# Asthma: Closing in on the Biology of a Complex Life-course Disease

The term asthma (or strictly "ἄσθμα") was first used to describe a constellation of respiratory symptoms in the fourth century B.C. Long before we had any knowledge of the complexities underlying the pathophysiology of the disease, there were compellingly accurate descriptions of the symptom complex, namely wheeze, chest tightness, and breathlessness, sometimes with excessive cough. In the 20th century, there was a notable divergence between the guidelines industry, which favored a one size fits all approach, and investigators who realized personalized medicine was essential. Indeed, the one size fits all approach nearly cost us inhaled corticosteroids (ICS), oral corticosteroids, and the anti-IL5 monoclonal antibody mepolizumab as treatments for asthma (reviewed in [1]). Although so many people with asthma respond dramatically to low-dose ICS, for the many others who do not, paying careful attention to personalizing medicine is essential.

The airway disease in which the greatest recent advances have been made is, without a doubt, cystic fibrosis, in which transformative medications are becoming available for more than 90% of adults and which are increasingly being licensed in babies and young children (2). These gene class-specific therapies have been developed only because the fundamental molecular biology of the cystic fibrosis transmembrane regulator gene has been unraveled. Although many effective biological treatments have been made available for severe asthma (3), there are still many gaps in knowledge, including how to select among several different treatments available for asthma characterized by type 2 inflammation, the lack of good biomarkers of response in children, and how best to treat non-type 2 disease.

This issue of the *Journal* is focused on understanding some of the complex biology of asthma across the life course. The roots of asthma are preconception, and indeed even before the conception of the parents of the child (4). One big gap is our inability to predict which apparently normal babies will go on to develop asthma and what steps to take for secondary and even primary prevention. Early-life risk factors are important determinants of lifetime respiratory and all-cause morbidity and mortality. However, lung function trajectories may not be as rigidly set as we thought, as reported here by the BAMSE investigators (pp. 406–415), encouraging us that there must be potential treatments to reverse lifelong low trajectories. Early acute wheeze attacks, combined with early multiple aeroallergen sensitization and tobacco exposure, are strong predictors of progression to school-age atopic asthma (5). Fayon and colleagues (pp. 416–426) have, for the first time, related wheeze attacks to early structural airway wall changes, validating their findings in a second cohort. A better understanding of the cellular and molecular pathways of remodeling may also lead to new therapies to prevent disease progression.

Airway infection is also coming to the fore in asthma. Although it was once considered heresy to treat asthma with antibiotics, there is now a suggestion that perhaps some endotypes may be infection-driven. After all, who would have thought that a duodenal ulcer was curable with antibiotics? Son and colleagues (pp. 427–437) detected autoantibodies to antimacrophage receptor collagenous structure (MARCO) and correlated this local immune deficiency with reduced bacterial uptake by macrophages *in vitro* and a greater risk of infection-driven asthma attacks *in vivo*. CC16 is a host defense protein that is secreted by nonciliated epithelium and has been reported to be reduced in the airways of severe asthmatics. In a study by Li and colleagues (pp. 438–451), lower expression was associated with type 2 inflammation, another potential asthma–infection link.

There is also a major focus on airway smooth muscle in this issue. Airway smooth muscle is far more than just a series of elastic bands around the airway; it is the source of numerous key mediators of inflammation and remodeling. However, remodeling is not a single process but is heterogeneous along the airway and between individuals, a striking and as-yet unexplained finding which may contribute to some of the variability in the disease, as discussed by James and colleagues (pp. 452–460). There is ample evidence that obese asthma is not lean asthma surrounded by layers of fat. Yon and colleagues (pp. 461–474) studied T-helper cells from obese children and showed they had an uninhibited chemotactic phenotype and were more adherent to obese airway smooth muscle cells. This was associated with the upregulation of genes and increased expression of proteins associated with smooth muscle proliferation and, conversely, with nonatopic T-helper cell activation.

