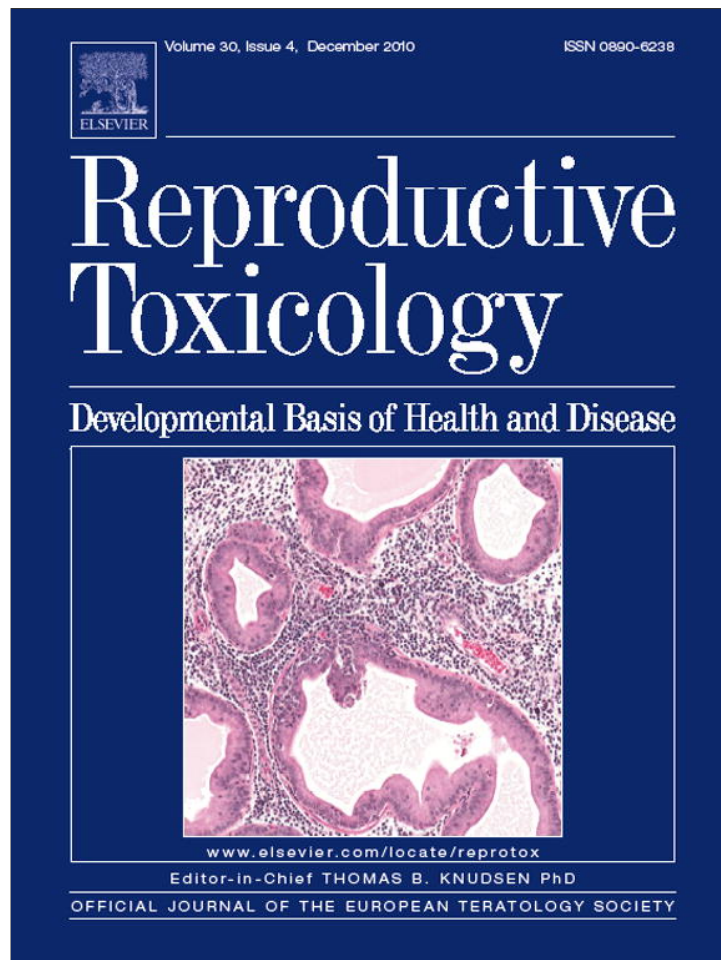


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## Review

# Childhood asthma and use during pregnancy of acetaminophen. A critical review

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## ABSTRACT

The possible association between acetaminophen use during pregnancy and childhood asthma has been a subject of interest based on the theory that acetaminophen metabolism may deplete glutathione in the developing lung, leading to oxidative damage and inflammation. Epidemiology studies from eight centers have reported conflicting results. In some cases, end points of these studies have included wheezing in very young children, which is a poor predictor of asthma. Other study problems have included the common use of acetaminophen as the analgesic and antipyretic of choice during pregnancy. Because acetaminophen use may be a marker for infectious or inflammatory disorders, the results of the epidemiology studies may be influenced by confounding by indication. A placebo-controlled randomized trial of acetaminophen use during pregnancy would be helpful in resolving the question of whether acetaminophen use causes childhood asthma. At present, the evidence is inconclusive that any such association is causal.

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## 1. Introduction

The possible relationship between maternal use of acetaminophen during pregnancy and wheezing or asthma in the offspring was first suggested by a group in the United Kingdom in 2002 [1]. Since that time, seven additional studies have appeared from Europe, Asia, and the United States, all but one of which conclude that there is such an association and that it may be causal.

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Acetaminophen is considered the analgesic and antipyretic of choice for use during pregnancy, and acetaminophen use by pregnant women is common. Wheezing in childhood is also common. Asthma is a complex disease that is difficult to diagnose before age 6 years. Most infants who wheeze have transient conditions and have no increased risk of asthma or allergies later in life [2]. Wheezing before age 1 is not a good predictor of wheezing at six years. A diagnosis of asthma occurred in 22.5% of children with late onset wheezing and 46.0% of those with persistent wheezing through 6 years [2]. Early wheezing and wheezing at age 6 years or later should be considered separately, and wheezing per se does not imply a diagnosis of asthma.

Because acetaminophen use during pregnancy and childhood wheezing are so common and because both are associated with many other factors, including febrile illness, the possibility of a causal association between acetaminophen use during pregnancy and childhood wheezing or asthma has not been easy to investigate. The objective of this paper is to review the available prenatal and childhood clinical studies to determine whether valid conclusions are possible in light of difficulties in trial design, potential confounders, and conflicting results. Before turning to the studies that have evaluated the association, we will discuss the theoretical basis for supposing that acetaminophen might cause asthma and the potential confounders that may be involved in studies of exposures during pregnancy and childhood asthma.

## 2. Proposed mechanism of action

It has been proposed that acetaminophen may cause asthma by producing oxidative injury in the respiratory epithelium. Acetaminophen is biotransformed to *N*-acetyl-*p*-benzoquinone imine (NAPQI), a reactive intermediate that is detoxified by binding to glutathione (GSH) [3]. The consumption of GSH more rapidly than it can be regenerated decreases one of the body's antioxidant defenses and might permit more oxidative injury. There are four studies cited to support this proposed mechanism.

A mouse study found lung glutathione to be transiently reduced after intraperitoneal administration of acetaminophen 300 mg/kg and to show a more sustained reduction after injection of 375 mg/kg [4]. Blood levels of acetaminophen were not reported, but these doses of acetaminophen are more than 20 times the human therapeutic dose on a weight basis. In a rat study, an oral dose of 3000 mg/kg was associated with a transient 50% reduction in lung GSH [5]. Blood levels were not reported, but peak lung GSH was reported to be 92  $\mu\text{g/g}$  tissue. For comparison, typical human therapeutic blood concentrations of acetaminophen are less than 10  $\mu\text{g/g}$  (10  $\mu\text{g/mL}$ ).

An in vitro study used pulmonary macrophages and type II pneumocytes isolated from human lung obtained at lobectomy or pneumonectomy for lung cancer [6]. Incubation of pulmonary macrophages with 0.05 mM (7.55  $\mu\text{g/mL}$ ) acetaminophen resulted in about a 25% reduction in intracellular GSH after 4 h. Incubation of type II pneumocytes with 0.1 mM (15.1  $\mu\text{g/mL}$ ) acetaminophen resulted in about a 20% reduction in intracellular GSH. It is not clear to what extent the history of smoking in these patients may have influenced the GSH response to acetaminophen exposure. The magnitude of the alterations reported in this study in GSH concentration are comparable to the diurnal variations seen in plasma GSH concentrations [7].

