

## Acetaminophen Use May Increase Risk of Asthma, Though Definitive Studies Are Still Lacking

*Etminan M, Sadatsafavi M, Jafari S, et al. Acetaminophen use and the risk of asthma in children and adults. Chest 2009;136:1316–23.*

### Study Overview

**Objective.** To evaluate the relationship between use of acetaminophen and risk of asthma.

**Design.** Meta-analysis and systematic review.

**Setting and participants.** The investigators conducted a systematic review by searching EMBASE, MEDLINE (PubMed), and the Cochrane Central Register of Controlled Trials (RCTs), Database of Abstracts of Reviews of Effects, ACP Journal Club, International Pharmaceutical Index, BIOSIS, and Web of Science through October 2008. The language of publication was limited to English. Selection criteria included search terms such as “asthma” and “acetaminophen” as well as related terms such as “allergen,” “bronchial disease,” “hypersensitivity,” and trade names for acetaminophen.

**Methods.** The evaluators selected observational studies that reported clearly defined asthma and wheezing diagnosis and exposure to acetaminophen use. Two blinded reviewers scored each abstracted study for quality using a 3-point scale. The 2 evaluators independently selected and reviewed eligible studies and achieved agreement through discussion. The investigators weighted individual study odds ratios (OR) by the inverse of their variances. They used a random-effects model to estimate aggregate risk of wheezing and asthma among both children and adults associated with acetaminophen use. For studies that examined prenatal exposure to acetaminophen, they used a fixed effects model to estimate pooled OR for the exposure period. The authors also calculated the  $I^2$  statistic, which measures the percentage of total variation in the studies due to heterogeneity. In addition, they used metaregression to attempt to identify sources of heterogeneity and a regression model to look for publication bias.

**Main results.** The evaluators identified a total of 2599 relevant articles, and selected 19 studies that met inclusion criteria. These trials included 13 cross-sectional studies, 4 cohort studies, and 2 case-control studies comprising 425,140 participants. A total of 9 studies examined risk of asthma in

both children and adults, 6 studied wheezing in children, and 5 reported risk of wheezing in children after prenatal exposure. The pooled OR for asthma among participants using acetaminophen was 1.63 (95% confidence interval [CI], 1.46–1.77). The authors reported an increased risk of asthma in children who used acetaminophen in the year prior to asthma diagnosis and within the first year of life (OR, 1.60 [95% CI, 1.48–1.74] and OR, 1.47 [95% CI, 1.36–1.56], respectively). Only 1 study recorded the association between high acetaminophen dose and increased risk of asthma in children (OR, 3.23 [95% CI, 2.9–3.6]). The investigators also reported an elevated risk of asthma and wheezing associated with prenatal use of acetaminophen (OR, 1.28 [95% CI, 1.16–1.41] and OR, 1.50 [95% CI, 1.10–2.05], respectively). The authors noted higher levels of heterogeneity in the studies of wheezing in children ( $I^2 = 66\%–70\%$ ) compared with studies of asthma in adults ( $I^2 = 23\%–43\%$ ) and children ( $I^2 = 0\%–23\%$ ). An Egger regression did not suggest publication bias for asthma in adults ( $P = 0.08$ ) or wheezing in children ( $P = 0.90$ ). The metaregression analysis did not suggest heterogeneity due to differences in the quality score given by the authors to the studies ( $P = 0.07$ ).

**Conclusion.** This meta-analysis suggests that acetaminophen may be associated with an increased risk of asthma in both children and adults.

### Commentary

Global rates of asthma are increasing, especially in the developed world. Many theories exist to explain this observation including the popular hygiene hypothesis, which suggests that lower levels of microbial exposure in the developed world may be associated with altered activation of the immune system leading to allergic predisposition [1]. A more recent theory associates the increased use of acetaminophen for antipyretic and analgesic modalities with the rise in asthma.

This study sought to evaluate through meta-analysis techniques whether acetaminophen use is associated with increased rates of asthma and wheezing in children and adults. The authors found that acetaminophen use increased the odds of asthma by over 60% compared with non-users.

The odds of asthma were increased by 50% among acetaminophen users in the first year of life and in the year prior to asthma diagnosis. The authors also found that prenatal acetaminophen use increased risk of asthma and wheezing by 28% to 50%.

