Update in paediatric asthma

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Purpose of review
The field of paediatric asthma is rapidly moving, with the advent of new biologicals for severe asthma and increased understanding of preschool wheeze amongst other developments and insights.

Recent findings
There is increasing evidence of efficacy in children for biologics directed against Type 2 inflammation (especially mepolizumab and dupilumab) as well encouraging evidence that Tezepelumab may be effective against Type 2 low phenotypes. The importance of airway remodelling and infection in the pathophysiology of preschool wheeze is increasingly appreciated. The treatment of preschool wheeze is moving from symptom-based to biomarker driven therapies. Other important areas are prediction of risk of asthma attacks, the SMART regime, the importance of climate change and reducing greenhouse gas emissions from inhalers while ensuring adequate therapy for young children, the association of early adverse environmental factors including childhood poverty and deprivation and the switch to race-neutral lung function equations.

Summary
We are increasingly moving towards personalized medicine and the use of biomarkers to guide treatment of wheeze at all ages, but we need to move from counting cells to determining their functional status. Airway wall structural changes rather than inflammation may drive the progression of preschool wheeze to school age asthma

Keywords
airway inflammation, airway remodelling, climate change, eosinophil, preschool wheeze

INTRODUCTION

Asthma is defined here as wheeze, chest tightness, breathlessness and sometimes abnormal cough. There are no assumptions about pathology, and to determine the type of asthma present, the airway is deconstructed into components of fixed and variable airflow obstruction, inflammation and infection to determine especially what treatable traits are present, and to define treatment success [1]. This manuscript therefore covers wheezing from 1 to 18 years. A literature search was performed using the terms <asthma> OR <wheeze> limited to humans, children and English language over the past 12 months. 1751 hits were scrutinized, and the text is based on a personal selection from this search, references from my personal archive and additional references from the bibliographies of the selected manuscripts. The two main advances covered are the biologicals in severe paediatric asthma, and the new insights into preschool wheeze management. Other areas briefly highlighted include prediction of risk of an asthma attack, the SMART regime, the implications of climate change and childhood deprivation, and the move to race-neutral spirometric normal ranges.

MONOCLONAL ANTIBODIES IN PAEDIATRIC SEVERE ASTHMA

In the UK, the licensed monoclonals are Omalizumab [binds circulating immunoglobulin E (IgE)], Mepolizumab [binds circulating interleukin (IL)-5], Benralizumab (blocks the IL-5 receptor), Dupilumab (blocks the IL-4/IL-13 receptor α-subunit), all licensed in children aged six years and over) and Tezepelumab (binds circulating TSLP, licensed age

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KEY POINTS

- There is an increasing armamentarium of biologics with an evidence base of efficacy in children, but it is essential to get the basics right before using them, because they are expensive and invasive
- We are moving from symptom-based management of preschool wheeze to biomarker based, personalized medicine, albeit needing more data
- There is increasing evidence of the importance of infection and airway remodelling being at least as important as inflammatory parameters in the pathophysiology of preschool wheeze
- It is becoming increasingly clear that phenotyping based on cell numbers (neutrophils, eosinophils) needs to be replaced by more sophisticated measures of cell function; not all neutrophils are equal, for example
- Management of asthma is more than pharmacotherapy, and there is accumulating evidence of the adverse effects of poverty and deprivation on asthma prevalence and outcomes

12 years and over) [2▪]. Omalizumab is a well established treatment [3] and is not considered further in this update.

Research has been shamed by the progress made in cystic fibrosis with highly effective modulator therapy, in which a series of focused trials in ever younger children has led to a solid evidence base even in infants [4,5]. Mepolizumab, the second biologic to be licensed in children, was initially licensed in children age twelve years and over on the basis of only 34 children age 12–17 years in an otherwise adult study [2▪]! A further difficulty has been the use of adult blood eosinophil counts to determine eligibility for treatment, despite the fact that normal paediatric levels are substantially higher than in adults [6].

