EuroPrevall: insights into the allergic disease epidemic

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'Asthma' is now recognised as an umbrella term that includes a heterogeneous group of phenotypes whose aetiology and prognosis vary. This heterogeneity is even more significant in asthma diagnosed before 5 years, using the symptom of wheeze as the predominant criterion, even though not all wheeze is asthma. Therefore, wheezing, which is common in preschool children, is often incorrectly labelled as asthma. Two pragmatic clinical phenotypes[1] with distinct risk factors[2 3] have been used to describe early life wheeze and assist in determining asthma in early childhood: episodic viral wheeze (EVW) and multitrigger wheeze (MTW). Prognosis is good in recurrent mild EVW although remission is uncommon in atopic MTW and children usually go on to develop asthma. Care should be taken when using these categories, as individual children can change category over time.[1] Cohort studies have also described phenotypes of early childhood wheeze by using changing 'asthma' symptoms with age and determining distinct patterns in underlying groups (using latent class analysis and latent class growth analysis). These include investigations on cohorts using either symptoms of wheeze (the Melbourne Atopy Cohort Study (MACS),[4 5] the Avon Longitudinal Study of Parents and Children (ALSPAC),[6] the Prevention and Incidence of Asthma and Mite Allergy (PIAMA)[7] (Columbia Center for Children's Environmental Health)[8]) or symptoms of wheeze and cough (the Leicestershire cohort[9]). The aetiology and prognosis of each of these phenotypes have been found to vary significantly with many early life factors including gender, atopy, eczema, parental allergic disease, breast feeding, exposure to tobacco smoke, siblings, exposure to pets, day care attendance, respiratory tract infections and body mass index. Risk factors associated with each phenotype, however, show similar findings across all these analyses independent of populations studied and specific statistical methods, adding to the robustness of the paradigm of wheeze phenotypes in early life.

Despite increasing interest in clarifying the aetiology and prognosis of early wheeze, there have been no multicentre international studies of early life wheeze unlike the large-scale global studies conducted for childhood asthma[10] and young adult asthma,[11] which have led to multiple insights about the aetiology and prognosis of this condition. Selby *et al*'s study published in *Thorax* fills this important gap.[12] Although their wheeze measure used does not differentiate any of the early childhood asthma/wheeze phenotypes described to date, their findings on the substantial variation in wheeze prevalence across a number of countries and differential patterns of risk factors provide valuable insights and will inform future research.

Between 2005 and 2009, more than 12 000 neonates in nine European sites (Iceland, UK, Netherlands, Germany, Poland, Vilnius, Madrid, Milan, Athens) were recruited into the European Union-funded EuroPrevall birth cohort study. Its primary aim was to 'establish and compare the prevalence of confirmed allergic reactions to food.'[13] Secondary aims were to investigate possible determinants of food allergies. As a result, comprehensive data on many risk factors for common childhood allergic diseases were collected in early life for a large, population-based sample. These extensive data have now enabled the current study on early life wheeze prevalence and associated risk factors. The major strength of this work is the large sample size and volume of prospectively collected data from multiple sites representative of many areas in Europe using consistent and validated methodology.

From the 12 049 infants recruited at birth, 8805 contributed to the current analysis. A huge variation was found in wheeze prevalence in the second year of life ranging from <2% (Lodz and Vilnius) to 17% (Reykjavik). Early life wheeze identified in the EuroPrevall cohort will be a mixture of early transient wheeze, early persistent wheeze and to a less extent the highly atopic intermediate-onset wheeze phenotypes, as identified by the latent class analyses of PIAMA, ALSPAC and MACS. Prior literature suggests that the risk factor profiles for these three early life wheeze phenotypes (early transient, persistent and intermediate onset) include an increased risk in the presence of lower respiratory tract infection, sensitisation, maternal history of asthma, smoking during pregnancy, male gender and child care, and decreased risk for breast feeding.[5 14] Similarly, when EuroPrevall pooled the data for all centres, they found that lower respiratory tract infections, day care attendance and postnatal smoke exposure increased the risk of early childhood wheeze. However, they found no relationship to breast feeding, food allergy or other previously identified exposures, which is perhaps surprising. This unexpected finding may be related to a number of factors. One reason could be the lack of clarity around different phenotypes of early life wheeze. As children in the highly atopic intermediate-onset wheeze phenotype had wheezing symptoms starting from around 18 months to 2 years, this phenotype may have been missed or under-represented in the EuroPrevall analyses which investigated wheeze in the second year of life, and consequently may be responsible for the lack of association found between food allergy and wheeze in this analysis. Additionally, we previously found that breast feeding was a protective factor only for the early transient wheeze phenotype.[5] Lack of delineation of early transient wheeze from other wheeze phenotypes (intermediate-onset or early persistent wheeze) in the EuroPrevall analysis may have influenced the ability to find this association. Another reason Selby *et al*'s analysis did not find more previously identified associations could be their approach to model construction, which was more predictive modelling in nature without consideration of potential causal pathways when variables are included in the models, which may lead to underestimates of associations.[12] For example, a model including both breast feeding and any potential mediators that lie in the causal pathway between breast feeding and wheeze may mask the association. A further reason for lack of relationship found for common risk factors could be that the relationships may differ between sites. Estimates of associations between exposures and wheeze were

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pooled across centres when there is clear evidence of a protective effect or risk effect for some centres and not in others (table S6 in Selby *et al*[12]).

Selby *et al* provide a snapshot of the differences in early life wheeze prevalence across Europe. As mentioned, phenotyping early life wheeze is important because of the differing long-term prognoses and associated risk factors which likely reflect different causal mechanisms requiring differing prevention and treatment approaches.[12] The holy grail of childhood wheeze is to be able to easily identify wheezing infants who will go on to have asthma from those who will have a benign resolution of their wheeze. As only approximately 30% of all early life wheeze persists as asthma in later childhood, this diagnostic dilemma influences treatment decisions; adequate treatment of a potentially lifelong illness versus inappropriate treatment of a benign transient condition. If the differential prevalences of early childhood wheeze between countries are similar to the same country-specific prevalences of asthma in later childhood, then the aetiological factors driving wheeze are likely to be similar to those related to asthma. It also suggests that the risk factors for the varied prevalence of transient and persistent wheeze are site specific. Although the general pattern of early life wheeze prevalence between different countries appears similar to the pattern of asthma prevalence in later childhood, it is important to understand whether the conversion rate between early wheeze and later asthma is the same for all countries/sites, which future follow-ups of EuroPrevall population will be able to determine. If differences are found, determining the site-specific influences related to increased or decreased risk of asthma in early life wheezers may provide aetiological clues for asthma development and avenues of prevention.

Globally, we are experiencing an allergic disease epidemic. Monitoring the rates of allergic disease, including wheeze and asthma, is a vital first step for establishing prevalence trajectories, and for untangling the factors responsible for initiating and maintaining this epidemic. The EuroPrevall cohort has unique data in early life on many environmental and familial exposures, which may influence the risk of common childhood allergic diseases. The present study documents prevalence of early life wheeze in children for individual countries and pooled across all sites. Their pooled analysis also provides evidence on risk factors that may be important for all the sites. However, where the real power of such studies lies is in their potential ability to explain the large differences in prevalence between the varied geographical sites. These differences may elucidate aetiological determinants and ultimately preventive strategies to reduce the epidemic of allergic disease.

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