The meta-analysis was large and well-conducted. The authors included studies totaling over 400,000 patients from over 30 countries, and the consistent findings suggesting an association with both asthma and wheezing in children, adults, and with prenatal exposure are compelling. Though only 1 study reported high-dose acetaminophen exposure, there appears to be a dose-dependent risk gradient for asthma. Furthermore, plausible biological hypotheses exist to support their findings. Among the most likely are those related to the propensity of acetaminophen to reduce glutathione levels in the lung tissue. Decreased glutathione may impair respiratory antioxidant defenses, thereby contributing to oxidative damage from reactive oxygen species [2]. It may also shift cytokine production away from  $T_H1$  toward  $T_H2$ , causing a concomitant increase in risk of atopy [2]. Finally, acetaminophen use has increased especially among children due to decreases in aspirin use caused by concerns about the development of Reye syndrome and aspirin-sensitive asthma/atopy. However, some researchers note that aspirin inhibits COX-2, thereby decreasing prostaglandin E2 (PGE2), a potent initiator of the  $T_H2$  cascade; thus, increasing use of the acetaminophen (no COX-2 activity) broadly across the population may be associated with higher levels of PGE2, especially among children [3].

A number of key limitations deserve mention. First, all of the studies in this review are observational, including a majority that are cross-sectional. The authors were unable to find any randomized controlled trials in this area. Thus, a number of important sources of bias could exist. Among these, confounding bias is most problematic. Confounding by indication may be a particular problem, in which children with more frequent or severe asthma may be more predisposed to receive acetaminophen for viral infections, fevers, or pain that may precede or be associated with the asthma diagnosis. Thus, it might appear that acetaminophen is on the causal pathway to disease even if it is simply a marker for treatment of early manifestations or true causes of the disease. This problem is particularly acute when the outcomes like wheezing are nonspecific. Whether this confounding bias is present in large enough form to influence the results of these observational studies is difficult to judge. However, it certainly points to the need for randomized controlled trials in this field. Second, high degrees of heterogeneity existed among some of the studies. In particular, those

that analyzed wheezing outcomes in children were quite heterogeneous, again because wheezing is such a broad diagnostic category. Third, a paucity of data existed regarding control variables used in the different studies to account for potential confounding. We lack detail from the authors regarding whether their quality scores adequately accounted for this issue. Finally, new data continue to emerge in this active field. A recent prospective study published after this meta-analysis looked at 1505 pregnant women and their children until 6 years of age; the authors found no relationship between prenatal acetaminophen use and asthma risk in the children (OR, 0.76 [95% CI, 0.53 to 1.10]) and no evidence of a dose-response curve [4]. Whether this study and other future reports would change the findings of the meta-analysis is an open question, but at least seems to point to the fact that this is an active field of research in need of more investigation.

### **Applications for Clinical Practice**

A large meta-analysis of observational studies conducted across the world suggests a possible association between acetaminophen use and increased risk of asthma. While plausible biological hypotheses exist to support this link, the lack of randomized controlled trials and heterogeneity of some of the studies should promote caution in interpreting the findings given the possibility of confounding by indication. For now, clinicians should be aware of the emerging, but not yet definitive, evidence supporting this association. They should follow the literature on this important topic over the next few years to see if more high quality evidence emerges to support this study and change clinical practice, especially since the alternatives to acetaminophen each have their own already well-established risks and side effects.

—Review by Asaf Bitton, MD

### **References**

1. von Mutius E. Allergies, infections, and the hygiene hypothesis—the epidemiological evidence. *Immunobiology* 2007;212:433–9.
2. Farquhar H, Crane J, Mitchell E, et al. The acetaminophen and asthma hypothesis 10 years on: a case to answer. *J Allergy Clin Immunol* 2009;124:649–51.
3. Varner AE, Busse WW, Lemanske RF Jr. Hypothesis: decreased use of pediatric aspirin has contributed to the increasing prevalence of childhood asthma. *Ann Allergy Asthma Immunol* 1998;81:347–51.
4. Kang EM, Lundsberg LS, Illuzzi JL, Bracken MB. Prenatal exposure to acetaminophen and asthma in children. *Obstet Gynecol* 2009;114:1295–306.