The first big randomized, placebo-controlled, year-long trial of mepolizumab was MUPPITS-2 [7]. In this well constructed study, socioeconomically disadvantaged children and adolescents aged 6–17 years, had had $\geq$2 asthma attacks in the preceding year and a peripheral blood eosinophil count $>$150 cells/$\mu\lambda$ were randomly assigned to placebo ($n = 144$) or mepolizumab ($n = 146$). This blood eosinophil count is in many cases *below* the midpoint of the age-corrected normal range. The primary endpoint was corticosteroid (OCS)-treated asthma attacks. Although there was a statistically significant reduction in attacks with mepolizumab, the results were far less dramatic than in, for example the DREAM study [8,9], despite a big reduction in blood and sputum eosinophils. Also, significant numbers of patients continued to experience attacks despite treatment with mepolizumab. It is possible that this was related to the effect of airborne pollutants on attacks via noneosinophilic mechanisms in this deprived group. However, it should be noted there are developmental changes in the pathology of severe asthma, with bronchoalveolar lavage IL-5 being lower in younger children, thus making mepolizumab a less attractive treatment.

Importantly, the investigators then went on to challenge the paradigm that a simple eosinophil count is adequate to drive treatment decisions [10▪▪]. They obtained sputum from 53 MUPPITS-2 participants and grouped airway eosinophils into subsets by mass cytometry and unsupervised clustering analyses of 38 markers. They defined three eosinophil subsets with varied CD621 expression. As a group, the mepolizumab treated patients had lower sputum eosinophils, but $CD62L^{int}$ and $CD62L^{hi}$ eosinophils were higher in those who continued to have attacks. These eosinophils had significantly higher activation marker and eosinophil peroxidase expression. This suggests we need to move beyond the concept that all eosinophils are equal and that we need to look beyond the IL-5 pathway in at least some children with attack prone, eosinophilic asthma, and be more selective in choosing which monoclonal for an individual patient.

Dupilumab was initially used in children with severe eczema [11], but the efficacy in paediatric asthma was established by the year-long, randomized, placebo-controlled VOYAGE study [12], and the open-label extension, EXCURSION [13▪▪]. VOYAGE randomized 408 children divided into two subpopulations; what they termed a type 2 inflammatory phenotype ($\geq$150 blood eosinophils/$\mu\lambda$ *or* fractional exhaled nitric oxide (FeNO) of $\geq$20 ppb at baseline); and those with $>$300 eosinophils/$\mu\lambda$. In both groups, the primary outcome, asthma attacks, were reduced and there were also improvements in %predicted first second forced expired volume (FEV_1) and asthma control. Dupilumab was safe but was associated with increase viral infections. Importantly, the annualized asthma attack rate in the placebo group dropped from 2.16 to 0.67 with no change in asthma medication, a well described effect of entering a clinical trial. This underscores how much can and should be achieved by getting basic management right before prescribing an expensive and invasive monoclonal [14,15].

In EXCURSION, VOYAGE placebo patients were given dupilumab, while the active patients continued dupilumab for a further year. Safety and efficacy findings were similar to VOYAGE. Other manuscripts

based on VOYAGE included a pharmacokinetic study, establishing the correct dose of dupilumab in children [16▪]; sub-analyses of VOYAGE showed Dupilumab was efficacious even if the child did not have allergic asthma [17▪] and irrespective of prescribed inhaled corticosteroid (ICS) dose [18▪]; another sub-analysis of the considerable improvements in spirometry in those children in whom it was abnormal at baseline [19▪▪]; and an important risk prediction study, discussed in more detail below [20▪▪].

Tezepelumab data are mainly from adults, in whom efficacy is clear even in those with no evidence of Type-2 inflammation, which is also an important advance in children [21▪,22▪]. Surprisingly, Benralizumab has been licensed in children aged 6–11 years on the basis of a pharmacokinetic and safety study in only 30 children [23▪]! There was an efficacy signal (the study was not powered to detect this) and eosinophils were almost totally depleted. This is not necessarily desirable; an adult study comparing the three anti-IL-5 strategies (mepolizumab, reslizumab and benralizumab) showed that benralizumab therapy was associated with greater eosinophilic depletion and more infections [24]; there is increasing evidence of important host defence roles for eosinophils [25,26], which may need to be borne in mind when choosing a biological.

