The report from ISAAC Phase Three is the largest and most important contribution to date on the growing literature, summarised well by Beasley and colleagues, on paracetamol use and childhood asthma. It ends, appropriately, with a question rather than a conclusion and that question is about causality. The authors, and I, can offer informed opinion—or educated guesses—on the causal effects of paracetamol on incident childhood asthma. The studies to date are suggestive but not definitive enough to recommend a wholesale change in antipyretic use in children. Paracetamol has known benefits for paediatric febrile illness as well as known toxicities. The drug might contribute to asthma incidence and it might be prudent to minimise casual use of this—and all—drugs in otherwise healthy children. However, we need to take the guess-work out of recommending and prescribing antipyretic drugs for children. I agree with Beasley that a population-based randomised trial of adequate power and duration to examine childhood asthma incidence, with paracetamol compared with an active control such as ibuprofen and placebo, is warranted. In view of the heterogeneous nature of asthma, the pharmacogenetics of such a study is likely to be fascinating.

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Rhinitis as predictor of adult-onset asthma

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Sneezing and wheezing are common bedfellows.[1] Because a large proportion of people with asthma have symptoms of rhinitis either attributable to allergic sensitisation or to viral infections, it is hard to know whether sneezing leads to wheezing or whether wheezing and sneezing are part of the same process. However, several studies indicate that rhinitis can precede new onset of asthma.[2-4] Rafea Shaaban and colleagues,[5] in today's *Lancet*, reinforce this idea by showing that rhinitis, even in the absence of atopy, was a strong predictor of adult-onset asthma in the European Community Respiratory Health Survey, which included more than 6000 patients in 14 countries. The strongest risk occurred in patients with allergic rhinitis who were sensitised to several inhalant allergens, particularly house-dust mites.

These data have interesting parallels to the findings of the Multicentre Allergy Study (MAS) birth cohort,[6] in which the development of sensitisation to perennial but not seasonal allergens in the first years of life determined the development of persistent asthma, which was also mediated by increases in airway responsiveness. The role of rhinitis was not assessed in the MAS cohort, but there are data from the longitudinal Tucson Respiratory Study.[3] In that study, children who developed rhinitis in the first year of life

were more likely to have physician-diagnosed asthma by age 6 years, although they were no more likely to have a positive skin-prick test.

These findings could merely indicate the close association between viral infections and nasal symptoms. Alternatively, rhinitis apart from colds and atopy could be a clinical manifestation of impaired mucosal function. Such loss of function might entail a weakened mucosal barrier leading to increased allergen uptake and mounting of IgE responses, eventually resulting in allergic airway inflammation, airway hyper-responsiveness, and asthma. Conversely, an impaired mucosa of the upper and lower airways might also be more susceptible to viral infections which could interact with the process of allergic sensitisation and thereby increase the risk of asthma.[7] In this context it is noteworthy that mutations in the gene that codes for filaggrin, a protein known to have an important role in the integrity of the epidermal barrier,[8] were also associated with the prevalence of allergic rhinitis in independent populations.[9]

The idea that allergic rhinitis could cause asthma raises the possibility of preventing asthma by preventing atopic sensitisation, which could in turn prevent allergic rhinitis. The potential of subcutaneous and sublingual immunotherapy for asthma prevention in children with allergic rhinitis has been investigated in two open studies.[10–13] The uncontrolled study design of both trials urges caution in interpretation. Of greater concern is that, in the PAT study,[11] the therapy had no effect in two out of six participating centres, and airway hyper-responsiveness was not affected during 5-year and 10-year follow-up.[10–12] Moreover, other factors that potentially influence asthma risk, such as a family history of asthma and exposure to environmental tobacco smoke, were not taken into account in the randomisation. In the SLIT study, objective markers of airway hyper-responsiveness were missing and the findings were only based on subjective reports.[10]

