# Asthma Research Review™

Making Education Easy

Issue 7 - 2023


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**Abbreviations used in this issue:**

**COPD** = chronic obstructive pulmonary disease; **COVID-19** = coronavirus-19; **FEV1** = forced expiratory volume 1; **GORD** = gastro-oesophageal reflux disease; **pMDI** = pressurised metered dose inhalers; **RV** = residual volume; **SA** = severe asthma; **SAD** = small airway dysfunction; **TLC** = total lung capacity; **TSLP** = thymic stromal lymphopoietin.

## Welcome to issue 7 of Asthma Research Review.

In this issue, we reflect on the diverse research being undertaken in asthma and related conditions. These studies range from explorations of our clinical practice, through interventional and biomarker studies, to discovery science. We have selected papers that deal with the challenging, practical issues clinicians grapple with on a regular basis, such as diagnosis, managing transition, physiological assessment, and prognostication. Additionally, we highlight research that deals with the pressing need to consider both the impact of our changing environment and the substantial carbon footprint of inhaled medicines.

We hope you enjoy this update in asthma research, and we always welcome your comments and feedback.

Kind Regards,


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### Patient and physician factors associated with symptomatic undiagnosed asthma or COPD

**Authors:** Cherian M et al.


**Summary:** This study included 451 patients with symptomatic obstructive lung disease and 205 symptomatic control participants with physician-diagnosed obstructive lung disease. The results of this study discovered that participants with undiagnosed obstructive lung disease had a lower mean pre-bronchodilator forced expiratory volume than those who were diagnosed. They also reported greater psychosocial impacts from symptoms such as worse energy and fatigue, than those diagnosed with obstructive lung disease. Undiagnosed obstructive lung disease was more common in participants whose family physicians were practising for >15 years, and in those whose physicians reported that they were likely to prescribe respiratory medications without doing spirometry. Undiagnosed obstructive lung disease was more common among participants who had never undergone spirometry or were never referred to a specialist. Undiagnosed obstructive lung disease was also less common among participants who had required emergency department care.


**Comment:** We recognise that airway disease is commonly misdiagnosed: this may be underdiagnosis or labels being applied to people with other reasons for their symptoms. The former issue is likely to have worsened in Australia with a significant fall in primary care use of spirometry around the COVID-19 pandemic. Cherian and colleagues put in a commendable effort to undertake a population-based case-finding exercise for airway disease. Their findings are both disappointing and predictable. People with undiagnosed obstructive lung disease were disproportionately physically and psychologically affected, and they had more often entrusted their care to older clinicians who did not follow guidelines. These types of findings should encourage all of us to be more proactive in the early detection of and intervention for airway disease to reduce avoidable harm.

***Reference: Eur Respir J. 2022;61:2201721***
Abstract

## Mortality of asthma, COPD, and asthma-COPD overlap during an 18-year follow up.

**Authors:** Mattila T et al.

**Summary:** This study was based on a national health examination survey representing Finnish adults aged 30 years or older performed in 2000-2001. From the 5922 patients included in this analysis, asthma and COPD were significantly associated with higher total mortality in Cox's model, which was adjusted for sex, age, smoking, education level, BMI, leisure time, physical activity, cardiovascular disease, diabetes, and hypertension. Hazard ratios for asthma, COPD and asthma-COPD overlap were, 1.29, 1.50, and 1.26, respectively. Additionally, asthma and COPD were associated with cardiovascular mortality. Although Asthma-COPD overlap did not predict mortality in the whole cohort, there was a significant association with mortality risk.

**Comment:** The prevalence of smoking in people with asthma is approximately the same as that in the general population. As asthma is so prevalent, this creates many thousands of people who have both asthma and smoking-related lung disease: the asthma-COPD overlap syndrome. Mattila and colleagues followed up with participants in the Finnish national health study to investigate the relative courses of these conditions. The diagnostic criteria used for the asthma-COPD overlap syndrome and COPD employed in the study are spirometric and therefore introduce a fatal misclassification issue for these clinical entities. However, taken as a follow-up of obstructive lung diseases, the results are still of interest. The three groups experienced more deaths than would be expected, with cardiovascular mortality significantly elevated. These risks were similar to those with existing heart disease or diabetes. These results should encourage us to consider the vascular effects of both obstructive lung disease and the treatments we use (oral steroids, and sympathomimetics) and manage co-existing risk factors.