Asthma biologics are a major advance in children, and the placebo-controlled trials have established an evidence base. There is a need for more data, especially about biomarkers predictive of treatment response in children. There is also a need to find ways to lengthen the interval between injections as in adults [27▪]; or will this be another option that will not be evidenced in children?

RECENT ADVANCES IN PRESCHOOL WHEEZE

A really important ERS Task Force (TF) has just been published [28▪▪]. Previous TFs [29,30] were based purely on symptom patterns (episodic viral wheeze, EVW and multiple trigger wheeze, MTW), which is clearly not acceptable for school age asthma; why should it be acceptable in the preschool years? The three aims of the manuscript were to establish definitions for preschool wheezing for use in clinical guidelines and research studies; to review the evidence on the physiology, pathology and mechanisms underpinning preschool wheezing; and to describe the important outcomes for patients, caregivers and clinicians. It marks a big step forward to applying the treatable traits approach [31] in this age group.

A plausible hypothesis now mouldering in the graveyard of 'it seemed a good idea at the time' was that, since ICS are valuable treatment for school age asthma, starting them early in a high-risk group would prevent the development of asthma. Three randomised controlled trials have been unequivocally negative [32–34], and in support, a bronchoscopic study of severe preschool wheeze in children median age 12 months showed no evidence of eosinophilic inflammation or airway remodelling even in atopic children with reversible airflow obstruction [35], implying that the mechanisms initiating asthma are different from those driving the disease. Recent publications have focused on the airway wall as a driver of evolution to asthma. An early follow up study of severe preschool wheezers who underwent bronchoscopy [36] showed in small numbers that the best predictor of asthma at age 6–11 years was airway smooth muscle area fraction, and not inflammation or reticular basement membrane (RBM) thickness [37]. A study in which a discovery ($N = 56$) and a separate validation ($N = 44$) cohort of severe 1–5-year-old wheezers underwent endobronchial biopsy to determine remodelling parameters (epithelial integrity, RBM thickness, the mucus gland, fibrosis and bronchial smooth muscle areas, blood vessel density and the distance between bronchial smooth muscle and RBM [38▪▪]). Latent class analysis led to a two-class model with very different outcomes in terms of wheeze attacks. There were no differences in any inflammatory parameter between the two classes. 66 patients were followed up to school age [39▪]. The two groups exhibited significantly different disease trajectories in terms of age at the first wheeze attack and persistence of symptoms; atopy; spirometry and lung volumes; and treatment responses. What is not known are the mechanistic pathways, but these manuscripts suggest that if the progression to asthma is to be halted, then research into the pathobiology of remodelling may be a fruitful source of new therapies.

An important meta-analysis [40▪▪] on whether prednisolone works in acute preschool wheeze suggested small improvements in wheeze score at 4 h which had disappeared by 12 h, and a marginal shortening of hospital length of stay by around 3 h. There were better results in those with 'asthma', whatever was meant by that. There was no parental input on whether a course of steroids or three hours more in hospital is preferable. This parent and grandparent would choose the latter every time. The INFANT study suggested in a post hoc analysis that response to ICS therapy was best predicted in preschool wheezers by a combination of aeroallergen sensitization and an eosinophil count $\geq$300 cells/μλ [41]. However, a study from Copenhagen has cautioned that very early in

life, eosinophils seem less relevant to wheeze or atopic dermatitis, again giving biological plausibility to the finding that ICS do not prevent progression to asthma and cautioning that perhaps 1–2-year-olds will need a different approach to 4–5 years olds [42▪]. Careful phenotyping and personalized medicine, not one size fits all, is likely the answer.

