Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children

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Background: Several studies have reported an association between use of over-the-counter antipyretics during pregnancy or infancy and increased asthma risk. An important potential limitation of these observational studies is confounding by indication.

Objectives: We investigated the association of antipyretic intake during pregnancy and during the first year of life (infancy) with asthma-related outcomes before and after controlling for early-life respiratory tract infections.

Methods: We included 1490 mother-child pairs in Project Viva, a longitudinal prebirth cohort study. We categorized prenatal acetaminophen exposure as the maximum intake (never, 1-9 times, or ≥10 times) in early pregnancy or midpregnancy and ibuprofen intake as presence or absence in early pregnancy. We expressed intake of antipyretics in infancy as never, 1 to 5 times, 6 to 10 times, or more than 10 times. We examined the associations of acetaminophen and ibuprofen (per unit increase in exposure category) during pregnancy and infancy with wheeze, asthma, and allergen sensitization in early childhood (3-5 years of age, n = 1419) and midchildhood (7-10 years of age, n = 1220).

Results: Unadjusted models showed an increased asthma risk in early childhood for higher infant acetaminophen (odds ratio [OR], 1.21; 95% CI 1.04-1.41) and ibuprofen (OR, 1.35; 95% CI, 1.19-1.52) intake. Controlling for respiratory tract infections attenuated estimates for acetaminophen (OR, 1.03; 95% CI, 0.88-1.22) and ibuprofen (OR, 1.19; 95% CI, 1.05-1.36). Prenatal acetaminophen was associated with increased asthma (OR, 1.26; 95% CI, 1.02-1.58) in early childhood but not midchildhood.

Conclusions: Adjustment for respiratory tract infections in early life substantially diminished associations between infant antipyretic use and early childhood asthma. Respiratory tract infections should be accounted for in studies of antipyretics and asthma to mitigate bias caused by confounding by indication. (J Allergy Clin Immunol 2015;135:441-8.)

Key words: *Asthma, antipyretic, analgesic, respiratory infection*

Epidemiologic studies have documented an increase in the prevalence of asthma in the United States since the 1980s, especially among children less than 5 years old.[1]

Although it remains unclear why the prevalence of asthma has increased at such an alarming rate, a concomitant increase in acetaminophen and ibuprofen intake among children was also observed during this time period after reports of an association between aspirin use and Reye syndrome among children.[2] Although some aspirin-sensitive patients with asthma experience cross-reactivity with the use of acetaminophen or nonsteroidal anti-inflammatory drugs, these over-the-counter medications might play a role in the pathogenesis of asthma, even among subjects without a known sensitivity to aspirin. Studies in both children and adults have suggested that acetaminophen intake might be associated with allergic disease, incident asthma, and increased asthma symptoms.[3-13] Prenatal exposure to acetaminophen has also been linked to increased wheeze and asthma in childhood.[14-20] Few studies have examined the use of ibuprofen; one cross-sectional study of adults found no association between ibuprofen use and asthma.[6] A randomized trial of ibuprofen versus acetaminophen for treatment of fever in children found a reduction in outpatient visits for asthma among asthmatic children 6 months to 12 years of age in the ibuprofen group but no difference in hospitalization rates for asthma.[3] Without a placebo group, it is unclear whether the observed effect was due to increased risk from acetaminophen intake or possible protective effects of ibuprofen. One of the major limitations of observational studies on intake of medications is the potential for confounding by indication.[21] Confounding by indication can occur when those patients who take a drug differ from those who do not according to the medical indication for the drug.[22] In observational studies of asthma, confounding by indication can occur if respiratory tract infections lead independently both to wheeze and other symptoms, such as fever, malaise, or headache, for which acetaminophen or ibuprofen are administered. Many studies of acetaminophen use and asthma do not adequately address this potential source of confounding. Others do adjust for infection in early life but

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Abbreviations used
BMI: Body mass index
OR: Odds ratio

do not simultaneously consider exposure to both acetaminophen and ibuprofen.[9,23-26]

The primary aim of the current study was to investigate the associations between intake of either acetaminophen or ibuprofen during the first year of life (infancy) and asthma-related outcomes in early childhood and midchildhood after adjusting for respiratory tract infections in infancy. In light of the frequent coexistence of asthma with other allergic disorders, we also examined the potential association between acetaminophen or ibuprofen intake and allergen sensitization. Lastly, we investigated the link between maternal intake of acetaminophen or ibuprofen during pregnancy and the incidence of wheeze, asthma, and allergen sensitization in children.

