# Multi-trigger and viral wheeze: describing symptoms or defining diseases?

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**Multi-trigger and viral wheeze track over time but it is unclear whether they represent separate disease entities** http://ow.ly/El7w30eO9fb

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Preschool wheeze is a highly prevalent clinical problem [1] which, while typically mild, can present within a wide spectrum of severity and is associated with considerable healthcare costs [2]. The natural history is favourable and the majority of preschool wheezers will outgrow their symptoms regardless of any intervention [3–5]. However, a solid evidence base with which to guide clinicians as to which preschool wheezers would benefit from treatment, if any, is lacking.

It has long been recognised that different phenotypes of preschool wheezer can be identified based on, for example, symptom patterns over time [1, 6], type of symptoms [7–9], physiologic measurements (*e.g.* lung function) or risk factors (*e.g.* family history, atopy) [9–11]. Whether any of these phenotypes reflect different disease entities remains controversial. One of the most popular classifications of preschool wheeze emerged from the Tucson cohort, describing the temporal classifications of early transient wheeze, late onset wheeze and persistent wheeze [1]. This categorisation is defined retrospectively, precluding its use in clinical decision making. Other commonly used classifications are those of episodic viral wheeze (EVW) and multiple trigger wheeze (MTW) [8, 12, 13]. EVW is characterised by symptoms exclusively triggered by viral respiratory tract infections, while MTW can also be triggered by other precipitants (*e.g.* allergens, exercise and tobacco smoke). It has been suggested, but not proven, that MTW is an early indication of later allergic asthma and may be more likely to respond to asthma treatment than EVW [14, 15]. In an effort to guide clinicians a European Respiratory Society (ERS) Task Force in 2008 proposed phenotype-driven management in preschool wheezers using a symptom-based classification [15]. These recommendations were based on expert opinion with very low levels of evidence and several reports and an update of the Task Force [16] have questioned the clinical validity of this phenotype-driven approach. For example, Garcia-Marcos *et al.* proposed that any differences between EVW and MTW may merely be a reflection of disease severity [17], while others have pointed out that the limited temporal stability of the phenotypes hampers their usefulness in clinical care [13, 18].

In the current issue of the *European Respiratory Journal*, Spycher *et al.* [19] provide an impressive analysis of the natural history of MTW and EVW in two large independent birth cohorts. With an elegant and convincing statistical approach the authors show that, among children with persistent symptoms,

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phenotypes track over time. This is the first analysis to show that temporal stability remains after adjustment for measures of symptom severity at baseline. Hence, it is unlikely that phenotype tracking can be explained by symptom severity alone. The findings were replicated in an independent birth cohort with similar results, further strengthening the conclusions. This is the largest analysis of the temporal stability of MTW and EVW to date and the reported prevalence of the phenotypes over time actually fits neatly with previous reports with smaller sample sizes [13, 18]. This level of consistency in independent populations of wheezing preschoolers around the world is remarkable. It could indicate that MTW and EVW reflect different diseases entities but does not prove it. A previous review by Spycher *et al.* [20] summarised other factors which could indicate that phenotypes represent different disease entities, namely: 1) association with features not used to define the phenotypes; 2) distinctive risk factors; 3) stability over time; 4) ability to predict future outcomes; and 5) differential responses to treatment.

So, how do MTW and EVW perform with respect to the items listed here? MTW has previously been shown to be associated with lower lung function [14] and higher risk for atopy [7] than EVW but there was considerable overlap between the two groups. The current analysis confirms the stability of phenotypes over time but this is taking into account the fact that the majority outgrew their symptoms over a 2-year interval. Consequently, the actual ability to predict the future outcome of symptom persistence on the basis of the MTW and EVW classification at baseline remains limited. A differential response to treatment may be the most convincing and relevant indication that phenotypes represent different disease entities. If a one-size-fits-all effective treatment for preschool wheezers was available, the search for phenotypes would be clinically irrelevant. Meta-analyses have shown significant but modest effects with inhaled corticosteroids in preschool wheezers. Results indicate that continuous use is effective in MTW while intermittent treatment may be better for EVW [21, 22]. However, a major methodological issue arises in that insufficient studies were done of both phenotypes separately in order to be able to perform a fair comparison. A recent review reported no effect for montelukast in preschool wheeze [23] and the authors speculated that there may be a "montelukast-responding phenotype" while suggesting that ways to identify this in the clinical setting should be sought. The present study by Spycher *et al.* [19] replicating and validating the temporal stability of MTW and EVW phenotypes is an important step towards achieving this. The question still remains, however, as to whether these phenotypes are truly the best reflection of the actual underlying disease entities.

So, what does this study mean for clinicians faced with preschool wheezers today? Previous publications have reported that a minority of children with a given phenotype still had the same phenotype at follow-up [13, 18], thereby questioning their clinical relevance. Spycher *et al.* [19] show evidence of tracking phenotypes among children that remain symptomatic but confirm that a large proportion become asymptomatic. About half of all MTW and over two-thirds of all EVW cases outgrew their symptoms during each 2-year interval. For clinicians this will have a major impact on any management decision and there is no way of knowing in which child symptoms will persist. As such, MTW and EVW are not yet suitable for decision making in clinical care and the search for symptoms and biomarkers to improve phenotyping needs to continue. In this respect, the availability of new high-throughput technologies such as genomics, proteomics and metabolomics are promising [24]. However, it remains to be seen whether this approach will facilitate the identification of better and clinically relevant phenotypes. In the meantime clinicians will have to accept that available classifications are not perfect and, while MTW and EVW track and may to some extent describe different disease entities, their overall prognostic value is low. Including more prognostic descriptors complicates interpretation but it can improve prediction [5, 25] and, as suggested in a recent ERS Task Force update, it seems reasonable to at least include severity of symptoms as an important factor in the assessment of any preschool wheezer [16]. With present knowledge, treatment with moderately effective drugs that may have side effects should still depend on the actual burden of symptoms on child and family. Based on the limited available evidence, oral steroids should not be used in the outpatient setting [26]. However, initiation of inhaled steroids or leukotriene receptor antagonists can be considered using a trial and error approach with appropriate follow-up [22, 27, 28]. It should be noted that observed improvements cannot simply be attributed to the effects of treatment but need to be considered in the context of seasonal variations and overall favourable natural history. Furthermore, the concept of N-of-1 trials may be a pragmatic way of achieving optimal evidence-based individualised treatments in this diagnostically challenging age group [29].

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