Decades ago, preschool wheeze was labelled as 'bronchitis' and treated with antibiotics. This practice was discredited as the role of viruses and bronchospasm became appreciated. Now the focus has returned to a potential role of bacterial and viral infection in preschool wheeze, starting with the seminal COPSAC manuscript showing hypopharyngeal colonization of any combination of *S. pneumoniae*, *M. catarrhalis* and *H. influenzae* were more likely to have subsequent early life recurrent wheeze and asthma [43], albeit the effects diminishing over time and disappearing by age 18 years [44▪▪]. An early bronchoalveolar lavage (BAL) study defined two clusters in severe preschool wheeze; 'Moraxella' and 'mixed microbiota' [45]. The former had a neutrophilic BAL compared with the mixed group, and there was a trend for more episodic viral wheezers in the Moraxella group. These observations were extended by a much larger cluster analysis performed in 136 children aged 1–5 years, of whom 105 had recurrent severe wheeze and 31 with other respiratory disease without wheeze [46]. Data driven cluster analysis using blood and BAL neutrophils and eosinophils, atopy, viral PCR, bacterial culture and whether ICS had been prescribed. Four clusters were identified: atopic, Moraxella dominated ($N = 24/134$, 17.9%); nonatopic, low infection rate, high ICS use ($N = 42/134$, 31.3%); nonatopic, high infection rate, *staphylococcal*, *pneumococcal* and *haemophilus* dominated ($N = 31/134$, 23.1%); and nonatopic, low infection rate, no ICS ($N = 37/134$, 27.6%). The clusters did not relate to the clinical descriptors EVW and MTW, and indeed 31 children could not be placed in either cluster. Another group coined the phrase 'silent, rhinovirus (RV) associated bronchoalveolitis' to describe similar children who are clinically well (otherwise their bronchoscopy would have been rescheduled, despite which there was infection and neutrophilic inflammation on BAL [47▪▪]. There was no cluster analysis despite 850 patients being included. There were 341 children with no BAL pathogens and 127 children in whom RV was the only isolate. 148 children had other viral and bacterial BAL pathogens; this group was not described in detail. In comparison to the no pathogen group, the RV positive children were more likely to be neutrophilic with or without eosinophilia. Blood examination showed elevated neutrophils and CRP, but not eosinophils or IgE in the RV group.

Importantly, just as there are subtypes of eosinophils, the same is true for neutrophils. In a study in preschool children with wheeze, neutrophils differentially expressed 495 genes in those with and without allergic sensitization [48▪▪]. Neutrophil responses to viral infection were less effective in the allergic sensitized. There was more degranulation and NETS formation and reduced pro-inflammatory cytokine formation, as well as signalling monocytes to an anti-inflammatory (M1) state. This is another indication that we need to move beyond counting cells to functional studies.

Whereas these manuscripts turn the spotlight firmly on infection, whether infection is of pathophysiological significance and antibiotics would be beneficial is unclear. RV bronchoalveolitis was associated with high dose ICS, and it is possible that ICS result in topical mucosal immunosuppression and hence infection [49], although a recent large study was reassuring [50▪]. A pilot study which attempted to evaluate phenotype directed therapy (antibiotics for infection, ICS for those with blood eosinophilia) turned out to be fraught with problems, not least documented poor adherence to ICS [51]. We badly need adequately powered intervention studies to see if targeted antibiotics will be a beneficial treatment strategy. Finally, because bronchoscopy is required to determine these phenotypes, their stability over time, and their relevance to milder wheezers is not known.

OTHER IMPORTANT UPDATES

There is insufficient space to do justice to these topics, but recent important manuscripts are highlighted.

Determination of asthma attack risk

Sadly, asthma attacks still kill children, almost inevitably as a result of failure of basic management [52,53,54▪], and the best predictor of a bad attack is a previous bad attack [55]. Risk factors for poor control and asthma attacks differ [56]. The VOYAGE investigators showed that children with a normal FeNO and blood eosinophil count were at very low risk of attacks [20▪▪]. A meta-analysis [57▪] of three randomised controlled trials in preschool children [58–60] suggested that blood eosinophil count alone or combined with sensitization to food or aeroallergens was at best only a guide to risk, but it is unclear how generalizable these findings are. We showed in a primary care study that blood eosinophil counts vary over time but counts $\geq$300 cells/$\mu\lambda$ are predictive of an asthma attack within three months of the point of care test [61▪]. Exhaled breath volatile

organic compounds also show promise [62▪▪]. Much more work is needed to enable attack risk to be measured.

