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## IN THEORY

## Studies Suggest an Acetaminophen-Asthma Link

By CHRISTIE ASCHWANDEN  
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## THE HYPOTHESIS



*Acetaminophen increases the risk of childhood [asthma](#).*

## THE INVESTIGATOR

*Dr. John T. McBride, Akron*

*Children's Hospital.*

The sharp worldwide increase in childhood asthma over the past 30 years has long perplexed researchers, who have considered explanations as varied as improved hygiene and immunizations. Over the last decade, however, a new idea has emerged.

The asthma epidemic accelerated in the 1980s, some researchers have noted, about the same time that aspirin was linked to Reye's syndrome in children. Doctors stopped giving aspirin to children with fevers, opting instead for acetaminophen. In a paper published in *The Annals of Allergy and Asthma Immunology* in 1998, Dr. Arthur Varner, then a fellow in the immunology training program at the University of Wisconsin School of Medicine, argued that [the switch to acetaminophen might have fueled the increase in asthma](#).

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Since then, more than 20 studies have produced results in support of his theory, including a large analysis of data on more than 200,000 children that found an increased risk of asthma among children who had taken acetaminophen. In November, Dr. John T. McBride, a pediatrician at Akron Children's Hospital in Ohio, published a paper in the journal *Pediatrics* arguing that [the evidence for a link between acetaminophen and asthma is now strong](#) enough for doctors to recommend that infants and children who have asthma (or are at risk for the disease) avoid acetaminophen.

Dr. McBride based his assertion on several lines of evidence. In addition to the timing of the asthma epidemic, he said, there is now a plausible explanation for how acetaminophen might provoke or worsen asthma, a chronic inflammatory condition of the lungs. Even a single dose of acetaminophen can reduce the body's levels of glutathione, a peptide that helps repair oxidative damage that can drive inflammation

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in the airways, researchers have found.

“Almost every study that’s looked for it has found a dose-response relationship between acetaminophen use and asthma,” Dr. McBride said. “The association is incredibly consistent across age, geography and culture.”

A statistical link between acetaminophen and asthma has turned up in studies of infants, children and adults. Studies have also found an increased risk of asthma in children whose mothers who took acetaminophen during [pregnancy](#).

For instance, a study published in The Lancet in 2008 examined information collected on more than 205,000 children from 31 countries as part of the International Study of Asthma and [Allergies](#) in Childhood, known as the Isaac study. The 2008 analysis found that [children who had taken acetaminophen for a fever during the first year of life had a 50 percent greater risk of developing asthma symptoms](#), compared with children who had not taken the drug. The risk rose with increasing use — children who had taken acetaminophen at least once a month had a threefold increase in the risk of asthma symptoms.

A study published by British researchers in 2000 using data from the Isaac study found that the prevalence of asthma increased in lock step with sales of acetaminophen in the 36 countries examined. The more acetaminophen used in a country, the greater that country’s prevalence of asthma.

A meta-analysis published in 2009 calculated that children who had [taken acetaminophen in the past year had nearly double the risk of wheezing](#) compared with those who had not taken the drug. “We know that acetaminophen can cause increased bronchial constriction and wheezing,” said Mahyar Etminan, a pharmacoepidemiologist at the University of British Columbia and lead author of the study.

Still, Dr. Etminan believes it is not yet clear that acetaminophen itself is responsible for the increasing prevalence of asthma. “Children who take acetaminophen are usually getting it for fever control, and they get fevers because they have viral infections, which on their own are associated with developing asthma later in life,” Dr. Etminan said. “It’s hard to tease out whether it’s the drug or the viral infection.”

Another potential problem, Mr. Etminan said, is that many of the studies required parents to accurately recall how much acetaminophen they gave their children, and how often. Parents whose children have asthma are likely to scrutinize the events that preceded an attack, he said, and thus may be more likely than other parents to recall giving their children the drug.

So far, only one randomized controlled trial has investigated the link. Researchers at Boston University School of Medicine randomly assigned 1,879 children with asthma to take either acetaminophen or ibuprofen if they developed a fever. The results, published in 2002, showed that [children who took acetaminophen to treat a fever were more than twice as likely to seek a doctor’s care later for asthma symptoms](#) as those who took ibuprofen.

Other trials are in the works. Dr. Richard Beasley, a professor of medicine at the Medical Research Institute of New Zealand, is just completing a 12-week randomized controlled trial of acetaminophen to see if the drug provokes or worsens asthma in adults. The results of that trial will be completed next year. Dr. Beasley said the highest priority now should be rigorous trials to test whether acetaminophen use in infancy increases the risk of developing asthma.

“I cannot say with 100 percent certainty that acetaminophen makes asthma worse, but I can say that if I had a child with asthma, I would give him or her ibuprofen for the time being,” Dr. McBride said. “I think the burden of proof is now to show that it’s safe.”











Not all experts agree. “At this time I just don’t feel you can recommend one over the other,” said Dr. Stanley Szeffler, head of pediatric clinical pharmacology at National



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Jewish Health in Denver. "They both have advantages and disadvantages."

Aspirin and other nonsteroidal anti-inflammatory drugs, including ibuprofen, are known to provoke asthma attacks in some people, Dr. Beasley noted. He suggested a middle course for parents: Simply use acetaminophen (also known as paracetamol) more sparingly. "We should be reserving paracetamol for very high fevers or for major pain relief," he said. "We know that paracetamol is used much more widely than that — when a child is a bit irritable or teething or having an [immunization](#)."

Acetaminophen has been shown to reduce the antibody response to immunizations, so the drug should not be given to children in advance of a vaccination, Dr. Beasley also noted.

Dr. Szeffler and his colleagues are working on a study looking at early interventions for asthma that will also track asthma patterns in children who take either acetaminophen or ibuprofen for fevers. The data will not answer all the questions, Dr. Szeffler said, but they should provide more guidance for parents and pediatricians.

Dr. McBride, for one, is not waiting for results. "If studies prove that acetaminophen makes asthma worse," he said, "I can't imagine telling my patients that I knew about this five years ago, but I wasn't sure so I didn't mention it."

*This article has been revised to reflect the following correction:*

**Correction: December 22, 2011**

An article on Tuesday about studies linking childhood asthma to use of acetaminophen, using information provided by a researcher, described glutathione, a compound in the body that helps repair oxidative damage, incorrectly. It is a peptide, not an enzyme.

A version of this article appeared in print on December 20, 2011, on page D5 of the New York edition with the headline: Studies Suggest an Acetaminophen-Asthma Link.

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