

How Sex and Age of Asthma Onset Influence Difficult Asthma Heterogeneity



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Heterogeneity is a fundamental feature of asthma, with the scope of these variabilities becoming far more detailed and insightful, including contributions to the long-term consequences of disease. Included in our appreciation of asthma heterogeneity is the influence of sex and age of disease onset. At present, however, there is limited information and understanding as to how these 2 factors may collectively, and interactively, contribute to the “final” expression of difficult asthma in adults. Difficult asthma, or difficult-to-manage asthma, includes patients with “problematic” disease despite high-dose inhaled corticosteroid treatment, as well as remedial traits that contribute to treatment difficulties, for example, poor medication adherence, comorbidities, and environmental elements, including allergen and smoking exposure. In this issue, Azim et al¹ used a novel approach with a well-designed and informative questionnaire of patients being evaluated for difficult asthma to gain further insights into the phenotypic differences in the eventual expression of difficult asthma depending on the (1) age of asthma onset: early-onset versus adult-onset and (2) the patient’s sex: female versus male.

Data from 501 adult subjects with difficult asthma and a mean age of 50.6 years form the analyses by Azim et al.¹ The study subjects were invited to participate in the Wessex AsThma CoHort (WATCH) difficult asthma clinical cohort and, in so doing, completed an extensive questionnaire on their health and asthma-related histories at enrollment.² From these data, the investigators determined the influence of early-onset asthma, less than age 18 years, versus adult-onset asthma, age 18 years or older, as well as sex, males versus females, on phenotypic characteristics of difficult asthma. However, before highlighting key findings from their study, it is instructive to comment on the

“real-life” approach followed by the investigators to gather these data.

The National Institute for Health Research, Southampton Biomedical Research Center, developed a centralized asthma care strategy for patients with difficult asthma. Care for these UK patients takes place at regional centers to ensure that adult patients with difficult asthma “receive the same high-quality standard of care and that high cost treatments, e.g. biologics, be prescribed in a responsible manner.” Using the recruited WATCH cohort of difficult asthma provided a “real-life” pragmatic population for study and an operational model that combines standard clinical care and, importantly, an opportunity for the acquisition of research data within a single clinic visit.

With the WATCH cohort, the investigators’ primary goal was to determine the influences of the age of asthma onset and the patient’s sex on the phenotypic disease features of difficult asthma. Their analysis strategy focused on 2 binary variables: sex (females vs males) and age of asthma diagnosis (early <18 years vs adult ≥18 years of age). A summary of their findings is illustrated in Figure 3 of their article and details potential influences of the characteristics associated with these binary factors on the eventual expression of difficult asthma. What did they learn about early-onset versus adult-onset asthma and sex, female versus male, in relation to phenotypic features of difficult asthma?

Males with early-onset asthma had an asthma diagnosis at a younger age than females, as well as a higher prevalence of ever smoked, poorer lung function, high atopy, but low fractional exhaled nitric oxide (FENO) values. Clinical characteristics of early-onset asthma in the female group noted a high degree of atopy, high prevalence of obesity, high prevalence of salicylate sensitivity, low FENO, and preserved lung function. In comparison, females with adult-onset asthma had their disease begin earlier than males, were least atopic, had the highest prevalence of obesity, a moderate use of maintenance oral corticosteroid, and well-maintained lung function. These characteristics contrasted with adult-onset asthma in males who were predominantly atopic, with an interesting increase in fungal sensitivities, high FENO, high prevalence of ever smoked, poorer lung function, and the most frequent use of maintenance oral corticosteroids.

Comparing early-onset versus adult-onset asthma in males also noted differentiating features (Table IV of their article), including higher IgE and lower FENO in the early-onset group with similar levels of eosinophils and greater loss of lung function than the adult-onset cohort. These data raise an obvious possibility that a longer duration of disease is associated with greater compromises in lung function, and that the component of type (T)2 inflammation associated with lower lung function includes increased eosinophils and IgE but not FENO. In males with adult-onset asthma and compromised lung function, the

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putative T2 inflammatory pathway centered on increased eosinophils and FENO but not IgE. On comparing the 2 female groups, it was found that early-onset disease is marked by higher IgE levels, which differentiated early- versus adult-onset asthma in the eventual expression of difficult asthma. Interestingly, at least in the 2 female cohorts, lung function was preserved despite increases in 2 T2 biomarkers: FENO and eosinophils. These are associative, not causative, relationships that may provide potential clues to which components of T2 inflammation determine airway remodeling.

How may the data from Azim et al¹ be applied to clinical care of difficult asthma? First, knowing the age of asthma onset provides a probability into eventual characteristics of difficult asthma disease in women versus men and potential preventative pathways for this phenotype. Second, because difficult asthma has comorbidities that affect disease control, it is possible to consider which of these treatable traits aligns by sex and age of asthma onset to select interventions. To illustrate, McDonald et al³ evaluated the effectiveness of targeting treatable traits in severe asthma to improve disease control. They identified domains of treatable traits, including, for example, pulmonary and risk factors/behavior. By targeting treatable domains of an individual patient's disease with specific treatments, disease outcomes improved. Consequently, for males, with either early- or adult-onset asthma, efforts to improve asthma control would focus on pulmonary function. In contrast, females, either early- or adult-onset asthma, had a greater prevalence of functional comorbidities, which might also serve as effective treatable traits. However, it is important to note that overlaps exist between these 4 groups by age of disease onset and sex. Azim et al¹ have provided profiles on these phenotypic characteristics, early-onset versus adult-onset, which, along with sex, may influence disease-relevant features associated with difficult asthma in adults.

The authors note limitations to their findings, which may reflect the methods of assessment—a cross-sectional observation and use of a recall questionnaire. For example, the study team found that smoking had no apparent effect on long-term compromises of lung function. This is distinct from other studies in which smoking had adverse effects on lung function.⁴ However, their data on smoking effects were derived from a “yes or no” answer to “ever smoked” but without quantitation in pack-years. Consequently, we should not necessarily conclude that smoking does not adversely affect lung functions in difficult asthma.

Interestingly, there was also a high prevalence of salicylate sensitivity in females in both early-onset (28.9%) and adult-onset (35.1%) asthma and higher comparative values than males. However, markers of T2 inflammation were not distinct in females in the salicylate sensitivity group except for IgE, which, although not usually considered a distinguishing feature for aspirin-exacerbated respiratory disease, has recently been found as a potentially effective target for treatment of aspirin-exacerbated respiratory disease.⁵ Aspirin challenges were not performed as part of the WATCH registry study to confirm a salicylate sensitivity.

These limitations aside, Azim et al¹ provide expanded insights into phenotypic characteristics of adults with difficult asthma when evaluated in relationship to sex and age of disease onset. Their data further highlight and underscore the complexities of asthma heterogeneity. They also provide a strategic blueprint to gather key disease-related data at a single visit and from this information, further explore difficult asthma heterogeneity from a real-world perspective and assessment. The authors did not determine underlying mechanisms to explain these binary distinctions but rather identified traits of interest and end points to be probed to establish endotypes in difficult asthma. As clinicians face decisions on “next step” treatments for patients with difficult asthma, the authors provide guidance, and an instrument, as steps toward a more detailed and precise assessment of existing disease to direct more effective therapeutic approaches. Heterogeneity is the backbone of the many “asthmas,” and as these variables are identified in the context of the existing clinical disease, greater clarity and effective treatment will follow.

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