Getting SMART

Combining ICS usually with formoterol (in the USA albuterol) has been shown to improve asthma outcomes [63]. The evidence is weaker in adolescents [64], and very weak in children age 11 and under, which hopefully will soon be rectified [65], and the approach shows geographical variation [66]. This approach means that underdosing ICS while overdoing on SABA, both long known to be associated with bad asthma outcomes, cannot happen.

Going GREEN

Climate change is one of the biggest existential threats to the health of children. There is a complex relationship between ambient temperature and its fluctuations [67▪], but it is difficult to believe that global warming will improve asthma control [68▪]. Adverse effects of environmental exposures and temperature were the subject of a meta-analysis [69▪▪]. Propellants are a major source of greenhouse gases [70▪,71▪] and there is a strong move away from pMDIs in adults and older children [72▪]. However, it is essential that the needs of young children, for whom pMDIs and spacers are essential, are not forgotten [73▪▪,74▪,75▪].

Poverty and deprivation

Early life adverse events have lifelong consequences [76] and all over the world, social determinants are important in respiratory disease [77▪]. Recent important papers have highlighted early life homelessness and association with later asthma [78▪]; pregnancy exposure to fine particle pollutants and later wheeze and allergic sensitization [79▪]; intimate partner violence against women and childhood sexual abuse are also weakly associated with asthma, [80▪] and worryingly, with premature telomere shortening [81▪]; and low neighbourhood opportunity is also a risk factor for asthma [82▪]. Social deprivation is an important factor in asthma attacks [83▪].

Race neutral lung function?

Ethnic correction of lung function data [84] has been criticized as normalizing poverty and deprivation. Whether the Global Lung Initiative [85▪▪] or the American Thoracic Society [86▪▪] approach to this is correct [87▪], switching from race-corrected lung function will profoundly affect the classification of airway disease, especially in ethnic minorities [88▪,89▪].

Ending on a positive note: something can be done!

The huge benefits across many outcomes of the bans on smoking in workplaces has been well documented. The UK sugar tax, designed to reduce obesity, has led to a 20% reduction in asthma admissions in children [90▪▪], although whether the mechanism is due to reduction in obesity is arguable, given the duration of follow up. Legislation works!

CONCLUSION

Although much progress has been made in gathering an evidence base for the management of paediatric asthma, in particular MUPPITS-2 and VOYAGE/EXCURSION, children still remain the poor relations of asthma research. Contrast the SMART data (>8000 teenagers and adults) with the almost total absence of any data in young children; this scandal needs to cease. Preschool wheeze is ceasing to be an area where just asking questions is sufficient to guide treatment. Personalized medicine is becoming a reality for these young children, and we are on the verge of determining endotypes. Finally, although understanding pathophysiology and new treatments are so important, we could do so much now if we could give every child their human right, a clean and protective environment in which to grow up. Political action is essential if this is to be achieved, and political action is effective if there is a will to carry it through.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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This manuscript highlights that the predictive effect of nasopharyngeal colonisation with bacteria, described in the previous reference, diminishes with age and disappears at age 18 years.

45. Robinson PFM, Pattaroni C, Cook J, *et al.* Lower airway microbiota associates with inflammatory phenotype in severe preschool wheeze. J Allergy Clin Immunol 2019; 143:1607–1610.

46. Robinson PFM, Fontanella S, Ananth S, *et al.* Recurrent severe preschool wheeze: from prespecified diagnostic labels to underlying endotypes. Am J Respir Crit Care Med 2021; 204:523–535.

47. ■■ Teague WG, Griffiths CD, Boyd K, *et al.* A novel syndrome of silent rhinovirus-associated bronchoalveolitis in children with recurrent wheeze. J Allergy Clin Immunol 2024; 154:571–579.

This manuscript confirms the importance of infection in a big group of preschool wheezers, especially rhinovirus, at a time when the children were clinically well, as described in the previous two references. Although not discussed in detail it is very clear that there is also a substantial bacterial load in these children, also as previously described.

48. ■■ Fitzpatrick AM, Mohammad AF, Huang M, *et al.* Functional immunophenotyping of blood neutrophils identifies novel endotypes of viral response in preschool children with recurrent wheezing. J Allergy Clin Immunol 2023; 152:1433–1443.

