



To track or not to track: wheeze phenotypes in preschool children

To the Editor:

We applaud the robust statistical approach used by SPYCHER *et al.* [1] to assess the temporal stability of episodic viral wheeze (EVW) and multitrigger wheeze (MTW) phenotypes in young children. They reported that in two large population-based cohort studies, children who continued to wheeze at 4 and 6 years of age showed a tendency to maintain the same phenotype from the age of 2 years. The authors' conclusion, and that of the accompanying editorial, is that the EVW and MTW phenotypes in young children are stable and track over time [2], and that these phenotypes may represent different disease entities [1, 2]. We would like to call for caution in interpreting these results because they are based on statistical probability, not on clinical differential diagnosis.

The statistical analysis that the authors have used examines whether crossover between phenotypes is due to chance or whether there is any tendency to track. If the phenotype at follow-up had nothing to do with the phenotype at baseline (except for its severity, which was adjusted for because it is known that severe wheeze tends to persist), then phenotype distribution at follow-up would not differ from chance, with each phenotype appearing with a probability equal to its prevalence. The data of SPYCHER *et al.* [1] showed that this was not the case: the odds ratios of remaining in the EVW and MTW phenotypes between the ages of 2 and 4 years were 4.9–9.4 and 12.9–20.5, respectively [1]. Whilst this convincingly shows that the likelihood of phenotype persistence is larger than one would expect based on chance alone, it does not rule out or contradict phenotype switching over time, which has been described previously [3, 4].

First, the authors show that the majority of preschool-aged children with EVW and MTW will not have either EVW or MTW 2 years later as they will have become asymptomatic over time. This is in agreement with earlier population studies [5]. Second, figure 1 in the paper article by SPYCHER *et al.* [1] shows that ~10% of the 2-year-olds with MTW cross over to EVW and ~20% of the 2-year-olds with EVW cross over to MTW by the age of 4 years. These crossover proportions are lower than those in our original publication on the topic in 2010, in which we followed up preschool children treated in hospital-based paediatric practice with inhaled corticosteroids (ICS) for 1 year [3]. It appears, therefore, that phenotype changes in preschool children with recurrent wheeze do occur, and that such changes are more common in children treated with ICS for wheezing in primary and secondary care [3, 4] than they are at general population level [1].

Although the results of SPYCHER *et al.* [1] suggest that the pathophysiology of EVW and MTW may differ [1], we believe their findings should not yet lead to a different approach in the treatment of preschool wheeze. There is consensus among clinicians and researchers that the severity and frequency of wheeze symptoms determine the need for daily controller therapy in preschool children with recurrent wheezing [6]. There is convincing evidence from a large number of valid randomised controlled trials that ICS reduce the frequency and severity of wheeze episodes in preschool children with recurrent wheeze, independent of wheeze phenotype [7]. Adherence to ICS is the single most important determinant of asthma control in preschool children with recurrent wheeze [8]. By contrast, montelukast has not been shown to be effective in reducing wheeze episodes in preschool children with recurrent wheezing [9].

The relatively high remission rate in preschool children with EVW in the general population cohort of SPYCHER *et al.* [1] should not lead to therapeutic nihilism in patients with this condition. The likelihood of long-term remission is considerably lower in patients referred to hospital-based paediatric practice because of more severe symptoms [10]. These patients do have troublesome symptomatic wheezing that responds to daily controller therapy [7, 8].



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Wheeze phenotypes in preschool children are insufficiently stable and valid to base treatment decisions upon <http://ow.ly/HFhd30ivJyq>

Cite this article as: Brand PLP, Schultz A. To track or not to track: wheeze phenotypes in preschool children. *Eur Respir J* 2018; 51: 1800042 [<https://doi.org/10.1183/13993003.00042-2018>].

In conclusion, whilst the landmark study by SPYCHER *et al.* [1] shows a statistical likelihood larger than chance of phenotype persistence in preschool children with recurrent wheezing, a considerable minority of children with a given phenotype at the age of 2 years will switch to another phenotype at the age of 4 years if they remain symptomatic, and the majority will not remain symptomatic. As the accompanying editorial states, the overall prognostic value of the EVW–MTV classification is low [2]. As much as we would love to be able to predict which preschool wheezers become “true asthmatics” by the age of 6 years, the EVW–MTV phenotype distinction does not allow this, and it should therefore not be used as a basis for decisions on long-term daily controller therapy in these patients. The frequency and severity of wheeze symptoms in preschool children should remain the key considerations in the decision to prescribe daily preventer therapy in preschool children with recurrent troublesome wheezing [6], and ICS remain the preferred treatment option in preschool children with wheeze of sufficient severity to warrant such daily controller therapy, irrespective of wheeze phenotype [6, 7].

Paul L.P. Brand^{1,2} and André Schultz^{3,4}

¹Isala Women and Children’s Hospital, Zwolle, the Netherlands. ²UMCG Postgraduate School of Medicine, University Medical Centre and University of Groningen, Groningen, The Netherlands. ³Telethon Kids Institute, University of Western Australia, Perth, Australia. ⁴Dept of Respiratory Medicine, Princess Margaret Hospital for Children, Perth, Australia.

Correspondence: Paul L.P. Brand, Isala Women and Children’s Hospital, PO Box 10400, Zwolle, 8000 GK, the Netherlands. E-mail: p.l.p.brand@isala.nl

Received: Jan 07 2018 | Accepted: Jan 29 2018

Conflict of interest: None declared.

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