

### Frequent acetaminophen use and allergic diseases: Is the association clear?

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The reasons for the increase in asthma, as well as other allergic and respiratory diseases, over the last decades are not completely understood. However, during the last 6 years, there have been a number of studies indicating that regular use of acetaminophen (INN: paracetamol) does indeed carry a dose-dependent risk of allergy development in general and asthma development in particular, as well as worsening of other respiratory diseases and lung function (Table I).<sup>1-8</sup>

Three mechanisms have been suggested as an explanation for the increased morbidity caused by regular acetaminophen use.<sup>1,2</sup> Oxidative stress appears to play an important role in the development and progression of respiratory diseases. Glutathione, an endogenous antioxidant, is found in the respiratory tract lining fluid, of which 95% is present in the reduced form as an antioxidant,<sup>9</sup> and evidence suggests that decreased glutathione levels are associated with oxidant damage in the lung.<sup>10,11</sup> Furthermore, glutathione plays a role in drug detoxification, particularly in the metabolism of acetaminophen.<sup>12</sup> High doses of acetaminophen reduce levels of glutathione in the lung tissue of animals.<sup>13</sup> Therefore regular users of acetaminophen might, through depletion of glutathione, be at increased risk of lung tissue damage and ultimately of respiratory disease.

COX-2 activity and an increase of prostaglandin E<sub>2</sub> production might be stimulated by way of acetaminophen promoting T2 allergic pathways.<sup>14</sup>

The least data are available for the theory that suggests an IgE-mediated mechanism with acetaminophen as the antigenic agent.<sup>15,16</sup>

In 2000, Shaheen et al<sup>3</sup> were the first to report a correlation between the use of acetaminophen and asthma in a case-control study of asthma in adults. The adjusted

#### Abbreviation used

OR: Odds ratio

odds ratio (OR) for daily users of acetaminophen compared with those who never used the drug was 2.4 (95% CI, 1.2-4.6).

In an analysis of the Nurses' Health Study published by Barr et al<sup>4</sup> in 2004, 346 participants reported a new physician diagnosis of asthma. Increasing frequency of acetaminophen use was positively associated with newly diagnosed asthma (*P* for trend = .006). The multivariate rate ratio for asthma for participants who received acetaminophen for more than 14 days per month was 1.63 (95% CI, 1.11-2.39) compared with nonusers.

Using the population-based Avon Longitudinal Study of Parents and Children, Shaheen et al<sup>5</sup> determined associations of acetaminophen and aspirin use in late pregnancy (20-32 weeks) with asthma, hay fever, eczema (*n* = 8511), and wheezing (8381) in the offspring at 69 to 81 months and with atopy (*n* = 6527) and blood total IgE levels (*n* = 5148) at 7 years. Use of acetaminophen, but not aspirin, in late pregnancy was positively associated with asthma when comparing children whose mothers took acetaminophen "sometimes" and "most days/daily" with those whose mothers never took it (OR, 1.22 [95% CI, 1.06-1.41] and 1.62 [95% CI, 0.86-3.04], respectively [*P* for trend = .0037]; wheezing OR, 1.20 [95% CI, 1.02-1.40] and 1.86 [95% CI, 0.98-3.55], respectively [*P* for trend = .011]; total IgE level geometric mean ratio, 1.14 [95% CI, 1.03-1.26] and 1.52 [95% CI, 0.98-2.38], respectively [*P* for trend = .0034]). There was no association for hay fever, eczema, or skin test positivity. The proportion of asthma attributable to acetaminophen use in late pregnancy, assuming a causal relationship, was 7%.

McKeever et al<sup>1</sup> published a study in 2005 analyzing the third National Health and Nutrition Examination Survey data.<sup>17</sup> They could show that even taking into account smoking, the risk of reporting chronic obstructive pulmonary disease was significantly increased in persons using acetaminophen at least daily compared with those never using the drug (adjusted OR, 1.72; 95% CI, 1.36-2.18). No such trend could be shown for aspirin or ibuprofen use. The same was true for asthma (adjusted OR, 1.75; 95% CI, 1.34-2.28).