Another important manuscript documenting that merely counting cells is inadequate for phenotyping, and that we need to look beyond numbers to function.

49. Sabroe I, Postma D, Heijink I, Dockrell DH. The yin and the yang of immunosuppression with inhaled corticosteroids. Thorax 2013; 68:1085–1087.

50. ■ Sielinou Kamgang KH, Rhedin SA, Almqvist C, Wintzell V. Use of inhaled corticosteroids and the risk of hospitalisation for pneumonia in children with asthma: a nationwide cohort study. Thorax 2024; 79:395–402.

Big and reassuring study on the safety of ICS in children. Important given that ICS use has been associated with increased risk of pneumonia, tuberculosis and atypical *Mycobacterial* infection in adults.

51. Saglani S, Bingham Y, Balfour-Lynn I, *et al.* Blood eosinophils in managing preschool wheeze: lessons learnt from a proof-of-concept trial. Pediatr Allergy Immunol 2022; 33:e13697.

52. Dyer C. Coroner warns of 'multiple failures' that contributed to child's death from asthma. BMJ 2024; 384:q641.

53. Santana CVN, Pimentel Pinheiro G, Lima GS, *et al.* Another case of preventable death from asthma. J Asthma 2023; 60:2248–2251.

54. ■ Levy ML, Fleming L, Bush A. Asthma deaths in children in the UK: the last straw! Br J Gen Pract 2024; 74:244–245.

A sad review, summarising the catastrophic consequences of the inadequate management of asthma attacks. When will it be realised that asthma attacks are a significant red flag of inadequate management of a serious chronic disease.

55. Buelo A, McLean S, Julious S, *et al.* At-risk children with asthma (ARC): a systematic review. Thorax 2018; 73:813–824.

56. Ardura-Garcia C, Mallet MC, Berger DO, *et al.*, SPAC Study Team. Predictors of asthma control differ from predictors of asthma attacks in children: The Swiss Paediatric Airway Cohort. Clin Exp Allergy 2023; 53:1177–1186.

57. ■ Fitzpatrick AM, Grunwell JR, Cottrill KA, *et al.* Blood eosinophils for prediction of exacerbation in preschool children with recurrent wheezing. J Allergy Clin Immunol Pract 2023; 11:1485–1493.

A meta-analysis of three randomised controlled trials (next three references) seeking to determine the predictive value of peripheral blood eosinophils and allergic sensitization. The results were disappointing, but given all the children were enrolled in randomised controlled trials, may not be generalizable.

58. Bacharier LB, Phillips BR, Zeiger RS, *et al.* Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. J Allergy Clin Immunol 2008; 122:1127–1135.

59. Zeiger RS, Mauger D, Bacharier LB, *et al.* Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med 2011; 365:1990–2001.

60. Bacharier LB, Guilbert TW, Mauger DT, *et al.* Early administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses: a randomized clinical trial. JAMA 2015; 314:2034–2044.

61. ■ Perikleous A, Bowen SJ, Griffiths C, *et al.* Stability of blood eosinophil count and association with wheeze attacks in preschool children. Am J Respir Crit Care Med 2025; 211:263–265.

By contrast with [57▪], point of care blood eosinophil count predicted a subsequent wheeze attack in a milder group of patients. This is also the first study to document the variability of peripheral blood eosinophil counts in this population

62. ■■ Gmachowska K, Podlecka D, Bonikowski R, *et al.* Exhaled volatile organic compounds (VOCs) for prediction of asthma exacerbation in children. Int J Occup Med Environ Health 2024; 37:351–359.

Not yet ready for prime time, but surely exhaled breath analysis will become a powerful tool in the management of paediatric asthma, provided analysis is rapid so it can become a point of care test.

63. Hatter L, Bruce P, Braithwaite I, *et al.* ICS-formoterol reliever versus ICS and short-acting β_2-agonist reliever in asthma: a systematic review and meta-analysis. ERJ Open Res 2021; 7:00701–2020.

64. Papi A, Ferreira DS, Agache I, *et al.* European Respiratory Society short guidelines for the use of as-needed ICS/formoterol in mild asthma. Eur Respir J 2023; 62:2300047.