***Reference: Respir Med. 2023;207:107112***
Abstract

## Development of a tool to detect small airways dysfunction in asthma clinical practice

**Authors:** Kocks J et al.

**Summary:** This study investigated data using the multinational ATLANTIS (Assessment of Small Airways Involvement in Asthma) studies, which included the earlier developed SAD tool questionnaire. The results of this study found that the SAD tool item 8, "I sometimes wheeze when I am sitting or lying quietly", the patient's characteristics age, age at asthma diagnosis, and BMI could detect SAD. When spirometry and oscillometry were added, diagnostic ability increased. The study concluded that if access to respiratory tests is limited, patients with SAD could be identified by asking about wheezing at rest and identified with a few patient characteristics. The study noted that in advanced hospital settings, spirometry and oscillometry could identify patients with SAD with higher accuracy.

**Comment:** The small airways are important sites of airflow obstruction and inflammation in asthma, and understanding the degree of SAD may be prognostic or influence treatment. However, assessment of the degree of SAD in an individual is not trivial. Previous ATLANTIS studies have demonstrated little difference in the history between people with mild and severe SAD. The associations with duration of disease and BMI being insufficient to be discriminatory. Furthermore, the degree of SAD is not strongly correlated with standard spirometric measures: oscillometry, multiple breath nitrogen washout, and RV/TLC are more sensitive investigations. Kocks and colleagues have undertaken a worthy endeavour in attempting to create a SAD screening tool. One question shows some promise when combined with demographic data; "I sometimes wheeze when I am sitting or lying quietly". However, its performance is far lower than undertaking relatively simple tests such as oscillometry. This study also only included people with definite asthma. We disagree with the authors that the question could be used in primary care for people "treated with" asthma. It has not been tested in this setting, and false positives from other conditions would be more likely.

***Reference: Eur Respir J. 2022;2200558***
Abstract

## Associations between outdoor air pollutants and non-viral asthma exacerbations and airway inflammatory responses in children and adolescents living in urban areas in the USA

**Authors:** Altman MC et al.

**Summary:** This retrospective secondary analysis investigated data from the MUPPITS1 cohort and validated the findings of the ICATA cohort. This study included 168 participants from the MUPPITS1 cohort and 189 participants from the ICATA cohort. This study identified that increased air quality index values, driven predominantly by increased $PM_{2-5}$ and $O_3$ concentrations, were significantly associated with asthma exacerbations and decreased pulmonary function that occurred in the absence of a provoking viral infection. Furthermore, individual pollutants were significantly associated with altered gene expression in coordinated inflammatory pathways, including $PM_{2-5}$ with increased epithelial induction of tissues, kallikreins, mucus hypersecretion, barrier functions and $O_3$-increased type 2 inflammation. The study concluded that air pollution is a significant independent risk factor for asthma exacerbations in children living in urban areas and can potentially be linked to exacerbations through specific inflammatory pathways in the airway.

**Comment:** The effects of air pollution on asthma is an increasingly important area for research and one in which our knowledge continues to increase. Although Australia is not known for its megacities, air quality is still very important to people with asthma. Increasing trends in urbanisation, increasing road traffic, smoke from domestic burners, and bushfires affect people every week. Individuals are more aware of this due to the public availability of current air pollution levels (e.g. via Asthma Australia's AirSmart app). This article builds on previous knowledge of our understanding of non-allergic asthmatic triggers by correlating non-infectious asthma exacerbations with FEV1 and air quality values across two paediatric and young adult cohorts. The investigators also revealed promising signals regarding potential inflammatory pathways associated with individual pollutants through nasal secretion and nasal lavage samples. With increasingly strong evidence for a causative link between asthma exacerbations and both particulate and chemical pollutants and better information on the mechanisms by which this effect is exerted, further studies are needed to investigate what individual-level interventions may meaningfully ameliorate these risks.

