets or other animals d) pollen (grass, hay, trees, flowers) *

h) physical activities or intense emotions i) damp or cold indoor or weather conditions j) air pollution k) asthma (diagnosed, suspected, family history) l) other (e.g. hot temperature, irritants, teething)	e) food or drinks" (answer categories for a-d: yes/no/don't know) * only asked from age 4 years onward
Phenotype definitions* EVW: (1 or 2) and (3a or 3f with no other categories reported) MTW: (1 or 2) and (any of 3b, 3c, 3g-3j, or 3l) NCW: (1 or 2) and (no response to 3, or 3d or 3k with no other categories reported)	***Phenotype definitions**** EVW: 1 and (2 with no positive response to any of 3, 4a-4e) MTW: 1 and (any of 3, 4a-4e) NCW: 1 and (no positive response to any of 2, 3, 4a-4e)

Abbreviations: ALSPAC Avon Longitudinal Study on Parents and Children, LRC Leicestershire Respiratory Cohort 1998-b, EVW episodic viral wheeze, MTW multiple trigger wheeze, NCW non-classifiable wheeze

* Positive responses to listed questionnaire items required.

Table 2: Characteristics of study populations (Avon Longitudinal Study of Parents and Children and Leicester Respiratory Cohort Study) and prevalence of wheeze phenotypes at ages 2, 4 or 6 years

Characteristics	ALSPAC (n=10,970)		LRC (n= 3,263)	
	n/N*	%	n/N*	%
Socio-demographic data				
Sex male	5680/10970	52	1692/3263	52
Ethnicity white†	10266/10574	97	2761/3263	85
Maternal smoking in pregnancy	2635/10879	24	460/2865	16
Older siblings, ≥1 sibling			1837/2798	66
Crowding, >1 person/room	2285/9406	24	1150/2852	40
Pet ownership	5475/9805	56	1226/2903	42
Wheeze at 2 years				
Current wheeze	2261/9953	23	533/2355	23
of which‡: EVW	752/1680	45	229/524	44
MTV	928/1680	55	295/524	56
Wheeze at 4 years				
Current wheeze	1780/9391	19	504/2609	19
of which‡: EVW	519/1423	36	158/498	32
MTV	904/1423	64	340/498	68
Wheeze at 6 years				
Current wheeze	1129/8393	13	330/2077	16
of which‡: EVW	236/779	30	79/325	24
MTV	543/779	70	246/325	76

Abbreviations: ALSPAC Avon Longitudinal Study on Parents and Children, LRC Leicestershire Respiratory Cohort 1998-b, EVW episodic viral wheeze, MTW multiple trigger wheeze
*n/N = number of children with positive characteristic/total number of children

† In ALSPAC the remaining children are ethnically diverse while in Leicester 98-b the remaining children are of south Asian origin.
‡ Denominator represents children with current wheeze that can be classified into EVW or MTV. Excludes children with non-classifiable wheeze (Table 1) and thus does not equal the number with any current wheeze.

Table 3: Association between wheeze phenotypes and symptom severity in ALSPAC and the LRC at ages 2, 4, and 6 years

	ALSPAC			LRC		
Indicators of symptom severity*	**EVW**	**MTW**	**OR† (95%CI) for MTW vs. EVW**	**EVW**	**MTW**	**OR† (95%CI) for MTW vs. EVW**
Wheeze at age 2 years	**N=752**	**N=928**		**N=229**	**N=295**	
Frequent attacks	39.7	63.6	2.7 (2.2, 3.2)	11.5	45.9	6.5 (4.1, 10.4)
Shortness of breath	43.3	58.2	1.8 (1.5, 2.2)	39.9	76.2	4.8 (3.3, 7.0)
Sleep disturbance	NA	NA	NA	40.4	74.0	4.2 (2.9, 6.1)
Interference with activities	NA	NA	NA	38.0	73.6	4.5 (3.1, 6.6)
Wheeze at age 4 years	**N=519**	**N=904**		**N=158**	**N=340**	
Frequent attacks	45.3	74.0	3.4 (2.7, 4.3)	7.6	40.0	8.1 (4.3, 15.1)
Shortness of breath	50.2	64.1	1.8 (1.4, 2.2)	NA	NA	NA
Sleep disturbance	NA	NA	NA	41.7	71.3	3.5 (2.3, 5.2)
Interference with activities	NA	NA	NA	37.2	74.8	5.0 (3.3, 7.5)
Wheeze at age 6 years	**N=236**	**N=543**		**N=79**	**N=246**	
Frequent attacks	39.6	64.7	2.8 (2.0, 3.8)	5.1	41.1	12.9 (4.6, 36.4)
Shortness of breath	53.0	61.3	1.4 (1.0, 1.9)	NA	NA	NA
Sleep disturbance	52.4	62.4	1.5 (1.1, 2.1)	43.0	67.4	2.7 (1.6, 4.6)
Interference with activities	NA	NA	NA	29.1	78.7	9.0 (5.1, 16.0)
Speech limitation	8.1	13.4	1.8 (1.0, 3.0)	NA	NA	NA