65. Hatter L, Bruce P, Holliday M, *et al.* The Children's Anti-inflammatory Reliever (CARE) study: a protocol for a randomised controlled trial of budesonide-formoterol as sole reliever therapy in children with mild asthma. ERJ Open Res 2021; 7:00271–2021.

66. Bush A, Randerath W, Roche N. As needed ICS/formoterol: not all of Europe is equal. Eur Respir J 2024; 63:2400408.

67. ■ Yu J, Zhu A, Liu M, *et al.* The correlation between daily temperature, diurnal temperature range, and asthma hospital admissions in Lanzhou city, 2013–2020. BMC Public Health 2024; 24:2454.

Global warming is an existential threat and this paper reports the complex relationships between absolute temperature, temperature changes and asthma attacks.

68. ■ Landguth EL, Knudson J, Graham J, *et al.* Seasonal extreme temperatures and short-term fine particulate matter increases pediatric respiratory healthcare encounters in a sparsely populated region of the intermountain western United States. Environ Health 2024; 23:40.

Another warning manuscript. If you have asthma, high temperatures are not a good thing; global warming poses a serious threat.

69. ■■ Wang J, Cortes-Ramirez J, Gan T, *et al.* Effects of climate and environmental factors on childhood and adolescent asthma: A systematic review based on spatial and temporal analysis evidence. Sci Total Environ 2024; 951:175863.

An important synthesis of the evidence surrounding climate and environment on childhood asthma. Inhalers are good when used properly but are not the total answer.

70. ■ Wilkinson AJK, Maslova E, Janson C, *et al.* Greenhouse gas emissions associated with suboptimal asthma care in the UK: the SABINA health-CARe-Based envirONmental cost of treatment (CARBON) study. Thorax 2024; 79:412–421.

Asthma control is a good target in its own right, but controlling asthma also reduces greenhouse gas emissions.

71. ■ Vartiainen V, Woodcock AA, Wilkinson A, *et al.* Thoughtful prescription of inhaled medication has the potential to reduce inhaler-related greenhouse gas emissions by 85%. BMJ Open Respir Res 2024; 11:e001782.

A challenge to do better. Is your metered dose inhaler really necessary?

72. ■ Hatter L, Holliday M, Eathorne A, *et al.* The carbon footprint of as-needed budesonide/formoterol in mild asthma: a post hoc analysis. Eur Respir J 2024; 64:2301705.

Unsurprisingly, the use of a dry powder device (Turbuhaler) reduces greenhouse gas emissions. Adds to the evidence that we can do better without compromising care.

73. ■■ Levy ML, Bateman ED, Keith Allan K, *et al.* Global access and patient safety in the transition to environmentally friendly respiratory inhalers: the Global Initiative for Asthma perspective. Lancet 2023; 402:1012–1016.

A typically thoughtful piece from GINA, obviously endorsing the reduction where possible of greenhouse gas emissions, but also highlighting that there are groups of patients such as young children for whom metered dose inhalers *are* necessary

74. ■ Orlovic M, Tzelis D, Guerra I, *et al.* Environmental, healthcare and societal impacts of asthma: a UK model-based assessment. ERJ Open Res 2024; 10:00577–2023.

Another manuscript which should stimulate us to try to reduce greenhouse gases as a result of asthma, where we can.

75. ■ Brennan SK, Coates AC, Laube B, Sadreameli SC. Climate policy and pediatric asthma: how transition to nonhydrofluorocarbon propellants will disproportionately impact children. Ann Am Thorac Soc 2024; 21:1242–1244.

An important editorial highlighting the importance of remembering young children as well as the environment when public health policy about inhalers is being debated.

76. Bush A. Impact of early life exposures on respiratory disease. Paediatr Respir Rev 2021; 40:24–32.

77. ■ Bush A, Byrnes CA, Chan KC, *et al.* Social determinants of respiratory health from birth: still of concern in the 21st century? Eur Respir Rev 2024; 33:230222.

Asthma treatment is more than inhalers. This article documents the depressing extent to which multiple social factors impact asthma outcomes. We can do so much more by attending to basic human rights, without the need for expensive biologicals.