***Reference: Lancet Planet Health. 2023;7:e33-44***
Abstract

## Long-term safety and efficacy of Tezepelumab in people with severe, uncontrolled asthma (DESTINATION)

**Authors:** Menzies-Gow A et al.

**Summary:** This randomised placebo-controlled extension study investigated the long-term safety and efficacy of Tezepelumab in individuals with severe, uncontrolled asthma. This extension study used data from the NAVIGATOR and SOURCE studies and included research from 182 sites in 18 countries. For individuals who initially received Tezepelumab in NAVIGATOR, the incidence of adverse events over 104 weeks was 49.62 per 100 patient-years, compared with 62.66 for those receiving a placebo. For serious adverse events, the occurrence was 7.85 per 100 patient years for individuals who initially received Tezepelumab and 12.45 for those who received a placebo. From the SOURCE study, the incidence of adverse events was 47.15 per 100 patient years for those who initially received Tezepelumab and 69.97 for those who received a placebo. For serious adverse events, the occurrence was 13.14 per 100 patient-years for those who initially received Tezepelumab and 17.99 for those who received a placebo. The study concluded that Tezepelumab treatment was well tolerated for up to 2 years, resulting in sustained, clinically meaningful reductions in asthma exacerbations.

**Comment:** SA affects only a minority of individuals with the disease, but given the prevalence of asthma, this still results in thousands of people across the country with a challenging illness. In recent years people with eosinophilic or allergic asthma have gained access to effective monoclonal antibodies ("biologics") that have been transformative for many. However, others have only a partial benefit or are ineligible as their asthma is driven by other factors through other pathways. The resources required for their care remain disproportionately large, both directly and due to the comorbidities attributable to the chronic cumulative oral corticosteroid exposure. Tezepelumab is the first biologic approved by the US FDA (food and drug administration) and recommended by GINA (Global Initiative for Asthma) guidelines for type two low-SA. This stage III long-term extension study further builds on existing data showing the durability of the effect on exacerbation rate, asthma control, lung function, and quality of life. Generally, serious adverse events were more common in the placebo group with one exception; cardiac adverse events were marginally higher in the Tezepelumab group. Neither the investigators nor a masked independent adjudication committee could attribute causality despite appropriate analyses. In the context of the harm from uncontrolled SA and oral corticosteroid toxicity, we hope it will become possible for specialist centres in Australia to prescribe Tezepelumab under specific circumstances in future.

***Reference: Lancet Respir Med. 2023;S2213 published online***
Abstract

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### Independent commentary by Associate Professor John Blakey

John is a consultant respiratory physician at Sir Charles Gairdner Hospital, and an adjunct at Curtin University and UWA. John trained in the UK including working at severe asthma centres in Nottingham, Leicester, Birmingham and Liverpool. He has over 100 peer reviewed publications and maintains a research interest. John is the President of TSANZ WA Branch and Medical Advisor for Asthma Australia.

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### Independent commentary by Dr Alice Crawford

After recently completing her Asthma and Airways Fellowship at Sir Charles Gairdner Hospital in 2022, Alice is working as an early career clinician-researcher. Her main interests are optimising difficult-to-treat asthma and identifying it's mimics including VCD/ILO and dysfunctional breathing. Alice is an advocate for multi-site collaboration and data management and looks to further her research skills in the coming years.

## Understanding the feasibility and environmental effectiveness of a pilot postal inhaler recovery and recycling scheme

**Authors:** Murphy A et al.

**Summary:** This 12-month pilot postal scheme assessed the environmental impact of inhalers not being recycled. All inhalers were accepted into this scheme. The recovered pMDIs were dismantled, and component parts recycled where possible; the remaining propellant gas was extracted for reuse in refrigeration and air conditioning industries. Other inhaler types were incinerated in an energy-from-waste facility. Between 2021-2022, 20,049 inhalers were returned; 77% were pMDIs. The results of this scheme saved an estimated 119.3 tonnes of carbon dioxide emissions from entering the atmosphere. This scheme concluded that there is feasibility and effectiveness of a postal inhaler recovery and recycling scheme, which could be used as a foundation to build future initiatives.