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**TABLE I.** Studies investigating the association between acetaminophen use and respiratory diseases (modified and updated from Eneli et al<sup>2</sup>)

| Author and year of publication    | Study type                                                                                | Study objective                                                                                                                                      | Population                                                                                                                | Results                                                                                                                                                                                                                                                                                                     |
|-----------------------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Newson et al, <sup>7</sup> 2000   | Ecologic                                                                                  | Examine the rate of asthma and aggregate consumption of acetaminophen in 1994-1995                                                                   | English-speaking countries in the ECRHS study                                                                             | Prevalence of wheeze increased by 0.52% for 13- to 14-year-olds and by 0.26% for young adults for each gram increase in per capita acetaminophen sales                                                                                                                                                      |
| Shaheen et al, <sup>3</sup> 2000  | Case-control                                                                              | Determine whether frequent acetaminophen use is a risk factor for asthma                                                                             | Adults aged 16-51 y in South London; patients, n = 720 (51% response rate); control subjects, n = 980 (49% response rate) | Never users: OR, 1.06 (95% CI, 0.77-1.45); monthly users: OR, 1.22 (95% CI, 0.87-1.72); weekly users: OR, 1.79 (95% CI, 1.21-2.65); daily users: OR, 2.38 (95% CI, 1.22-4.64); <i>P</i> value for trend = .0002                                                                                             |
| Shaheen et al, <sup>8</sup> 2002  | Prospective cohort                                                                        | Examine the relationship between prenatal acetaminophen use and wheezing in offspring at 6 mo                                                        | 9400 women                                                                                                                | Frequent acetaminophen use over 20-32 wk prenatally; increased risk for wheezing before 6 mo (OR, 2.34; 95% CI, 1.24-4.40)                                                                                                                                                                                  |
| Barr et al, <sup>4</sup> 2004     | Analysis using the Nurses' Health Study                                                   | Examine the relationship between acetaminophen use and new-onset asthma                                                                              | 73,321 female nurses in the United States aged 44-69 y                                                                    | Increased risk of diagnosis of new-onset asthma with frequency of use ( <i>P</i> value for trend = .006; adjusted RR, 1.63; 95% CI, 1.11-2.39)                                                                                                                                                              |
| Shaheen et al, <sup>5</sup> 2005  | Avon Longitudinal Study of Parents and Children                                           | Examine the relationship between acetaminophen use in late pregnancy and asthma, wheezing, and other atopic outcomes in the child at school age      | Mothers of 8511 children and their offspring                                                                              | Positive association with asthma comparing children whose mothers took acetaminophen with "neveruser" mothers: asthma OR, 1.22 (95% CI, 1.06-1.41) and 1.62 (95% CI, 0.86-3.04), <i>P</i> for trend = .0037; wheezing OR, 1.20 (95% CI, 1.02-1.40) and 1.86 (95% CI, 0.98-3.55), <i>P</i> for trend = .011) |
| McKeever et al, <sup>1</sup> 2005 | Cross-sectional analysis using the Third National Health and Nutrition Examination Survey | Investigate the associations between use of pain medication, asthma, COPD, and FEV <sub>1</sub> in adults                                            | 6303 male and 7189 female subjects aged 20-80 y (mean, 44.9 y)                                                            | Dose-response association of acetaminophen use and asthma (adjusted OR, 1.20; 95% CI, 1.12-1.28; <i>P</i> for trend = .001); dose-dependent association with COPD (adjusted OR for increasing category of intake, 1.16; 95% CI, 1.09-1.24; <i>P</i> for trend = .001)                                       |
| Davey et al, <sup>6</sup> 2005    | Cross-sectional survey                                                                    | Determine the relationship between acetaminophen use and asthma and explore potential biases in acetaminophen use in a developing country population | 7649 adults and children from Butajira, Ethiopia                                                                          | Allergic symptoms increased significantly with frequency of acetaminophen use, with ORs in those using >3 tablets in the past month relative to none being 1.89 (95% CI, 1.51-2.36) for wheeze, 2.14 (95% CI, 1.72-2.67) for nocturnal shortness of breath, and 2.52 (95% CI, 1.99-3.20) for rhinitis       |

ECRHS, European Community Respiratory Health Survey; COPD, chronic obstructive pulmonary disease; RR, relative risk.

