

The acetaminophen and asthma hypothesis 10 years on: A case to answer

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It is now just over 10 years since the hypothesis was first proposed that acetaminophen might increase the risk of asthma and that the change from aspirin to acetaminophen use in the United States in the 1980s might have contributed to the increasing prevalence of childhood asthma during this period.¹ Since then, there has been evidence presented that the risk of asthma might be increased with exposure to acetaminophen in the intrauterine environment,²⁻⁸ infancy,^{2,9} later childhood,⁹ and adult life¹⁰⁻¹⁵ and that this risk might also extend to rhinoconjunctivitis and eczema. Furthermore, the patterns of acetaminophen use might explain to some extent the worldwide variations in the prevalence of asthma and related allergic conditions.⁹ It is important for allergists and clinical immunologists to be aware of this evidence and for randomized controlled trials to be undertaken to determine the nature of the associations between acetaminophen use and the development of asthma and its severity.

INTRAUTERINE EXPOSURE

There are now 6 studies that have reported that the use of acetaminophen in pregnancy is associated with an increased risk of childhood asthma.²⁻⁸ This association is present for persistent wheezing rather than transient infant wheezing, extends to asthma at the age of 7 years, and is observed with hospital admissions for asthma in childhood, suggesting an effect on both the occurrence and severity of asthma. The observation that the association between the frequent use of acetaminophen in pregnancy and wheeze in preschool children is restricted to nonasthmatic mothers⁶ indicates that this association cannot be due to mothers

with asthma using acetaminophen in preference to aspirin or other nonsteroidal anti-inflammatory drugs. In 3 studies^{2,7,8} data suggest that the effects might depend on the timing of prenatal exposure to acetaminophen; however, there are also data to suggest that the risk of childhood asthma might be present with acetaminophen use at any time during pregnancy.⁴

ACETAMINOPHEN USE IN INFANCY AND CHILDHOOD

The main evidence for an association between the use of acetaminophen in infancy and the risk of childhood asthma comes from the International Study of Asthma and Allergies in Childhood, which included data from 72 centers in 31 countries worldwide.⁹ After adjustment for potential confounding variables, the administration of acetaminophen to infants was associated with a 46% increased risk of current asthma symptoms at the age of 6 to 7 years. Similar increased risks were observed with rhinoconjunctivitis and eczema, suggesting that the association extends to these related allergic conditions. It was notable that the association was present in countries throughout the world with different patterns of childhood febrile illnesses and differences in medical practice and over-the-counter medication use. There were a number of potential biases relevant to the interpretation of these findings, including but not limited to confounding by indication.¹⁶⁻¹⁹ This can occur if paracetamol is given for lower respiratory tract infections, such as respiratory syncytial virus and rhinovirus, which are associated with an increased risk of asthma in later childhood.^{20,21} It is evident that the extent to which confounding by indication might have contributed to the association between acetaminophen and asthma in the International Study of Asthma and Allergies in Childhood is uncertain and that the presence of confounding does not exclude the possibility of a coexisting causal relationship.¹⁹

The International Study of Asthma and Allergies in Childhood also reported an association between acetaminophen use in the 6- to 7-year-old children and current symptoms of asthma, rhinoconjunctivitis, and eczema.⁹ Importantly, in the 6- to 7-year-old-children there was a dose-dependent increased risk of current asthma symptoms, with a 1.6- and 3.2-fold increased risk for moderate and high versus no use, respectively. There was also a dose-dependent increased risk of severe asthma, suggesting that acetaminophen use might influence both the occurrence and severity of asthma. It was considered that reverse causation was unlikely to explain the findings because there was also an association between acetaminophen use and eczema independent of asthma, with the symptoms and complications of eczema not typically associated with acetaminophen use.

The only randomized controlled trial investigating the effect of acetaminophen use for fever and asthma outcomes was

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TABLE I. Summary of the evidence linking paracetamol use and asthma based on Bradford Hill criteria of causation³⁴

Strength of effect	Increased asthma risk of up to 2.1 (paracetamol exposure <i>in utero</i>), ²⁻⁸ 1.5 to 3.2 (paracetamol use in infancy or childhood), ^{2,9} and up to 2.9 (paracetamol use in adults) ¹⁰⁻¹⁵
Dose response	Present for paracetamol exposure <i>in utero</i> , ^{2,3} in childhood, ⁹ and in adults ^{10,12-14}
Consistency/coherence	Consistency between different studies in different age groups in different populations worldwide ^{2-15,22}
Exposure before response	Observed in studies of paracetamol exposure in the intrauterine environment, ²⁻⁸ in infancy, ⁹ and in adult life ^{14,15}
Biologic plausibility	Through increased oxidant-induced inflammation and potentially enhanced T _H 2 response ²⁷⁻³¹
Removal of exposure prevents disease	Not yet examined
Specificity	No increased risk of asthma associated with aspirin or other nonsteroidal anti-inflammatory drugs ^{35,36}
Temporal association	International trends of increasing paracetamol use and increasing prevalence of asthma ^{1,25,26}
Analogy	Oxidant-induced airway inflammation in asthma (eg, ozone) ³⁷ ; protective effects of antioxidant diet in asthma ^{38,39}