A human study was performed in nine healthy men and six healthy women who were not on any medications except oral contraceptives [8]. Smoking status of the subjects was not discussed. Acetaminophen 1000 mg was given by mouth after which blood was sampled hourly for four hours. Subjects were then given acetaminophen 1000 mg by mouth four times daily.

They returned for hourly blood sampling after the final dose. Serum acetaminophen peaked one hour after a single dose at a mean  $\pm$  standard error concentration of  $5.25 \pm 0.70 \mu\text{g/mL}$ . After 14 days of treatment, the serum acetaminophen peak was  $7.14 \pm 0.66 \mu\text{g/mL}$ . Serum total antioxidant capacity, measured using a chemiluminescence assay, decreased by about 8% after the single dose of acetaminophen. Prior to the last dose on day 14, the baseline antioxidant capacity had decreased about 12% from the value prior to the first dose and it decreased an additional 14% three hours after the last dose was taken. There was a net 25% decrease in serum antioxidant capacity comparing the nadir after the last dose on the 14th day compared to the level prior to acetaminophen having been administered on the first day.

## 3. Potential confounders

A confounder is a variable that is related to both the exposure and the outcome, but not as an intermediary on the causal pathway. Confounding may explain an apparent association between the exposure and outcome. Respiratory illness in the pregnant woman, for example, could confound an apparent association between acetaminophen use during pregnancy and asthma in the offspring if respiratory illness prompted maternal acetaminophen use and independently increased the incidence of childhood asthma. In fact, maternal respiratory illness during the pregnancy has been shown to be associated with childhood asthma (odds ratio 1.91, 95% confidence interval 1.14–3.22), although adjustment for maternal smoking was incomplete [9].

Other potential confounders of an association between acetaminophen use during pregnancy and childhood asthma are maternal fever, influenza and other maternal infections, antibiotic use, depression, and chorioamnionitis [10–14]. The risk with chorioamnionitis is above that of prematurity, which is itself a risk factor for childhood asthma. The epidemiology studies reviewed here evaluated possible confounding to different extents. Not all the factors that were adjusted in these studies would meet the criterion of being associated with both the exposure and the outcome.

## 4. Studies of acetaminophen use during pregnancy (Table 1)

### 4.1. The Avon Longitudinal Study of Parents and Children

Pregnant women in the former county of Avon, UK, were given a questionnaire at 18–20 weeks and again at 32 weeks on which information was solicited on the use of acetaminophen and aspirin [1]. There were almost 14,062 live births in the study of which 13,988 survived to one year of age. When their infants were six months old, mothers were asked whether acetaminophen had been given to the child and whether the child had wheezing or whistling in the chest. Mothers were asked about wheezing or whistling in the chest of their child every 12 months until 42 months of age. Women were also asked at 30 months about symptoms of eczema in the child. Complete data were available for 9400 children.

The outcome of interest was asthma symptoms at 30–42 months of age. Potential confounders included in the analysis were sex of the child, mother's education, housing, ethnicity, parity, age, anxiety score, smoking, body-mass index, history of asthma or atopic disorders, migraine, infections in late pregnancy, breast-feeding, season of birth, multiple pregnancy, the child's gestational age at birth, birth weight, length, and head circumference, day care exposure, antibiotic use in the first six months, tobacco exposure in the first six months, and pet exposure in the first year.

More than half of the women had used acetaminophen during pregnancy, and fewer than 9% of the women used aspirin [15]. There was a statistically significant association between a

**Table 1**  
Studies of acetaminophen use in pregnancy.

Study title	Location	Study design	Population	Number of patients	Study results
The Avon Longitudinal Study of Parents and Children [1]	UK	Observational study using a questionnaire completed by mothers	Infants 30–42 months of age.	14,062 live births 9400 completed.	There was statistically significant difference between a child's asthma symptoms and maternal use of acetaminophen (APAP) during the period of 20–32 weeks gestation (aOR 2.10, 95% CI 1.30–3.41) but not during the period 0–20 weeks gestation.  There was statistically significant association with "sometime" APAP exposure during the period of 20–32 weeks gestation and childhood asthma (aOR 1.22, 95% CI 1.06–1.41) but not with APAP use "most days" or "daily" (aOR 1.62, 95% CI 0.86–3.04). There was a statistically significant trend test across the three levels of APAP exposure (never, sometimes, most days/daily).
The Singapore Children's Asthma and Allergy Network [17]	Singapore	Observational and skin testing	Children 3–10 years of age with physician diagnosis of asthma and with a healthy non-asthmatic sibling in the same age range.	83 eligible – 38 asthmatic children (cases) with their non-asthmatic siblings (controls) + four more non-asthmatic siblings participated.	In 19 pairs of cases and controls, more cases than controls had mothers taking acetaminophen during pregnancy (35% vs. 0%, $P=0.03$ )  In 33 pairs of cases and controls, any paracetamol intake between birth and 6 months was associated with asthma in the child (29% vs. 0%, $P=0.008$ ).
The Danish National Birth Cohort [18]	Denmark	Observational study using a questionnaire completed by telephone interview	Mothers during pregnancy, 6 and 18 months after child's birth, and when the child was age 7.	Women responding: 90,549 during pregnancy and 6 months after child's birth, 66,445 18 months after child's birth, and 12,733 when the child was age 7.	APAP use during any time of pregnancy was associated with a statistically significant increased risk of physician-diagnosed asthma or bronchitis among children at 18 months (RR 1.18, 95% CI 1.13–1.23). Hospitalizations due to asthma up to 18 months (hazard ratio 1.24, 95% CI 1.11–1.38). Physician-diagnosed asthma at 7 years (RR 1.15, 95% CI 1.02–1.29). Highest risks were observed for APAP use during the first trimester of pregnancy and persistent wheezing (wheezing at both 18 months and 7 years) (RR 1.45, 95% CI 1.13–1.85).
The Peer Education in Pregnancy Study [19]	US	Interventional study using a questionnaire completed by mothers	Pregnant women at risk for having children with asthma based on family history of asthma, hay fever, or eczema. Questioned mothers in first trimester, 4–5 months gestation, 7–8 months gestation, and postpartum.	483 women enrolled – 383 randomized to general health education alone or general health education plus home visits.	Use of acetaminophen in middle to late but not early pregnancy was significantly related to wheezing (OR 1.8, 95% CI 1.1–3.0) and to wheezing that disturbed sleep (OR 2.1, 95% CI 1.1–3.8) in the first year of life.
Murcia (Spain) Study [20]	Spain	Observational study using a questionnaire completed by parents of pre-school children	Pre-school children aged 3–5 years.	1741 children after elimination of incomplete questionnaire responses (61% of the invited sample).	65/1741 mothers identified themselves as asthmatic.  Overall prevalence of current wheezing children was 20%; percentage of wheezing children was statistically significantly higher in the group with asthmatic mothers than the group with non-asthmatic mothers.