**Comment:** Inhaled therapy has been the mainstay of treatment for airway diseases for decades. Millions of inhalers are consumed annually across the country. There are, therefore, major cumulative environmental costs to the manufacturing, shipping and disposal of these limited-use plastic devices. Moreover, the propellants used in pMDIs are potent greenhouse gases, and much of the propellant is released when inhalers are disposed of. Murphy and colleagues provide a very welcome report on the potential for an inhaler recycling scheme. The project demonstrated an impressive and increasing number of inhaler returns and highlighted the major beneficial effect such schemes could have on the carbon dioxide equivalent release from inhaler use. Although the scheme is highly commendable, the bottom line is that this effort, as with other (unpublished) pharmaceutical industry-funded projects in the past, has not led to the type of long-term solution that is urgently needed.

***Reference: NPJ Prim Care Respir Med. 2023;33:5***
Abstract

## Mendelian randomization analysis reveals a complex genetic interplay among atopic dermatitis, asthma, and gastroesophageal reflux disease

**Authors:** Ahn K et al.

**Summary:** This study applied the Mendelian randomisation analysis to explore whether GORD is related to atopic disorders of the lung and atopic dermatitis. This study involved three different methods; each revealed a similar magnitude of casual estimates that were directionally consistent across the sensitivity analysis. This study used an inverse variance-weighted method, the most significant side effect of this method was detected for asthma predisposition to atopic dermatitis, followed by atopic dermatitis to asthma. A significant association was detected for genetically determined asthma on the risk of GORD but not genetically determined atopic dermatitis on GORD. In contrast, GORD equally increased the risks of asthma and atopic dermatitis.

**Comment:** Asthma is a syndrome that can be the end result of several different pathways, with the contribution of genetic and environmental influences varying between individuals and interacting in a complex manner. For these reasons, it is highly challenging to research the aetiology of asthma. A further complication is the study of characteristics such as GORD that might reasonably be a factor in the development of asthma or a consequence of asthma (and its treatment). Anh and colleagues use the potentially very powerful Mendelian randomisation approach to attempt to unpick this relationship and use results from very large study populations. Although the size of the study is impressive, there are key areas of limitation. Most importantly, the information included about individuals was very limited not only in terms of the accuracy and nature of their diagnoses but crucially also their timing and sequence. More thorough and elegant studies will be needed to use Mendelian randomisation to investigate the aetiology of asthma or its intermediate phenotypes.

***Reference: Am J Respir Care Med. 2023;207:130-7***
Abstract

## Nasal TSLP and periostin in infants with severe bronchiolitis and risk of asthma at 4 years of age

**Authors:** Garcia-Garcia ML et al.

**Summary:** This observational, longitudinal, post-bronchiolitis, hospital-based, follow-up study investigated children hospitalised for bronchiolitis, currently aged approximately 4 years. A total of 248 children were included in this study, with the primary outcome to assess the use of nasal TSLP and periostin with severe bronchiolitis. Overall, 21% had never been diagnosed with asthma, and 37% had wheezed in the last 12 months. Measurable nasal TSLP was detected at admission in 27 cases and periostin in 157. Admissions for asthma tended to be more frequent in children with TSLP detection. In the multivariate analysis, adjusting for potential confounders, the detection of TSLP remained independently associated with chronic and current asthma. In the multivariate analysis, periostin was associated with a lower risk of asthma at 4 years, independently of the atopic status.

**Comment:** Asthma is a heterogeneous syndrome that can be difficult to diagnose. These diagnostic difficulties are especially evident in young children who may present with wheezing illnesses that do not evolve into persistent asthma. In this paper, Garcia-Garcia and colleagues collected samples from a group that is known to have a greatly elevated chance of subsequent asthma diagnosis: infants with severe bronchiolitis. In this enriched population, nasopharyngeal aspirates were examined for levels of the alarmin TSLP and periostin, a protein involved in eosinophilic and allergic inflammation (amongst other processes). The authors found that children with higher levels of TSLP were more likely to have a wheeze by age 4, have been repeatedly admitted or be on asthma therapy. The opposite was true for periostin. It is tempting to create a pathophysiological explanation for these findings. However, it should be noted that they contradict the only other similar study previously undertaken. It is also far from clear that all these four-year-olds have asthma rather than damage from recurrent or severe infection or that other children might not go on to develop asthma at a later age. In this very challenging area, more studies are required that are more extensive in their assessments and have longer follow-ups.