The article by Davey et al<sup>6</sup> published in this issue of the Journal adds an important facet to the growing number of reports that point toward a dose-response relationship between use of acetaminophen and the development of allergic and respiratory diseases. Because most studies were conducted in economically developed countries, the authors assumed that there might be biases arising from the medical contraindication to use of aspirin or other nonsteroidal anti-inflammatory drugs in asthma. They also argue that reverse causation, such as treatment of headache caused by asthma therapy, is much less likely to have a strong influence in developing countries, where awareness of the adverse effects of aspirin and use of medication to treat asthma are both relatively low. Their hypothesis was that acetaminophen use is associated with an increased risk of allergic symptoms and sensitization in a cross-sectional survey of children and adults in Ethiopia.

The prevalence of all outcomes rose in relation to increasing category of acetaminophen use, with the exception of cockroach sensitization, which was increased in the highest dose category only. After adjustment for age, sex, area of residence, presence of any parasite, smoking status, and educational level, statistically significant dose-response relationships were seen for wheeze, shortness of breath at night, eczema, and rhinitis ( $P$  for trend < .001). ORs for more than 3 tablets in the past month compared with none ranged from 1.89 for wheeze to 2.52 for rhinitis. The adjusted odds of cockroach sensitization was also significantly increased in those consuming more than 3 tablets of acetaminophen a month relative to none by a ratio of 1.40 (95% CI, 1.10-1.79), but there was no significant adjusted association between acetaminophen use and either self-reported asthma or dust mite sensitization. Restriction of analysis to persons without self-reported asthma resulted in similar or slightly stronger associations with acetaminophen use (adjusted ORs for more than 3 tablets compared with none = 1.88 [95% CI, 1.47-2.40] for wheeze, 2.25 [95% CI, 1.78-2.86] for shortness of breath, 1.93 [95% CI, 1.37-2.70] for eczema, 2.81 [95% CI, 2.16-3.67] for rhinitis, and 1.38 [95% CI, 1.07-1.79] for cockroach sensitization).

The study results are consistent with previous research demonstrating a positive association between acetaminophen use and the prevalence of respiratory diseases. It shows statistically significant dose-response associations between acetaminophen use and a range of allergic symptoms and sensitization in a population of a developing country. The results are similar to those reported in populations from developed countries, making it probable that these associations reflect an influence on the cause of allergic disease.

To follow up on these findings, it might be of interest to look at the situation in the former East Germany. It has been well established that after the fall of the Berlin Wall and reunification (1989-1990), the rates of allergic diseases that before were much lower than in West Germany are now approaching or have already reached Western levels.<sup>18</sup> Acetaminophen was only available in suppositories for children, and the list of available drugs published

in 1988<sup>19</sup> mentions that an introduction of acetaminophen was expected for the fourth quarter of 1988, indicating that a wide availability of the drug did not exist before at least the beginning of 1989. An analysis of medication use in the former East German states after 1988 could look at the use of acetaminophen and might give an indication whether there might be an additional explanation for the increase in allergic diseases in those regions.

Eneli et al<sup>2</sup> argue that physicians need to be cognizant of analgesia intolerance in some asthmatic patients but that it is premature to recommend any change in current analgesic-prescribing patterns for adults and children with asthma.

However, the most important question raised by the research discussed in this editorial is whether the data accumulated over the last 6 years warrant a warning to the general public that daily use of acetaminophen might lead to an increase in the personal risk of allergic diseases, including asthma, as well as other respiratory diseases.

The data from the Third National Health and Nutrition Examination Survey analysis<sup>1,17</sup> and the results derived from the Nurses' Health Study,<sup>4</sup> as well as the data of Davey et al,<sup>6</sup> seem to be sufficient to justify giving a word of caution to the huge number of persons who use acetaminophen as over-the-counter medication regularly without a physician's advice. Furthermore, data from Shaheen et al<sup>5</sup> suggest that acetaminophen exposure in late gestation might cause asthma, wheezing, and increased IgE levels in children of school age.

The pathologic mechanisms that lead to the increases in allergic and respiratory diseases when ingesting acetaminophen regularly need to be better understood, and it is presently uncertain how sensitization through the suggested acetaminophen-directed IgE-mediated mechanism might occur.

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