The Yale Study [21]	US (New England)	Prospective study using home/telephone interview questionnaire	Pregnant women interviewed at 24 weeks gestation, within 1 month of delivery, and when child was 6 years old.	3413 invited to participate – 1505 completed.	<p>Frequency of acetaminophen usage was similar among asthmatic and non-asthmatic mothers. Compared to mothers who never took acetaminophen, there was a significant association between the mother having taken acetaminophen at least once monthly during pregnancy and her offspring wheezing at preschool age, but only among non-asthmatic mothers (OR 1.94, 95% CI 1.34–2.79 vs. OR 1.05, 95% CI 0.21–5.08).</p> <p>Acetaminophen was used by 69% of women during pregnancy: Use of acetaminophen did not significantly increase the risk of asthma (aOR 0.76, 95% CI 0.53–1.10). Acetaminophen use during both the 1st and 3rd trimester was associated with significant reduced risk of asthma (aOR 0.59, 95% CI 0.36–0.98). There was no evidence of a dose response, and consumption &gt;10,400 mg per month did not increase risk (aOR 0.99, 95% CI 0.19–5.30).</p>
Columbia Center for Children's Environmental Health Study [22]	US (North Manhattan and South Bronx)	Observational study utilizing questionnaires and blood sampling for genotyping and IgE titer	Expectant mothers of African-American race or Dominican Republic origin genotyped for polymorphisms of glutathione-S-transferase <i>Pi</i> (GSTP1). Questionnaire administered at birth and regular intervals until the child was 5 years old.	1442 pregnant women enrolled – 725 children completed	<p>Thirty-four percent of mothers reported acetaminophen use during pregnancy and 27% of children had current wheeze at 5 years: Prenatal acetaminophen exposure predicted current wheeze (multivariate RR, 1.71; 95% CI 1.20–2.42; <math>P=0.003</math>). Risk increased monotonically with increasing number of days of prenatal acetaminophen exposure (<math>P</math>-trend &lt;0.001). Sixty-eight percent of children had a least one copy of the GSTP1 minor allele (Val). The risk of wheeze was modified by GSTP1 (additive interaction <math>P=0.009</math>) and was observed only among children with the GSTP1 minor allele.</p>
Oslo Environment and Asthma Study [23]	Oslo, Norway	Prospective follow-up from birth using questionnaires and pulmonary function testing at 10 years of age; pregnancy exposure information was collected by questioning mothers in the maternity ward.	All children born in Oslo during the 15 months that began January 1, 1992 were invited.	3754 children in the initial study; follow-up at 10 years included 1016 of these children	<p>No association between maternal use of acetaminophen during pregnancy and diagnosis of childhood asthma at age 10.</p> <p>Acetaminophen use during the first trimester of pregnancy not associated with bronchial hyper-responsiveness to methacholine after adjustment for unstated confounders. Statistically significant association between bronchial hyper-responsiveness in girls and first-trimester use of acetaminophen (aOR 5.48, 95% CI 1.37–21.82).</p>

child's asthma symptoms and maternal use of acetaminophen on most days or daily during the second questionnaire period (20–32 weeks gestation, adjusted odds ratio 2.10, 95% confidence interval 1.30–3.41) but not during the first questionnaire period (0–20 weeks gestation). There was no association with aspirin use in either questionnaire period. No comparable associations were seen for eczema symptoms. Use in the child of acetaminophen more than once in the first six months of infancy was also associated with asthma symptoms (adjusted odds ratio 1.29, 95% confidence interval 1.05–1.57).

A further analysis of this sample presented results of maternal questionnaires administered when the child was 6–7 years of age [15]. There were 8511 children with available information. Child asthma symptoms at this age were said to correlate well with reports of a physician diagnosis of asthma. Children also underwent allergen prick skin testing with dust mite, cat, and grass, and serum total IgE levels were measured.

There was a statistically significant association with “some-time” acetaminophen exposure during the second questionnaire period (20–32 weeks gestation) and childhood asthma (adjusted odds ratio 1.22, 95% confidence interval 1.06–1.41) but not with acetaminophen use most days or daily (adjusted odds ratio 1.62, 95% confidence interval 0.86–3.04), although a trend test across the three levels of acetaminophen exposure (never, sometimes, most days/daily) was statistically significant. There was no association between acetaminophen use during early pregnancy (0–20 weeks gestation) or aspirin use in either questionnaire period and childhood asthma. Skin test positivity was not significantly associated with acetaminophen use during either period of pregnancy. Total serum IgE in 7-year-old children showed a significant increasing trend across the three levels of acetaminophen exposure during the 20–32-week gestation period. The authors believed that the objective measurement of IgE circumvented any bias the mothers may have had leading to over-reporting of asthma symptoms or diagnoses.

An analysis of acetaminophen use by mothers and of their partners after pregnancy investigated the possible confounding effects of familial behaviors on childhood asthma [16]. Maternal prenatal and postnatal use of acetaminophen was statistically significantly associated with childhood asthma and wheezing, but partner use of acetaminophen was not associated with childhood asthma or wheezing.

#### 4.2. *The Singapore Children's Asthma and Allergy Network*

The Children's Asthma and Allergy Network of Singapore's National University Hospital recruited children between 3 and 10 years of age with a physician diagnosis of asthma and with a healthy sibling in the same age range [17]. The healthy siblings could not have symptoms of asthma, rhinitis, eczema, urticaria, or angioedema. Of the 622 asthmatic children screened, 82 were eligible and 38 asthmatic children with their non-asthmatic siblings participated in the study. An additional four non-asthmatic siblings were recruited. All children were skin tested with 11 allergens and categorized as allergic if they had a reaction to any of the allergens. Five cases and six controls were excluded because the case child had non-allergic asthma. Mothers were questioned about their use of acetaminophen during pregnancy and during the first six months of life and of their children's use of acetaminophen during the first six months of life. Differences between the asthmatic and non-asthmatic children in each pair were analyzed.