Even if the long-term preventive effect of immunotherapy is still unknown, immunotherapy in patients with allergic rhinitis can improve nasal symptom scores and reduce airway responsiveness and therefore help reduce asthma burden.[14] By contrast, treatment of nasal symptoms with topical steroids or leukotriene antagonists,[1] because they are symptomatic rather than immunomodulatory, will probably have no role in the secondary prevention of asthma. Lastly, even if immunotreatments work, the fairly low population-attributable risk might diminish the overall effect of this therapeutic approach. This risk is the incidence (new cases) of a disease that would be avoided if the exposure, in this case rhinitis, would be eliminated. The population-attributable risk in Shaaban and colleagues' study ranged from 27% to 32%, and was only higher in men with allergic rhinitis (48%). Therefore a cure of rhinitis would prevent only some cases of new-onset asthma. In the end, potential risks and management options should be discussed cautiously with patients with allergic rhinitis.

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House-dust mite

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Transition from childhood to adult asthma

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If a child has more than one episode of bronchitis in infancy, parents and doctors are concerned about whether the child will outgrow the disease or develop chronic obstructive airway disease—ie, asthma. In today's *Lancet*, Debra Stern and colleagues[1] report data on the prediction of adult asthma at 22 years of age by evaluation of early-life factors at 6 years of age in the Tucson Children's Respiratory Study, one of the oldest birth-cohort studies. Longitudinal studies analyse time courses in disease development and progression and can find relations between exposure factors and outcome (figure).[2]

Although no real cure for asthma exists, early identification of patients at risk of disease progression could lead to better treatment opportunities and, hopefully, improved outcomes in adulthood. Nevertheless, early intervention has not yet been shown to be beneficial in terms of disease modification, which might be because of the failure to identify appropriate subgroups of responders. Studies during early childhood have not shown a clear benefit of early anti-inflammatory treatment in terms of symptom-free days after the treatment period in preschool children.[3] However, inhaled steroids seem to reduce the accelerated decline in forced expiratory volume in 1 s and airway remodelling in adulthood.[4] A kind of tracking (those who start low, remain low) in terms of lung function seems to exist,[5,6] and children with wheezing disorder before 2 years of age compared with those who started wheezing at school age and girls compared with boys probably have poorer lung function in early adulthood.[7]

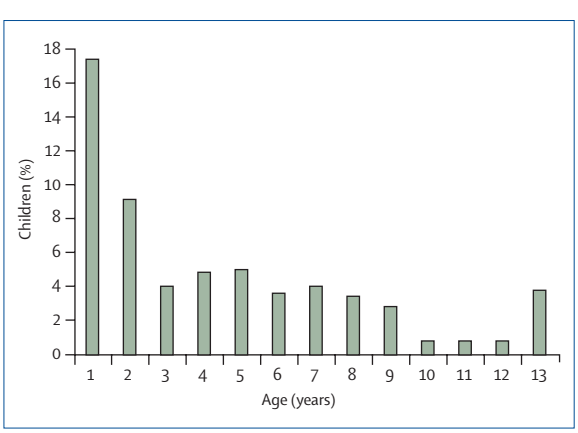

Figure: **Incidence of childhood asthma**
Data are from German MAS study.[2]

Cohort studies have tried to identify different wheezing phenotypes, which were mainly defined by onset and prolongation of symptoms (early onset, late onset, persistent) and presence and absence of atopy.[8,9] One study used latent class analysis, a statistical method developed for the social sciences to identify distinct subsets or classes underlying the observed heterogeneity in a population, to distinguish phenotypes of childhood wheeze and cough.[10] The investigators described five phenotypes: persistent and transient cough, atopic and non-atopic persistent wheeze, and transient viral wheeze. The most common phenotype was atopic wheeze at 8 years of age; however, no prediction for adulthood has been made so far.

In an unselected birth cohort study from New Zealand, 25% of the children had wheezing that persisted from childhood to adulthood or that relapsed after remission.[11] Factors predicting persistence or relapse were sensitisation to house-dust mites, airway hyperresponsiveness, female sex, smoking, and early age at onset. Nevertheless, prediction of outcome seems to be difficult for childhood asthma.