Derived with modification from Beasley et al.¹⁹

undertaken in asthmatic children who were not known to be sensitive to nonsteroidal anti-inflammatory drugs.²² Compared with asthmatic children who received acetaminophen treatment for a febrile illness in the community, those who received ibuprofen had a reduced risk of an outpatient visit for asthma. The increased risk with acetaminophen was dose dependent and related to respiratory febrile illnesses rather than other causes of fever. It was not possible to determine whether the effect was due to an increased risk with acetaminophen or a reduced risk with ibuprofen, for which evidence of a protective effect exists.²³

ACETAMINOPHEN USE IN ADULTS

The initial evidence of an association between acetaminophen use and asthma in adults came from a United Kingdom-based case-control study.¹⁰ This study reported both a dose-dependent association between acetaminophen use and asthma and a progressively greater risk in those with more severe disease, with an 8-fold risk in those with severe asthma, suggesting once again an effect on both the causation and severity of disease. The association was present in both users and nonusers of aspirin and could not be attributed to aspirin avoidance by patients with asthma. These findings have now been extended with the Global Allergy and Asthma European Network case-control study in 12 centers in Europe,¹¹ in which weekly acetaminophen use was positively associated with asthma. Compared with less frequent use, there was a 2.9-fold increased risk, with no significant heterogeneity observed between the centers.

Complementing these studies are 2 population-based surveys from Ethiopia¹² and the United States¹³ in which dose-dependent associations between acetaminophen use and asthma were observed. The Ethiopian study reported similar associations with rhinitis and eczema, whereas the United States-based study also reported positive associations with chronic obstructive pulmonary disease and an inverse correlation with lung function. In both studies there was no evidence to suggest that the association could be attributed to aspirin avoidance or reverse causation. There are also 2 cohort studies from the United States¹⁴ and Denmark¹⁵ in which frequent acetaminophen use was positively associated with newly diagnosed (adult-onset) asthma over a 7- and 8-year period, respectively. These studies provide evidence that exposure to acetaminophen might precede the development of asthma, as has been observed with intrauterine exposure and use in infancy.

ECOLOGIC ASSOCIATIONS

At the population level, positive associations have also been reported between per capita consumption of acetaminophen and the prevalence of asthma in both children and adults.²⁴ The key finding of this analysis was the very high per capita use of acetaminophen in English-speaking countries, which had among the highest prevalence rates of asthma worldwide. This provides a possible reason for the previously unexplained higher prevalence of asthma and related allergic disorders in many English-speaking countries. Completing this epidemiologic evidence is the observation that the prevalence of asthma has increased worldwide over the last 40 to 50 years,²⁵ a trend that has occurred contemporaneously with the increasing use of acetaminophen, such that it is now probably the most commonly prescribed medicine in children.²⁶

POTENTIAL MECHANISMS

There are a number of potential mechanisms whereby the frequent use of acetaminophen might increase the risk of asthma and related allergic disorders and their severity.²⁷ First, acetaminophen might decrease the amount of reduced glutathione in the lung, thereby impairing respiratory antioxidant defenses.^{28,29} Reactive oxygen species might contribute to epithelial damage and mucus secretion, cause smooth muscle contraction and increase bronchial responsiveness, and impair β -adrenergic function, all effects that could potentially contribute to the pathogenesis of asthma.³⁰ Decreased glutathione levels might also cause a shift away from T_H1 to T_H2 cytokine production, thereby predisposing to atopic disorders, such as asthma.^{29,31} Acetaminophen might also influence COX-2 activity and the production of prostaglandin E₂.¹ Another potential mechanism for which there is conflicting evidence^{32,33} is that by suppressing fever, acetaminophen might reduce the predominant T_H1 cytokine storm that occurs as part of the febrile response.

SUMMARY

As summarized in Table I,^{2-15,19,22,25-31,34-39} there is evidence to suggest that acetaminophen use might be an important risk factor for the development of asthma and might have contributed to the increasing prevalence of asthma and allergic disorders over recent decades. Although further epidemiologic and laboratory-based studies will undoubtedly be informative, the priority is to undertake randomized controlled trials to explore the association of acetaminophen with both the development and maintenance of

asthma. Indeed, it is a concern that no randomized controlled trials have been undertaken of the long-term use of acetaminophen and the development of asthma and its severity. We propose that there is a case to answer and that such randomized controlled trials should now be a high priority for the research community. Only then will it be possible to determine the role of acetaminophen in the pathogenesis of asthma and related disorders and for evidence-based guidelines for the recommended use of acetaminophen to be made.

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