In 19 pairs, both siblings were considered allergic by skin testing. Among the 17 mothers who answered the question of acetaminophen use during each of the pregnancies, responses were positive for six of the asthmatic children and none of their siblings. The difference between the proportions exposed (asthmatic

vs. non-asthmatic siblings) was statistically significant. There was no significant difference in the proportion of asthmatic children exposed to acetaminophen during pregnancy compared to their allergic and non-allergic siblings, that is, in the entire sample of 33 pairs. Among the 28 pairs of children for which information was available, eight mothers reported use of acetaminophen in the asthmatic child during the first six months of life and none had reported use of acetaminophen by the non-asthmatic child. These proportions were significantly different. There was apparently frequent use of acetaminophen use by non-asthmatic children, however, because a table in the paper reports the indication for acetaminophen use in 23 asthmatic children and 18 non-asthmatic siblings.

#### 4.3. *The Danish National Birth Cohort*

This population-based study was based on 90,549 women who completed a questionnaire and participated in a telephone interview during pregnancy and six months after pregnancy [18]. Interviews were conducted with 66,445 women 18 months after birth, and 12,733 women completed another questionnaire when the child was 7 years old. Three-quarters of the women completing the questionnaire at 7 years had also participated in the 18-month interview. Mothers were asked for information about their use of acetaminophen, aspirin, ibuprofen, and other analgesics. Mothers identified the weeks of pregnancy during which they took medications and indicated whether the child had been given acetaminophen during the first 18 months of life.

At 18 months, mothers were asked if their child had wheezing or whistling in the chest and whether a physician had diagnosed asthma or bronchitis in the child. At seven years, women completed a questionnaire on asthma symptoms or physician-diagnosed asthma in the preceding 12 months. Adjustment was made for maternal asthma, gestational age at birth, child's sex, socioeconomic status, duration of breastfeeding, maternal smoking, and antibiotic use.

More than half of the mothers had used acetaminophen at some time during pregnancy. Statistically significant associations were found at 18 months for use of acetaminophen at any time during pregnancy and physician-diagnosed asthma or bronchitis, wheezing, and hospitalization for asthma. The relative risk for hospitalization with asthma was 1.24 (95% confidence interval 1.11–1.38). When evaluated by trimester, relative risks were similar by trimester for each of the end points at 1.09–1.17 and lower bounds of the 95% confidence intervals were all above unity.

Analysis of the data for 7-year-olds showed statistically significant elevations of the relative risk for physician-diagnosed asthma and persistent wheezing (wheezing at the 18-month and 7-year assessments). Physician-diagnosed asthma and persistent wheezing were associated with acetaminophen exposure in the first and third but not the second trimesters. The highest relative risk was for persistent wheezing with any exposure to acetaminophen at 1.37 (95% confidence interval 1.07–1.75). First trimester exposure was associated with the severity of asthma as estimated by wheezing events disrupting sleep. The authors noted that their identification of first-trimester effects is in disagreement with the findings of the Avon Longitudinal Study of Parents and Children, discussed above.

Adjusting the estimates by indication for use did not change the results except for a small increase in the acetaminophen–asthma association when acetaminophen was used for inflammation or infection. Use of antibiotics further increased the association in women taking acetaminophen for inflammation or infection. Use of aspirin or ibuprofen during pregnancy was not associated with an increase in physician-diagnosed asthma, wheezing, or hospitalization for asthma, but the association between physician-diagnosed

asthma and wheezing at 18 months was more consistent when mothers took acetaminophen and avoided aspirin than when mothers used both acetaminophen and aspirin.

#### 4.4. *The Peer Education in Pregnancy Study*

This US intervention study recruited pregnant women at risk for having children with asthma based on family history of asthma, hay fever, or eczema [19]. All women received general education and half the women had home visits to identify and decrease asthma triggers. Of the 483 women initially enrolled, 383 were randomized to education alone or education plus home visits. No information was given on acetaminophen use as part of the intervention. The paper reports follow-up of 351 of the children to 1 year of age.

Acetaminophen use was ascertained by questionnaire in the first trimester, at 4–5 months gestation, at 7–8 months gestation, and postpartum. Acetaminophen was used by 70% of women at some time during pregnancy. Infant outcomes were assessed by questionnaire or telephone calls throughout the first year of life. End points included wheezing or whistling, cough, physician diagnosis of asthma, and hospitalization for breathing problems. One-third of mothers reported wheezing in the child at some time in the first year and one-fifth of mothers reported wheezing that disturbed their child's sleep.

Adjustment was included for maternal smoking, breastfeeding, family history of asthma, antibiotic use during pregnancy, the child's birth weight, antioxidant food or supplement intake, and intervention group assignment. There was a statistically significant association between acetaminophen use at any time during pregnancy and wheeze that disturbed sleep with an adjusted odds ratio of 2.3, 95% confidence interval (1.1–4.6). Wheeze, cough that disturbed sleep, emergency department visit or hospitalization for respiratory problem, and asthma diagnosis were not significantly associated with acetaminophen use during pregnancy. When evaluated by trimester of exposure, middle and later pregnancy exposure to acetaminophen was associated with wheezing and with wheezing that disturbed sleep, but early pregnancy exposure to acetaminophen was not associated with any end point. More than 90% of the women reported infections during pregnancy and inclusion of infection in the analysis did not alter the outcomes.

#### 4.5. *Murcia (Spain) Study*

Preschool children from the three main cities in the province of Murcia, Spain, were evaluated based on parental questionnaires distributed through the schools [20]. The mothers of 1784 children (61% of the invited sample) responded. Maternal asthma, frequency of maternal use of acetaminophen during pregnancy, and the presence of asthma symptoms in the child were solicited. Based on maternal report, 20% of the children experienced wheezing. Sixty-five of the 1741 women who provided information identified themselves as asthmatic. Adjustment was made in the analysis for maternal smoking, duration of breastfeeding, the presence of older or younger siblings, cat ownership, and preterm delivery. Childhood wheezing was associated with use of acetaminophen during pregnancy at least once per month (adjusted odds ratio 1.71, 95% confidence interval 1.15–2.53), but only when the analysis excluded asthmatic mothers.