Abbreviations: ALSPAC Avon Longitudinal Study on Parents and Children, LRC Leicestershire Respiratory Cohort 1998-b, EVW episodic viral wheeze, MTW multiple trigger wheeze. The data in the columns EVW and MTW represent prevalence (in %) of severity indicators among children with these

phenotypes. * Definitions of severity indicators are provided in the supplementary Table S1. † From logistic regression excluding children without wheeze or with non-classifiable wheeze

Table 4: Likelihood of keeping or switching the wheeze phenotype with age in children from ALSPAC and the LRC

Age at baseline	Age at follow-up	Phenotype at baseline	EVW at follow-up				MTW at follow-up			
			Crude RRR* (95% CI)	P	Adj. RRR*† (95% CI)	P	Crude RRR* (95% CI)	P	Adj. RRR*† (95% CI)	P
ALSPAC										
2	4	No wheeze	1	0.004	1	<0.001	1	<0.001	1	<0.001
		EVW	9.4 (7.4, 11.9)		4.6 (3.3, 6.4)		7.7 (6.1, 9.7)		3.2 (2.3, 4.3)	
		MTW	5.9 (4.4, 7.8)		2.2 (1.5, 3.3)		20.5 (16.8, 24.8)		6.2 (4.6, 8.4)	
4	6	No wheeze	1	0.002	1	<0.001	1	<0.001	1	<0.001
		EVW	23.1 (16.5, 32.3)		8.0 (4.9, 13.1)		8.7 (6.2, 12.3)		2.0 (1.2, 3.3)	
		MTW	14.1 (9.8, 20.5)		3.3 (1.9, 6.0)		44.9 (35.4, 56.9)		6.7 (4.3, 10.4)	
LRC										
2	4	No wheeze	1	0.868	1	0.564	1	<0.001	1	0.004
		EVW	4.9 (3.0, 8.0)		4.1 (2.2, 7.5)		3.1 (2.0, 4.9)		1.8 (1.0, 3.2)	
		MTW	5.1 (3.0, 8.7)		3.3 (1.4, 7.7)		12.9 (9.1, 18.2)		4.1 (2.1, 7.9)	
4	6	No wheeze	1	0.114	1	0.074	1	<0.001	1	<0.001
		EVW	15.4 (8.1, 29.1)		15.5 (7.3, 32.9)		5.1 (2.8, 9.3)		4.0 (2.0, 8.0)	
		MTW	8.3 (4.2, 16.4)		7.0 (2.6, 18.9)		27.3 (18.9, 39.6)		15.6 (8.3, 29.2)	

Abbreviations: ALSPAC Avon Longitudinal Study on Parents and Children, LRC Leicestershire Respiratory Cohort 1998-b, EVW episodic viral wheeze, MTW multiple trigger wheeze, RRR relative risk ratio

* Results from multinomial regression analysis. As an example for interpreting the RRR assume that among non-wheezers at baseline the risks for EVW and no wheeze at follow-up are 4% and 90% respectively. The risk ratio (RR) for EVW among non-wheezers is thus 0.044. If, in children with EVW at baseline the corresponding risks are 20% and 60%, i.e. RR=0.333, this would translate to a relative risk ratio (RRR) for EVW at follow-up of 7.5 (0.333/0.044). The regression analysis also included children with non-classifiable wheeze in a separate category (see Table 1) but results for this category are not reported.

† Adjusted for symptom severity at baseline (frequent attacks, shortness of breath, sleep disturbance, interference with activities and speech limitation).

‡ P-values of tests for equality of RRRs between EVW and MTW at baseline. Such equality implies absence of tracking. For instance, equality of RRRs for EVW at follow-up means that, after excluding children with MTW at follow-up, those with EVW and MTW at baseline are equally likely to have EVW at follow-up.

Figure legend

Figure 1. Transition probabilities from episodic viral wheeze (EVW) and multiple trigger wheeze (MTW) to EVW, MTW and no wheeze (NW) from 2 to 4 years and from 4 to 6 years in ALSPAC (A) and LRC (B).