Does paracetamol cause asthma in children? Time to remove the guesswork

Paracetamol (or acetaminophen) was first synthesised in 1878,[1] and has been in widespread use since its introduction in the mid-1950s. 580 million tablets were sold in the UK in 2001–02.[2] In today's *Lancet*, Richard Beasley and colleagues (from the ISAAC Phase Three study) show that most children in samples in Africa, the eastern Mediterranean, the Indian subcontinent, the Americas, Europe, and New Zealand were given paracetamol in their first year of life.[3] Despite this widespread use, a large randomised trial to test the long-term safety of paracetamol in children has not been done.

ISAAC Phase Three reveals an association of moderate magnitude (odds ratio 1·5, 95% CI 1·4–1·6) of reported use of paracetamol in the first year of life with current wheeze at age 6–7 years in a very large sample of children from 31 countries. Similar supportive results were found for symptoms of rhinoconjunctivitis and eczema (1·5, 1·4–1·6; and 1·3, 1·2–1·4, respectively). The study has many strengths, including its large size, use of standardised measures and methods, and generally consistent results across multiple sites and countries with widely varying prevalences not only of paracetamol use (9–91%) but also of current wheeze (2·4–23·7%), and competing risk-factors for asthma.

However, I think the ISAAC Phase Three investigators would agree that a cross-sectional survey with a retrospectively ascertained primary exposure is not a design on which we prefer to make therapeutic decisions. Recall bias (parents of children with asthma might better remember giving paracetamol in the first year of life) and reporting bias (parents more attuned to their children's maladies might be more likely to give paracetamol and report the current wheeze) could account for the findings. Furthermore, although many important potential confounders were included in multivariate analyses, confounding by underlying respiratory disease, differences in hygiene, and use of other antipyretics might also explain the findings.

In particular, neither aspirin use nor use of other non-steroidal anti-inflammatory drugs (NSAIDs) were reported. Although aspirin use was probably rare, other NSAIDs (eg, ibuprofen) are more widely used in children. Aspirin causes asthma exacerbations in a few patients with asthma;[4] however, effects of NSAIDs on cyclo-oxygenase and lipoxygenase pathways are highly variable between individuals (probably related to genotype[5–7]) and NSAIDs cause bronchodilation in some individuals.[8] In a cohort of adult women in which frequency of paracetamol use predicted a new diagnosis of asthma by the doctor, frequency of aspirin use was associated with a lower risk of asthma.[9] This finding is consistent with Varner's hypothesis that aspirin may protect against the development of asthma,[10] and has subsequently been confirmed in post-hoc analyses of large randomised trials of aspirin in men and women.[11,12] Although these findings for adult-onset asthma may or may not apply to children, they agree with the post-hoc analysis of the 4-week randomised trial of ibuprofen versus paracetamol for paediatric febrile illness,[13] which showed that outpatient visits for asthma were greater in the paracetamol group than the ibuprofen group.[14] Hence it remains unclear whether, on average, paracetamol might increase or NSAIDs might decrease asthma and asthma symptoms.

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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