#### 4.6. *The Yale Study*

Pregnant women from private practices and hospital clinics in southern New England were recruited to participate in a prospective study of acetaminophen use during pregnancy [21]. Women were interviewed at home before 24 weeks gestation and were interviewed again in the hospital after birth or by telephone dur-

ing the first month postpartum to ascertain use of acetaminophen. An interview was conducted at six years to determine whether the child had been diagnosed with asthma or had symptoms of wheezing or whistling in the chest. Bronchitis diagnosis, sneezing/runny nose, and allergy were also solicited. The women invited to participate included 1343 women with physician-diagnosed asthma and 2070 women without asthma.

Potential confounders included maternal age, ethnicity, marital status, education, smoking, asthma, asthma symptoms (cough, shortness of breath, chest tightness, wheezing), or other health conditions, eczema or allergies, and the child's gestational age at birth, low birth weight, preterm birth, siblings, preschool attendance, exposure to tobacco smoke, exposure to antibiotics or allergy medication, infectious diseases, asthma symptoms in the first or past year, emergency department visit or hospital stay for asthma, use of the intensive care unit, intubation, and breastfeeding. Father's ethnicity, education, history of asthma and other health conditions and home characteristics including mold, wetness, pets, cockroaches, wood-burning stove or fireplace, heaters, and air conditioning were also evaluated as potential confounders.

The analysis was based on 1505 women who completed the interview at six years. Almost 70% of women were exposed to acetaminophen during the first or third trimester of pregnancy. On univariate analysis, maternal asthma symptoms in aggregate or separately were associated with acetaminophen use during pregnancy. Maternal allergy and preterm delivery were also associated with acetaminophen use during pregnancy. These factors were also associated with childhood asthma on univariate analysis as were African American and Hispanic ethnicity, maternal smoking during pregnancy or exposure to second-hand smoke, and preterm labor and delivery. In the multivariate model, ethnicity, maternal asthma, and rhinitis or eczema in the child were independently associated with childhood asthma. Use of acetaminophen during the first or third trimesters was not associated with childhood asthma (adjusted odds ratio 0.76, 95% confidence interval 0.53–1.10). Separate analysis by trimester also showed no relationship between acetaminophen exposure and childhood asthma, although exposures only in the second trimester were not evaluated. Use of acetaminophen during both the first and third trimesters was associated with a protective effect for childhood asthma (adjusted odds ratio 0.59, 95% confidence interval 0.36–0.98) and persistent wheezing (adjusted odds ratio 0.67, 95% confidence interval 0.46–0.98).

#### 4.7. *Columbia Center for Children's Environmental Health Study*

The Columbia center screened 2844 pregnant African-American or Dominican women in Northern Manhattan or the South Bronx [22]. Inclusion criteria were met by 1442 women and 725 of their children completed the entire study. Women were asked during the third trimester about the use of acetaminophen, ibuprofen, and aspirin. Questionnaires were administered to the mothers after birth at intervals for five years. Mothers were asked about wheezing in the child, medication use for wheezing or difficulty breathing, and visits to the emergency department for wheezing or difficulty breathing. Five-year-old children had blood sampling for serum IgE to dust mite, mouse, cockroach, cat, and dog. Genotyping was performed for polymorphisms of glutathione-S-transferase Pi (GSTP1), a minor variant of which has been associated with impaired enzyme activity in African American and Dominican populations.

Potential confounders that were considered included race/ethnicity, maternal asthma, tobacco smoke exposure, a cat in the home, child's birth order and birth weight, maternal age, cockroaches, mice, maternal education, Medicaid, panic/anxiety attacks, neighborhood gang activity, homelessness, a maternal hardship variable (defined in a previous publication), and post-

natal use of acetaminophen by the child. The final model was adjusted for sex, ethnicity, birth order, maternal asthma, maternal hardship, tobacco smoke exposure, and postnatal acetaminophen use. Women who took acetaminophen during pregnancy were more likely to have headache and to have panic/anxiety attacks, but these variables did not appear in the final model.

Use of acetaminophen during pregnancy was associated with childhood wheezing at 5 years (adjusted relative risk 2.26, 95% confidence interval 1.40–3.63). Acetaminophen use during pregnancy was associated to a similar extent with disturbance of sleep by wheezing, use of medication for breathing difficulty, and a positive IgE to at least one of the tested antigens. Although acetaminophen use during pregnancy was not associated with wheezing at 1, 2, and 3 years on analysis of the individual year data, a statistically significant increasing trend for wheezing with age was identified in children with intrauterine acetaminophen exposure. When analyzed by trimester, acetaminophen exposure during the second and third but not the first trimester was associated with childhood wheezing.

The association between acetaminophen use during pregnancy and childhood wheezing was modified by GSTP1 genotype. The association with childhood wheezing and positive IgE was seen only for children with at least one copy of the minor allele, GSTP1(Val105). Children homozygous for the major allele did not show an association between acetaminophen exposure during pregnancy and wheezing or atopy.

#### 4.8. Oslo Environment and Asthma Study

All healthy children with a birth weight of at least 2000 g living in Oslo during the 15 months that began January 1, 1992 were invited to participate in a study of childhood asthma [23]. There were 3754 children in the initial sample. Follow-up at 10 years of age included 1016 of these children. Mothers had been asked in the maternity ward about their use of medications during pregnancy and about pregnancy complications, family health, environmental exposures, and socioeconomic factors. Ten-year-old children underwent pulmonary function testing including a methacholine challenge test, an exercise test, and measurement of fractional exhalation of nitric oxide. Parents were asked about medications used during childhood, episodes of upper and lower respiratory infection, dyspnea, chest tightness or wheezing, a doctor's diagnosis of asthma, or use of asthma medication by the child. Parents were also asked about environmental exposures, lifestyle, atopic eczema, and allergic rhinitis using questionnaire items from the International Study of Asthma and Allergy in Childhood (discussed below).

