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EDITORIAL

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The hope in redefining atopy

This editorial discusses the findings of the paper in this issue by F. L. Garden et al. [1], pp. 633–641.

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There is increasing interest in refining allergic phenotypes including asthma. This is driven by the belief that the reason for inconsistent evidence on the aetiology of these conditions is related to lack of clarity in outcome definitions. The study by Garden et al. [1] published in this issue of the Journal is another important step in this process.

The epidemic of allergies and asthma in westernized countries over recent decades has been well documented. The rapid increase in the prevalence of these conditions implies that environmental factors are important. However, it has proven remarkably difficult to identify environmental risk factors that are consistently related to increased risk of allergic disease.

This begs the question 'if environmental risk factors are important in the aetiology of asthma and allergic disease, why has it proven so difficult to identify consistent associations between these conditions and modifiable risk factors?' Identification of such associations is important, to both to understand the aetiology of these conditions, as well as to help lead to effective preventive strategies, which is currently sadly lacking. One of the possible reasons that we are not seeing any clear aetiological risk factors for allergic disease is that we are not defining the outcome(s) with sufficient acuity.

There has been increasing recognition that what is labelled as 'asthma' is really a symptom that has multiple aetiologies [2]. This has lead to calls to better group asthma into specific 'phenotypes', based on a range of presenting features. If each phenotype has different underlying patho-physiological processes, it is likely that they also have different underlying risk factors. By grouping multiple types of 'asthmas' together, we may be making it impossible to see clear risk factor profiles as the risk factors for each phenotype are distinct. If such a situation is correct, the risk factors that are identified will be those that are most strongly related to the most common 'asthma' or to a number of different 'asthmas'. Research that generates specific 'asthma' phenotypes offers the possibility that specific risk factors for each phenotype can be identified and lead to potential preventative strategies that target these specific phenotypes.

There is already evidence that specific phenotyping of asthma can advance the knowledge in this area. A number of attempts have been made to define wheeze according to age of onset and persistence of wheeze, following on from the seminal work based on the Tucson cohort [3]. The risk factors for these wheeze phenotypes seem to be distinct from each other, at least in terms of some genetic polymorphisms [4], even if not for a range of other potential factors [5]. Some groups have proposed separating childhood asthma into multi-trigger vs. virus induced wheeze [6]. We have shown that aetiology of childhood asthma associated with hayfever seems to differ from childhood asthma that is not associated with hayfever [7]. Similarly, the risk factors for adult atopic asthma seem to differ from that of non-atopic asthma [8].

Recently there has been a move to use data driven (a-theoretical) means of identifying clusters of wheeze outcomes. The benefit of such techniques is that it allows for the natural clustering within the data to be identified, without any preconceptions as to what groups 'should be' there. One of the leading forms of these has been latent class analysis (LCA), which may be used where the observed data are consistent with there being a small number of underlying, or latent, classes of the outcome at the population level. LCA has lead to the identification of new wheeze groups including 'intermediate onset wheeze' [9].

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Following along the lines of better phenotyping asthma, there have been moves made to better phenotype atopy. Atopy, or evidence of production of IgE to specific environmental allergens, as measured by either skin prick test (SPT) or RAST, is one of the most unifying features of allergic disease in early life. Atopy has been shown to predict the development of new allergic disease [10], and children with clinical allergic disease have higher rates of atopy than children without. As atopy is possibly a 'cleaner' outcome of 'allergy' than asthma or wheeze, it has the potential to allow clear and distinct phenotypes to be identified.

Historically, there have been a number of different ways of classifying atopy phenotypes. As with asthma, classifications have traditionally been coarse and theory based, with many studies still using any vs. no sensitisation, while others have divided sensitisation into food vs. inhalant, or perennial (e.g. house dust mite) vs. seasonal (pollen). We have also examined the associations with early life mono vs. poly sensitisation [11]. Like early life wheeze, atopy is complex. There is heterogeneity in terms of the age that children develop atopy, the allergens to which they are sensitized, and when and if their atopy goes into remission. This variability makes it difficult to group children into sensible categories that describe the observed atopy patterns.