78. ■ Keen R, Kim HH, Chen JT, *et al.* Longitudinal relationships between early-life homelessness and school-aged asthma and wheezing. J Epidemiol Community Health 2024; 78:624–631.

The same theme: give a child a decent home, and asthma morbidity will likely fall.

79. ■ Ojima K, Yoda Y, Araki S, *et al.* Exposure to ambient fine particulate matter components during pregnancy and early childhood and its association with asthma, allergies, and sensitization in school-age children. Environ Health Prev Med 2024; 29:34.

And again. Give pregnant women and young children clean air to breathe, and likely asthma outcomes will improve.

80. ■ Spencer CN, Khalil M, Herbert M, *et al.* Health effects associated with exposure to intimate partner violence against women and childhood sexual abuse: a burden of proof study. Nat Med 2023; 29:3243–3258.

Physical and sexual violence against women and children is more than just foul in its own right, but another association of adverse health effects, including asthma.

81. ■ Zhou Z, Lo CKM, Chan KL, *et al.* Child maltreatment and telomere length in middle and older age: retrospective cohort study of 141 748 UK Biobank participants. Br J Psychiatry 2023; 223:377–381.

This manuscript leads to the hypothesis that childhood abuse leads to premature aging (telomere shortening), and the more the different types of abuse, the greater the telomere shortening.

82. Aris IM, Perng W, Dabelea D, *et al.,* Environmental Influences on Child Health ■ Outcomes. Neighborhood opportunity and vulnerability and incident asthma among children. JAMA Pediatr 2023; 177:1055–1064.

Give a child opportunities and asthma will reduce. Vulnerable children are vulnerable and also to asthma.

83. Khalaf Z, Bush A, Saglani S, Bloom CI. Influence of age on clinical characteristics, pharmacological management and exacerbations in children with asthma. Thorax 2024; 79:112–119.

A big epidemiological study, highlighting that asthma attack prevalence and risk factors varied with age. At all ages, social deprivation a risk for asthma attacks.

84. Quanjer PH, Stanojevic S, Cole TJ, *et al.,* ERS Global Lung Function Initiative. Multiethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 2012; 40:1324–1343.

85. Bhakta NR, Bime C, Kaminsky DA, *et al.* Race and ethnicity in pulmonary ■■ function test interpretation: an official American Thoracic Society statement. Am J Respir Crit Care Med 2023; 207:978–995.

A must-read paper arguing for removing race from normal ranges.

86. Bowerman C, Bhatka NR, Brazzale D, *et al.* A race-neutral approach to the ■■ interpretation of lung function measurements. Am J Respir Crit Care Med 2023; 207:768–774.

Another must-read with a contrasting approach. Here GLI base their normative data on a mix of races, ensuring as many as possible are represented, rather than ignoring race altogether as is the proposal of the ATS (preceding reference).

87. Baugh A, Buhr RG, Bush A, *et al.* Strategies to classify lung function: it's not ■ black and white. Am J Respir Crit Care Med 2024; 209:19–20.

Whichever of the two different approaches in the previous two references you prefer, this provocative article argues the value or otherwise of each.

88. Forno E, Weiner DJ, Rosas-Salazar C. Spirometry interpretation after imple- ■ mentation of race-neutral reference equations in children. JAMA Pediatr 2024; 178:699–706.

An important paper on the effects of the change away from ethnic normal ranges; this has clinical consequences.

89. Sitarik AR, Wegienka G, Johnson CC, Joseph CLM. Impact of spirometry ■ race-correction on preadolescent black and white children. J Allergy Clin Immunol Pract 2023; 11:3097–3106.

Another making the same point as the previous paper.

90. Rogers NT, Cummins S, Jones CP, *et al.* The UK Soft Drinks Industry Levy and ■■ childhood hospital admissions for asthma in England. Nat Commun 2024; 15:4934.

The UK sugar tax was intended to reduce obesity. Surprisingly it has reduced asthma attacks, probably too quickly for it to be mediated via obesity. Let's encourage politicians to legislate to improve public health – it works!