There was no association between maternal use of acetaminophen during pregnancy and childhood asthma at age 10. A statistically significant association between use during the first trimester of pregnancy and bronchial hyper-responsiveness to methylcholine challenge was described as losing significance after adjustment for confounders, but no data were shown and it is not known which confounders explained the association. When girls and boys were analyzed separately, there was a statistically significant association between maternal use of acetaminophen during the first trimester and bronchial hyper-reactivity in girls (adjusted odds ratio 5.48, 95% confidence interval 1.37–21.82) but not boys. An increase in fractional exhalation of nitric oxide at 10 years of age was associated with maternal use of acetaminophen during the second and third trimesters of pregnancy.

Before discussing how these eight studies can be interpreted, we will briefly review information on the changes in asthma diagnosis over time and the studies on childhood use of acetaminophen and asthma, which have been cited as providing support to the theory that use of acetaminophen during pregnancy is associated with childhood asthma.

## 5. Ecological study

The relationship between sales of acetaminophen and asthma symptoms was evaluated using data from the International Study of Asthma and Allergies in Children (ISAAC) and the European Community Respiratory Health Survey in adults [24]. Wheezing, wheeze disturbing sleep, eczema, and rhinoconjunctivitis were assessed through questionnaires administered to parents of 6–7-year-old children and administered directly to 13–14-year-old children. Adults 20–44 years of age were surveyed using a similar questionnaire. Acetaminophen national sales data were available for 40 of the markets in the two surveys. Adjusting for gross domestic product per capita, acetaminophen sales per capita were statistically associated with all symptoms in children and adults except for dyspnea disturbing sleep in adults. Adults in the European Community Respiratory Health Survey also underwent metacholine bronchial reactivity testing and determination of IgE to dust mite, timothy grass, cat, and mold (*Cladosporium herbarium*) as an assessment of atopy. Acetaminophen sales were associated with bronchial reactivity but not with atopy.

The authors noted that the highest acetaminophen sales per capita occurred in the English speaking countries (United Kingdom, Eire, United States, Canada, Australia, and New Zealand). When analysis was adjusted for residence in one of these countries, the association between acetaminophen sales per capita and symptoms was lost except for eczema among 13–14-year-olds.

Ecological studies such as this one are prone to confounding because other factors may vary with the exposure and the outcome. The authors recognized this potential problem and were particularly sensitive to the possibility that a factor associated with the English-speaking culture may have provided an explanation for the observed association.

Although it has often been noted that asthma diagnoses are increasing, the prevalence of asthma has not been uniformly rising among developed countries (reviewed by Eder et al. [25]). There is even more variability for asthma symptoms, as distinguished from diagnosed asthma, for which no temporal pattern has been identifiable since the 1990s. Consideration of trends in asthma diagnosis and symptoms are complicated by the increasing awareness of asthma among health care providers and the public. When airway hyper-responsiveness is used as an objective measure of asthma, no consistent trends were identified. There has also been no consistent trend in the prevalence of atopy. Other factors that may influence the prevalence of asthma diagnoses or symptoms include tobacco smoke, air pollution, environmental allergens, obesity, diet, and exposure to microorganisms.

## 6. Studies of acetaminophen in children (Table 2)

The International Study of Asthma and Allergy in Childhood (ISAAC) was a multicenter cross sectional study to evaluate the association between acetaminophen use during the first year of life and parent-identified asthma symptoms in 6–7-year-old children. A report on the overall study results was preceded in two papers from participating centers in New Zealand and in Hong Kong.

In the overall study [26], the subject children were chosen from schools in 87 centers in 34 countries, although after exclusions for missing data on potential confounders, information was used from 47 centers in 20 countries for the fully adjusted models. Parents of children aged 6–7 years were given a questionnaire about acetaminophen use by the children for fever during the first year of life and during the previous 12 months and about symptoms of asthma, rhinoconjunctivitis, and eczema. Adjustments were made for age, region of the world, language, gross national income, maternal education, antibiotic use in the first year of life, breastfeeding, parental smoking, dietary fruits and vegetables, and younger or



**Table 2**  
Studies of acetaminophen in children.

Study title	Location	Study design	Population	Number of patients	Study results
International Study of Asthma and Allergy in Childhood (ISAAC) [26,27]	87 centers (34 countries)	Questionnaire for acetaminophen use for fever during the first year of life and for the past 12 months as well as parent-identified symptoms of asthma, rhinoconjunctivitis, and eczema. Study of 13- and 14-year-old children used direct questioning of the child.	Children 6–7 and 13–14 years of age	205,487 children from 31 countries enrolled for the younger age group; 322,959 adolescent children from 50 countries enrolled for the older age group.	Use of acetaminophen for fever in the first year of life was associated with an increased risk of asthma symptoms when aged 6–7 years (OR 1.46, 95% CI 1.36–1.56). Current use of acetaminophen was associated with a dose-dependent increased risk of asthma symptoms (OR 1.61, 95% CI 1.46–1.77 and OR 3.23, 95% CI 2.91–3.60) for medium and high use vs. no use, respectively. Acetaminophen use was similarly associated with the risk of severe asthma symptoms, with population-attributed risks between 22% and 38%. Acetaminophen use in the first year of life and in children age 6–7 was also associated with an increased risk of symptoms of rhinoconjunctivitis and eczema. In the 13- and 14-year-old children, use of acetaminophen in past 12 months was associated with increased risk of current asthma symptoms for medium use (aOR 1.43, 95% CI 1.33–1.53) and high use (aOR 2.51, 95% CI 2.33–2.70) compared to no use.
ISAAC – New Zealand sub study [29]	New Zealand	Questionnaires mailed to parents of each of two populations (Childhood infections and General population groups)	Childhood infections group identified from EpiSurv (Public Health Service database) – notifiable infections in children ages 0–4 born between 1994 and 1995. General population group identified through Wellington survey conducted April–October, 2002 in 6–7-year-old school children.	1584 – childhood infections (CI) group (57% response rate) 2539 – general population (GP) group (47% response rate).	There was little difference in prevalence of current wheezing between groups (23.5% CI, 24.3% GP). Site of infection (GI, invasive, or respiratory) was similar (prevalence 21.1–24.6%). There were associations with antibiotic (OR 1.78, 95% CI 1.49–2.14) or paracetamol (OR 1.38, 95% CI 1.04–1.83) use in the first year of life or recent paracetamol use (OR 2.10, 95% CI 1.78–2.49) and current wheezing.