Only recently has there been a move to apply clustering techniques to describe the pattern of atopy in children over time. Simpson et al. [12] applied a hidden Markov model to data from the Manchester Asthma and Allergy Study (MAAS) to identify five distinct atopy classes based on measures of sensitisation at ages 1, 3, 5, and 8 years. These authors found that the majority of children had no tendency towards atopy, with the remaining children having the following atopy phenotypes; 10.6% 'multiple early', 16.2% 'multiple late', 4.5% 'dust mite', and 9.5% 'non-dust mite'.

In this issue, Garden et al. use data from the Childhood Asthma Prevention Study (CAPS) to identify distinct atopy phenotypes [1]. In a cohort of children from Sydney, Australia, with a family history of allergic disease, skin prick tests were performed at 1.5, 3, 5, and 8 years to 10 food and inhalant allergens. Using a LCA, they identified four distinct atopy classes. Again, most children did not develop atopy (68%), while three distinct atopic groups were identified; 11% had 'late mixed inhalant sensitisation', 4% had 'mixed food and inhalant sensitisation, and 17% were 'HDM mono-sensitized'.

Garden et al. [1] achieved these results by fitting a latent class model to each child's pattern of SPT responses (up to 40 tests per child). In this instance, a latent class is represented by a series of time-specific probabilities of positive SPT. The observed data can be used to determine: (1) the number of atopy classes; (2) the proportion of the population in a particular atopy class; (3) the time-specific probabilities for a positive SPT for each class; and (4) how likely it is that a given participant belongs to a given atopy class based on their SPT data. Additional latent classes were added until a range of goodness-of-fit statistics indicated that further increasing the number of latent classes would not improve the fit of the model to the data. Associations between the observed atopy classes and early life risk factors, as well as asthma and allergic disease outcomes at age 8 were also reported.

The overall picture of results reported by Garden et al. [1] is similar to that of Simpson et al. [12], with some notable exceptions: (1) In both studies, mixed food and inhalant sensitisation was associated with the greatest risk of allergic disease and impaired lung function, but (2) there was no 'non-dust mite' group identified in the analysis of the CAPS, and the prevalence of mono-sensitisation to house dust mite was also much higher in the CAPS. It seems likely that the differences been the studies are due to population differences (MAAS is population based while CAPS is a high risk cohort) and geographic differences (levels of dust mite allergen in the Sydney based CAPS study are much higher).

The study by Garden et al. [1] has a number of important strengths and limitations. Garden et al. attempted to determine if the identified atopy classes have distinct risk factor profiles. Whilst this analysis is both novel and important, it had limited power, and no clearly distinct risk factors were identified for the different atopy phenotypes. This may mean that (1) there are no distinct risk factors; (2) there was insufficient statistical power to detect such distinct risk factor profiles; or (3) that Garden et al. simply did not looking at the 'right risk factors' in this analysis. Only a limited number of 'generic risk factors' were assessed, and exploration of more specific risk factors, may yet provide greater insights. Whilst the use of the data driven LCA approach, which 'allows the data to speak for itself', is a strength, it is also a data limited approach. Such clustering algorithms can only identify classes based on the frequency and the timing that the data was collected. Repeated skin prick testing to multiple relevant allergens is admirable, but by performing skin prick testing at 1.5 years for the first time, the authors may have missed a group of children with transient early food sensitisation.

In conclusion, better phenotyping of allergic disease and atopy outcomes is one of the key mechanisms by which allergic disease epidemiology may be able to move forward to identify clear and distinct risk factors, which may in turn inform preventive strategies. There has been numerous advances using this approach in asthma epidemiology, and we are only now starting to adopt such approaches when defining different sub-

groups, or phenotypes, of early life atopy. It would appear that larger studies, or analysis of combined studies, examining atopy specific risk factors will be needed to identify those exposures that may cause the induction of atopy. Furthermore, the utility of these atopy phenotypes in predicting future (rather than concurrent) allergic disease symptoms and lung function development remains to be established. The research in this area offers much hope, and future follow-ups of CAPS and similar studies will help to elucidate how much of this hope will be realized.

Conflicts of interest: All authors declare no conflicts of interest.

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