

Acetaminophen and Asthma

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The article by Perzanowski *et al* in this issue of *Thorax* (see page 118) adds one more piece of evidence supporting a possible role for acetaminophen in the development of asthma in children.¹ Five previous studies, including three prenatal prospective cohorts,^{2–5} have suggested that in utero ingestion of acetaminophen may increase the risk of asthma and respiratory symptoms in children.^{2–7} Increased risk of asthma from postnatal use of acetaminophen is also suggested by reports of children^{8–12} and adults.^{8 13–17} The possibility that acetaminophen may contribute to the development of asthma is supported by parallel time trends in dramatic increases in use of the medication in response to reports of associations of aspirin use with Reye syndrome^{18–20} and increases in asthma prevalence between the mid 1970s and mid 1990s.²¹

There is also biological plausibility. Acetaminophen,^{22–24} as well as one of its metabolites, the highly reactive *N*-acetyl-*p*-benzoquinoneimine,²⁵ has been associated with decreased glutathione. There is substantial literature documenting the antioxidant capacity of glutathione²⁵ as well as the role of reactive oxygen species in asthma morbidity.²⁶ In addition, decreased glutathione may affect the development of asthma by altering antigen recognition towards favouring T helper 2 (Th2) over Th1 cytokines.^{25 27} Other, less likely, possibilities relate to decreased suppression of cyclo-oxygenase or direct antigenicity of acetaminophen.²³

The study by Perzanowski *et al* notes that associations of prenatal acetaminophen use with asthma are present only in those with the minor allele variant (Ile/Val or Val/Val) in the glutathione *S*-transferase P1 gene (GSTP1).¹ There is an increasing body of literature suggesting that GST alleles may modulate environmental effects on asthma through altered ability to detoxify compounds.²⁸ Three genotypes that have been explored in some detail are GSTM1, GSTT1 and GSTP1. Null variants of GSTM1 and GSTT1 and the minor alleles of GSTP1 (with valine at amino acid

position 105) have shown protective effects in some^{29–32} but not all^{33–35} studies. GSTP1 is more prevalent in the lung than other GSTs and catalyses conjugation of glutathione to secondary oxidation products.^{25 33} Gilliland noted that children with the GSTM1 null variant and GSTP1 Val105 had slower lung growth²⁹ but that children homozygous for the GSTP1 Val105 variant, rather than being at increased risk, were at lower risk of respiratory illness.³⁴ Similarly, in another report, Gilliland noted that adults exposed to GSTP1 Val105 alleles were at lower risk of allergic response to second-hand tobacco smoke.³⁵ In addition to the current study there are two other large prospective birth cohorts showing increased effects of air pollution on atopy³¹ and persistent wheeze³² in children with the GSTP1 Val105 alleles. Others have shown associations of this allele with severity of disease.³⁶ Romieu and her group have a series of reports from a trial in Mexico in which effects of ozone exposure on lung function and inflammatory responses were modified by antioxidant supplementation and the presence of the GSTM1 null allele.^{30 37–39} The fact that findings are more consistent for modulation of environmental exposures than for direct effects of GST alleles suggests that the genetic variations are operative through detoxification of specific contaminants.

The growing literature relating acetaminophen with respiratory conditions must be viewed with some caution. There is always the risk of confounding by conditions leading to the use of the medication. Although Perzanowski's study did not examine indications of use, the investigators did look at antibiotic use and did not find an association with acetaminophen; nor did they find that antibiotic use confounded the results.¹ Similarly, the fact that pain was the main reason for acetaminophen use in the Danish study and that adjustment for indication of use did not affect the results suggests that the findings are not the indirect result of infections.⁵ In addition, although use of aspirin and other non-steroidal inflammatory medicine in these studies was low, in larger cohorts with sufficient numbers of participants similar effects were not seen with the other analgesics,⁵ and a randomised trial in children with asthma found significantly lower risk of outpatient visits for asthma in those randomised to ibuprofen versus acetaminophen.⁹

The lack of consistency among studies regarding timing of use in pregnancy has implications for biological plausibility. The current study found similar associations throughout pregnancy that were not significant in the first trimester.¹ Two of the three previous prospective cohorts noted stronger effects towards the end of the pregnancy,^{2–4} while the large Danish cohort noted stronger effects with use earlier in gestation.⁵ It has been suggested that the fetal liver is not able to metabolise acetaminophen early in pregnancy to *N*-acetyl-*p*-benzoquinoneimine.^{2–4 40} Effects from use in the first trimester would therefore imply other mechanisms related to GSTP1 genotypes.

Loss to follow-up and the fact that the relationships reached significance only in year 5 in this study is of some concern. In other cohorts the effects were seen at younger ages.^{2–5} The follow-up of this cohort is <69% suggested—301 of the original 714—and there could be biases inherent in the drop-out rate. Reassuring is the fact that there were no differences in reported acetaminophen use in those who did and did not remain in the study. The authors indicate, however, that follow-up was greater among Hispanics—there could have been other factors related to acetaminophen use, follow-up and diagnosis of asthma, such as differential prenatal and postnatal care, that could have affected the results.

Imprecise measures of dose and frequency could also account for some of the differences among studies. The study of Perzanowski *et al* found a significant dose response with days of use. Increased frequency had stronger associations in one,^{2 3} but not another, study,⁵ in which frequency of use was available. Data on medication use in all these studies, however, were not obtained by diaries and do not allow careful quantification of use. The lack of precision, however, should bias towards the null hypothesis, and, while contributing to differences among studies, could not account for the general consistency in overall results.

As is often the case, this paper in the context of emerging literature raises as many questions as it answers. If the effects seen are related to modulation of antioxidant defences can they be reversed, as shown by Romieu's group, with adequate nutrition? Are we comfortable changing our current recommendations of use of

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anti-inflammatory medication? It was estimated that in 2004, 65% of women took acetaminophen in pregnancy, with 18% taking ibuprofen and 4% taking aspirin.²⁰ A shift from acetaminophen to ibuprofen might have other associated risks.^{41–42} Can we justify a randomised controlled trial of acetaminophen versus other anti-inflammatories with and without antioxidant supplementation? Would a safer course perhaps be increased efforts at pollution control and continued recommendations to limit all medication in pregnancy? Finally, it is important to continue research in the area with animal models and more precise measures of the amount and timing of exposure, possible confounding associated symptoms, and benefit versus risk assessments of alternative approaches.

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