Next, to paraphrase Rudyard Kipling, "What do they know of asthma, who only airways know?" Asthma is a systemic disease with serious implications way beyond the airway (6). One of the major recent advances in the field has been the coming together of big groups of researchers, such as severe asthma research program (SARP) and unbiased biomarkers for the prediction of respiratory disease outcomes (U-BIOPRED), to probe the mechanisms of severe asthma. Here, the SARP group (pp. 475–484) shows that skeletal muscle adiposity and lung function decline are closely correlated, supporting a role for metabolic dysfunction in progressive loss of lung function. Far from the maddening laboratory is a letter by Feldman and colleagues (pp. 487–490) focusing on a very practical aspect of asthma treatment. If you do not perceive you are breathless, you will not take treatment. This is particularly relevant as the momentum for the use of as-needed combined inhalers builds. Here, we publish a pilot randomized controlled trial of a feedback intervention that improved symptom perception in adult asthmatics. Hopefully, this will be followed by a definitive trial, which the *Journal* would certainly like to see.



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Finally, a Pulmonary Perspective by Krings and colleagues (pp. 390–405) tackles one aspect of the vexing problem of asthma exacerbations (or, better, asthma lung attacks [7, 8]). It has long been known that overuse of short-acting β-2 agonists and underuse of ICS are factors in asthma deaths (9). There is a veritable tsunami of studies (10) showing that outcomes are better if instead of short-acting β-2 agonists, a combination of long-acting β-2 agonists and ICS (Symbicort) is used for reliever therapy, and this approach is recommended by global initiative for asthma (GINA) (11). The authors suggest that it is time for the United States to wake up to this evidence and stop using albuterol as rescue therapy. They also suggest that it is time a nonevidenced-based, dangerous treatment (Primatene MIST and aerosolized epinephrine) that is available over-the-counter is replaced by something for which there is overwhelming safety and efficacy data, namely over-the-counter budesonide–formoterol for acute relief of asthma symptoms. A challenge from the *Journal*: An American female legend, Dr. Frances Oldham Kelsey, decisively intervened to protect America from the ravages of thalidomide, rightly ignoring (largely male-led) protests (12); who is the 2023 Frances Oldham Kelsey who will help to protect the United States against asthma deaths?

We would like to thank the authors of these manuscripts and the corresponding editorialists for sending their excellent work to us, and we encourage them and others to send us asthma manuscripts in the future. This issue merely scratches the surface of a complex disease, and if your pet interest does not appear, this is because of space, not lack of interest. We want the best manuscripts on all aspects of asthma. Please keep them coming! ■

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## References

1. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, *et al.* After asthma: redefining airways diseases. *Lancet* 2018;391: 350–400.
2. De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. *Lancet Respir Med* 2016;4:662–674.
3. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, *et al.* Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2020;55: 1900588.
4. Bush A. Impact of early life exposures on respiratory disease. *Paediatr Respir Rev* 2021;40:24–32.
5. Belgrave DCM, Granell R, Turner SW, Curtin JA, Buchan IE, Le Souëf PN, *et al.* Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *Lancet Respir Med* 2018;6: 526–534.
6. Cheng Y-J, Chen Z-G, Yao F-J, Liu L-J, Zhang M, Wu SH. Airflow obstruction, impaired lung function and risk of sudden cardiac death: a prospective cohort study. *Thorax* 2022;77: 652–662.
7. FitzGerald JM. Targeting lung attacks. *Thorax* 2011;66:365–366.
8. Bush A, Pavord I. Following Nero: fiddle while Rome burns, or is there a better way? *Thorax* 2011;66:367.
9. Buelo A, McLean S, Julious S, Flores-Kim J, Bush A, Henderson J, *et al.* At-risk children with asthma (ARC): a systematic review. *Thorax* 2018; 73:813–824.
10. Hatter L, Bruce P, Braithwaite I, Holliday M, Fingleton J, Weatherall M, *et al.* ICS-formoterol reliever versus ICS and short-acting $\beta_2$-agonist reliever in asthma: a systematic review and meta-analysis. *ERJ Open Res* 2021;7:00701-2020.
11. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, *et al.* Global Initiative for Asthma strategy 2021: executive summary and rationale for key changes. *Eur Respir J* 2021;59: 2102730.
12. McFAdden RD. Frances Oldham Kelsey, who saved U.S. babies from thalidomide, dies at 101. *New York Times*; 2015 [accessed 2022 Nov 30]. Available from: https://www.nytimes.com/2015/08/08/science/frances-oldham-kelsey-fda-doctor-who-exposed-danger-of-thalidomide-dies-at-101.html.