Table 2 (Continued)

Study title	Location	Study design	Population	Number of patients	Study results
ISAAC – Hong Kong substudy [30]	Hong Kong	Parental questionnaire based on ISAAC questionnaire	Children age 2–6 living in Hong Kong recruited through nurseries and kindergartens.	3089	Prevalence of wheeze ever and current wheeze was 16.7% and 9.3%. Children born in China who migrated to Hong Kong (234) had a significantly lower prevalence of current wheeze (3.4% vs. 9.6%, $P < 0.01$ ). Use of foam pillows (OR 1.45, 95% CI 1.04–2.00) and cooking fuel (OR 1.68, 95% CI 1.03–2.75) were associated with wheezing attacks within the last 12 months. Frequent use of paracetamol was associated with wheezing attack in the past 12 months.
Boston University Fever Study [31]	US (Boston)	Randomized, double-blind acetaminophen-controlled trial to assess short-term use of ibuprofen on asthma morbidity in children	Children 6 months to 12 years of age treated for fever short-term and evaluated for inpatient and outpatient asthma treatment.	632 – acetaminophen 12 mg/kg. 636 – ibuprofen 5 mg/kg. 611 – ibuprofen 10 mg/kg.	Rates for hospitalization for asthma did not vary significantly by antipyretic assignment; compared with children who were randomized to acetaminophen; the relative risk for children who were assigned to ibuprofen was 0.63 (95% CI 0.25–1.6). Risk of outpatient visit for asthma was significantly lower in the ibuprofen group; compared to children who were randomized to acetaminophen, the relative risk for children who were assigned to ibuprofen was 0.56 (95% CI 0.34–0.95). Whether the observed difference in morbidity is due to increased risk after acetaminophen use or a decrease after ibuprofen cannot be determined.

older siblings. There were 103,284 children from 20 countries with complete data. The odds ratio for the association between acetaminophen use for fever during the first year of life and parent-identified asthma symptoms was 1.43 (95% confidence interval 1.30–1.58). A statistically significant association was also shown for rhinoconjunctivitis and eczema. Use of acetaminophen in the children during the year preceding the questionnaire was also associated with asthma symptoms, with a higher odds ratio for those children reported to have used acetaminophen at least once/month. Similar results were subsequently reported for 13- and 14-year-old children who were directly questioned about asthma and rhinoconjunctivitis symptoms [27].

This study involved a large number of children from different parts of the world; however, the putative association of acetaminophen with asthma and other atopic disorders is not clear. Exposed children were given acetaminophen for fever, at least during the first year of life. It is not known whether unexposed children did not have fever, had untreated fever, or had fever treated with other medications. The authors discounted the possible role of confounding by indication because there are different types of childhood febrile illnesses worldwide and there were likely to have been different medical practices and over-the-counter treatments available in the different communities. They do not, however, address the possibility that inflammatory mediators common to diverse febrile illnesses may have played a role in the association. Indeed, fever as an explanatory variable was supported by a study showing that adolescents with asthma or eczema had more febrile days per year as children than did adolescents without asthma or eczema [28].

Reverse causation, in which asthma or other atopic illnesses lead to symptoms such as fever that result in acetaminophen use, was discounted because the authors doubted that eczema symptoms were likely to lead to use of acetaminophen. The authors did not consider whether children with atopic illnesses may be irritable or feel generally unwell, leading their parents to give them acetaminophen. Indeed, parental attitude about illness and about medication treatment could lead to greater surveillance for symptoms among parents with greater enthusiasm for giving medication to their children. Inasmuch as aspirin use is discouraged in children and other NSAIDs may be unavailable or too costly, the use of acetaminophen could be a surrogate for the parental attitude that the child is sickly or uncomfortable.

One of the ISAAC centers in Wellington, New Zealand, evaluated the association between parent-reported childhood asthma or atopic disease symptoms and reportable infections [29]. The symptoms were obtained from the ISAAC questionnaire and infections were ascertained from a national data base. A weak protective effect of reportable infections was identified. Statistically significant associations were reported for childhood asthma and acetaminophen use during the first year of life or during the past year and with antibiotic use during the first year of life.

Another of the ISAAC centers in Hong Kong published a study of similar design in which children aged 2–6 years were evaluated by parental questionnaire for symptoms of asthma and atopic disorders [30]. Statistically significant associations with asthma symptoms were identified for monthly use of acetaminophen, cooking with gas during the first year of life, and use of a foam pillow. The authors also noted that current rhinoconjunctivitis or current flexural eczema was associated with wheezing.

As in the larger ISAAC report by Beasley et al. [26], the indications for acetaminophen use were not explored in the New Zealand or Hong Kong ISAAC substudies. Reverse causation and parental biases may have contributed to the findings of both substudies.

The Oslo Environment and Asthma Study [23] reported that acetaminophen use during the first 6 months of life was associated with a history of asthma in girls but not boys. This association

apparently did not extend to current wheezing or bronchial hyper-responsiveness as assessed using a methacholine challenge test, casting some doubt on the reliability of the history of asthma.

A randomized trial of ibuprofen compared to acetaminophen for the treatment of fever in children between 6 months and 12 years of age evaluated inpatient and outpatient treatment for asthma [31]. Children were followed for four weeks; therefore, this study evaluated only short-term outcomes. There was no significant difference in hospitalization for asthma between the treatments. Outpatient visits for asthma were decreased in the ibuprofen-treated children compared to the acetaminophen-treated children (odds ratio 0.56, 95% confidence interval 0.34–0.95). The authors indicated that their findings could be explained either by a protective effect of ibuprofen or an increased risk associated with acetaminophen.

## 7. The possible protective effect of aspirin and ibuprofen

The use of acetaminophen instead of aspirin or ibuprofen may be associated with an apparent increase in asthma if aspirin or ibuprofen has a protective effect against the development of asthma. The hypothesis that pediatric aspirin protects against the development of asthma was introduced by Varner et al. [32]. These authors posited that the decrease in childhood use of aspirin in response to concern about Reye's syndrome has led to removal of this protective intervention and a subsequent increase in the prevalence of asthma.