***Reference: Respir Res. 2023;24:26***
Abstract

## Health-related quality of life decreases in young people with asthma during the transition from adolescence to young adulthood

**Authors:** Odling M et al.

**Summary:** This study comprised of 2268 participants from the ongoing Swedish population-based prospective birth cohort BAMSE. At the 24-year follow-up, the adjusted median values of EQ-VAS (vertical visual analogue scale) were lower than the 16-year follow-up; among the participants with and without asthma. At the 24-year follow-up, participants with uncontrolled asthma had a lower adjusted median EQ VAS score than peers with controlled or partly controlled asthma. The study recognised that young adults with asthma who did not fulfil the World Health Organisation recommendations on physical activity had lower EQ scores than peers who did. This study concluded that young adults with asthma, uncontrolled disease, or who appear physically inactive, are particularly vulnerable.

**Comment:** Asthma is the commonest chronic condition in children. Many thousands of children with asthma each year are taking steps to become more independent with their asthma self-management and interactions with healthcare providers. They are also becoming more aware of the physical and social limitations that asthma may impose on them. Researchers using the well-characterised BAMSE cohort in Sweden set out to explore the relationship between asthma control, physical exertion and quality of life in adolescents and young adults with asthma. The findings are of concern. The health-related quality of life of younger people with asthma diverged from the reference population with increasing age. This lower quality of life was more notable in those with poor asthma control and/or lower physical activity levels. Previous results from this group also show asthma medication adherence is lower in young adults. It is evident that young people receive relatively little support in the transition to adult asthma care. It is worrying that in many areas of Australia, there is not a transparent, well-trodden pathway for the transition from paediatric care or dedicated resource for those with less severe diseases.

***Reference: BMC Pulm Med. 2023;23:34***
Abstract

## Impaired respiratory system resistance and reactance are associated with bronchial wall thickening in persistent asthma

**Authors:** Chan R et al.

**Summary:** This retrospective cohort study aimed to identify the clinical associations with bronchial wall thickness in moderate to SA. Ninety-two respiratory physician-diagnosed asthma-defined patients with moderate to SA were included in this study. The pooled analysis for all 4 bronchopulmonary segments showed that an area under the reactance curve ≥1.0 kPa/L, an R5-R20 ratio of 25% or more, having 2 or more exacerbations per year, and the presence of nasal polyposis, exhibited adjusted odds ratios of 3.54, 2.89, and 4.17, respectively. The study concluded bronchial wall thickness is associated with peripheral airway resistance and reactance, severe exacerbations, and nasal polyposis in persistent asthma.

**Comment:** Persistent asthma, whether manifested as inflammation or recurrent bronchoconstriction, leads to airway wall structural changes termed remodelling. The degree of remodelling demonstrated on bronchial biopsy has been shown to correlate with CT changes. However, it is not practical or safe to undertake serial CT scans for people with asthma. Chan and colleagues investigate if measures of airway resistance and reactance as measured by the oscillometry can serve as a proxy for CT-derived airway wall thickness. Oscillometry is relatively simple to undertake, effort independent and can describe small airway changes. In this study, small airway measures R5-R20 and AX were more strongly associated with airway wall area than FEV1. However, the clinical markers of persistent airway inflammation (recent exacerbations and nasal polyposis) or bronchospasm (poor symptom control) outperformed both objective measures. This is an instructive step on the way towards identifying individuals with airway wall remodelling and suggests we may be able to assess changes in this important aspect of asthma when new therapies undergo randomised controlled trials.

***Reference: J Allergy Clin Immunol Pract. 2023;S2213 published online.***
Abstract