The rationale for this theory is based on the difference between cytokine expression after activation of two populations of T helper cells called TH1 and TH2. The TH1 cytokines are interleukins 2 and 12 and interferon  $\gamma$ , which contribute to cell-mediated immunity and delayed hypersensitivity reactions. The TH2 response includes interleukins 4, 5, 10, and 13, which contribute to IgE-mediated inflammation and eosinophil activation. The response of T helper cells to respiratory infection may be affected by prostaglandins, particularly prostaglandin E<sub>2</sub>, which promotes the TH2 response and favors allergic sensitization. Prostaglandin E<sub>2</sub> is formed through the action of cyclooxygenase-2 (COX-2), which is inhibited by aspirin and ibuprofen but not by acetaminophen.

The hypothesis that aspirin prevents asthma is supported by an observational study and two randomized clinical trials in adults. In the Nurses' Health Study, increasing aspirin consumption was associated with a decreased likelihood of receiving a new diagnosis of asthma [33]. Participants made their own decisions about what medications to take, if any, and the indications for aspirin use were not reported. By contrast, the two randomized trials assigned aspirin or placebo use to apparently healthy adults. The Physicians' Health Study randomized men to receive aspirin 325 mg or placebo every other day. Men were followed for an average of almost five years and were assessed by questionnaire for a new diagnosis of asthma. There was a statistically significant 22% decrease in new asthma diagnoses in the group assigned to aspirin [34]. The Women's Health Study randomized female health care professionals to aspirin 100 mg every other day or placebo. Women were followed for 10 years with annual questionnaires inquiring about new diagnoses including asthma. There was a statistically significant 10% decrease in reported new diagnoses of asthma [35].

## 8. Synthesis

There are nine papers reporting the results of eight studies on acetaminophen use during pregnancy and childhood asthma or symptoms of asthma. Seven of the studies generally concluded that there may be a causal association between acetaminophen use during pregnancy and wheezing or asthma in children. Of the eight studies on pregnancy use of acetaminophen and childhood asthma,

three [19,20,22] evaluated childhood wheezing prior to age six, which may not be useful in predicting childhood asthma [2].

A physician diagnosis of asthma or serologic evidence of atopy was considered in the Avon Longitudinal study [1,15,16], the Singapore study [17], the Danish National Birth Cohort [18], the Yale Study [21], the Oslo study [23], and the Columbia study [22]. The Singapore study reported an association between use of acetaminophen during pregnancy and childhood asthma only in 17 atopic asthmatic children with atopic non-asthmatic siblings; using atopic and non-atopic siblings as controls eliminated the putative association with acetaminophen exposure during pregnancy. Other studies have suggested that an acetaminophen effect is more likely to involve non-atopic mechanisms (e.g., oxidative injury).

An important issue in interpreting these studies is the question of confounding by indication. Only the Danish study specifically evaluated maternal fever and infection during pregnancy as potential confounders of an acetaminophen–asthma relationship, although some of the other studies included maternal antibiotic use among the potential confounders that were examined. The study by Persky et al. [19] adjusted for maternal infection, but did not evaluate children beyond one year of age. The role of maternal stress in childhood asthma has received little attention. Only the Avon Longitudinal Study included maternal stress or anxiety as a potential confounder. The Columbia study found panic/anxiety attacks to be more prevalent among women who took acetaminophen, but did not apparently adjust for this variable in their analysis. The Oslo study reported that an apparent association between acetaminophen use during pregnancy and bronchial hyper-responsiveness at age 10 disappeared after adjustment for confounders, but the study report did not identify which confounders were responsible for the association [23].

There may be important differences between the seven studies that generally found an increase in childhood asthma or asthma symptoms associated with use during pregnancy of acetaminophen and that of the Yale group [21], which found no such association and, for use during the first and third trimesters, found a protective effect. The Yale Study by design included a large proportion of women with diagnosed asthma. In addition, the questionnaires solicited information about asthma symptoms in all women and found these symptoms to be more common in women who took acetaminophen. Asthma symptoms may reflect undiagnosed asthma or respiratory infection that was missed by the other studies. The Yale authors also believed that the other studies may have had incomplete ascertainment of acetaminophen usage, whereas their more open-ended questions resulted in more complete identification of acetaminophen exposure. A disadvantage of the Yale Study is that women using acetaminophen only during the second trimester would have been considered unexposed, resulting in a bias toward the null.

The glutathione hypothesis of acetaminophen action is supported by the Columbia study's findings that a glutathione-S-transferase variant conferring decreased activity affected the acetaminophen–asthma relationship [22]. No other study evaluated GSTP1 genotype as a factor in maternal acetaminophen effects of childhood asthma. The findings of the Danish study [18] and the Oslo study [23] of an association between first trimester acetaminophen exposure and childhood asthma is not consistent with the glutathione hypothesis because oxidative damage to respiratory epithelium would not be expected before respiratory epithelium develops later in pregnancy.

The adjusted risk estimates for those studies showing a statistically significant association between acetaminophen use during pregnancy and childhood asthma or asthma symptoms are generally below 2.0 and mostly below 1.5, the Columbia study being an exception. Although low risk estimates may indicate a low order increase in risk, they may also be susceptible to confound-

ing and bias. The negative results of the Yale Study [21], which adjusted for more potential confounders than did the other studies, suggests that confounding by indication (maternal fever or infection) or reverse causation (women with symptoms taking more acetaminophen) may have played a role in the findings of the positive studies.

Limitations of the available studies include inadequate or absent adjustment for passive cigarette smoke exposure and low participation rates. Retrospective study designs face the challenge of accurately ascertaining medication use. Errors in recalling medication use can lead to misclassification of exposed and unexposed subjects. When errors are systematic, as in recall bias, the results of the study may suggest an association between exposure and outcome when none, in fact, exists. The rodent studies that evaluated effects of acetaminophen on glutathione used unreasonably large dose levels of acetaminophen. These studies do not contribute to our understanding of possible effects of more realistic dose levels of this medication on pulmonary function.

A randomized trial may be the only way to resolve the question of whether acetaminophen use during pregnancy increases the incidence of childhood asthma. Contemplation of such a study raises the question of what comparator treatment would be used. Given the concerns about effects of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) during the third trimester, only a placebo control is likely to be acceptable. Such a trial would not be practical if there are insufficient numbers of participants willing to risk assignment to use of placebo for pain and fever.

The current data are insufficient to conclude that acetaminophen use during pregnancy causes childhood asthma. Acetaminophen remains the analgesic and antipyretic of choice during pregnancy.

## Conflict of interest

Dr. Scialli is a consultant for Cadence Pharmaceuticals, Inc.

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