METHODS

This study involved women and children enrolled in Project Viva, an ongoing longitudinal cohort study of pregnant women and their offspring. The design of this cohort study has been described in detail elsewhere[27] and is reviewed briefly here. Institutional review boards at all participating institutions approved the study.

Participants were recruited into Project Viva at 8 offices of Harvard Vanguard Associates in Eastern Massachusetts between 1999 and 2002. Exclusion criteria were multiple gestation, inability to answer questions in English, plans to move out of the study area before delivery of the infant, and gestational age at the time of presentation for prenatal care.

Of the 2128 women who delivered a live infant, we excluded 45 participants whose gestational age at birth was less than 34 weeks, 11 who were missing all exposure data (acetaminophen during pregnancy and during the first year), and 582 who were missing all outcome data (in early childhood [age 3-5 years] and midchildhood [age 7-10 years]). Overall, our sample size for the current analysis was 1490 mother-infant pairs during infancy, 1419 (95%) at age 3 to 5 years, and 1220 (82%) at age 7 to 10 years. Comparison of the 1490 participants in this analysis with the 593 excluded participants with delivery after 34 weeks showed some differences. For example, more of the included subjects were white (70% vs 60%) and highly educated (68% vs 55% with a college education) and had household incomes of $70,000/y or greater (63% vs 56%) than excluded participants, but the 2 groups did not differ on mean maternal prepregnancy body mass index (BMI), gestational age at delivery, or maternal history of asthma.

We performed structured interviews and administered questionnaires at the time of the woman's first prenatal clinic visit and at 26 to 28 weeks' gestation. During the first trimester, we gathered information regarding maternal age, prepregnancy maternal weight and height, household income, maternal history of asthma or eczema, and paternal history of asthma or eczema. Additionally, each mother completed questionnaires at 6 months and 1 year postpartum, with questions relating to the health of her child, including administration of acetaminophen, ibuprofen, and multivitamins to the child and occurrence of ear infections, bronchiolitis, pneumonia, bronchitis, croup, or other respiratory tract infections. The questionnaires also included questions regarding potential confounders, such as exposure to passive smoking, duration of breast-feeding, number of children less than 12 years old in the home, and presence of furry pets in the home.

Intake of acetaminophen and ibuprofen

Participants were asked to categorize their infant's acetaminophen intake during the first year of life as never, 1 to 5 times, 6 to 10 times, and greater than 10 times. Each dose of acetaminophen was counted as a single administration "time." Ibuprofen intake during the first year of life was assessed in a similar manner (never, 1-5 times, 6-10 times, and >10 times).

Acetaminophen intake during pregnancy was categorized as never, intermediate (1-9 times), or high (≥10 times). Because of the infrequent use, ibuprofen intake was categorized as either yes or no during pregnancy.

Exposures with more than 2 levels were analyzed as ordinal categorical variables after a linear dose response was verified for each increasing intake category versus the lowest intake level. Therefore the odds ratios (ORs) obtained for these exposures represent the risk associated with each increase in intake category.

In a set of alternate analyses, we computed overall cumulative exposure scores (prenatal plus infant) for both acetaminophen and ibuprofen. For the acetaminophen score, the maximum prenatal intake level (0, never; 1, 1-9 times during pregnancy; and 2, ≥10 times during pregnancy) was added to the infant intake level in the first year of life (0, never; 1, 1-10 times; and 2, >10 times) to produce an ordinal cumulative exposure score (range, 0-4). For the ibuprofen score, prenatal ibuprofen intake level (0, none during pregnancy; 1, at least once during pregnancy) was added to infant intake level in the first year of life (0, never; 1, 1-10 times; and 2, >10 times) to produce an ordinal cumulative exposure score for ibuprofen (range, 0-3). These scores were entered into models for early childhood and midchildhood asthma, recurrent wheeze, and sensitization outcomes, as described above.

Outcome measures

The asthma-related outcomes at early childhood were (1) *recurrent wheeze*, which was defined as mother's report of wheezing between 2 and 3 years of age (year 3 questionnaire) plus wheezing in either year 1 or year 2 versus no wheezing; (2) *asthma*, which was defined as mother's report of a doctor's diagnosis of asthma, wheeze, or reactive airway disease at any time between birth and age 3 years; and (3) *allergen sensitization*, which was defined as any specific IgE level of 0.35 IU/mL or greater to common indoor (*Dermatophagoides farinae*, cat, dog, and cockroach), mold (*Alternaria* or *Aspergillus* species), or food (egg white) allergens or a total IgE level of 75.6 IU/mL or greater (≥75th percentile for IgE).

The asthma-related outcome measures at midchildhood were as follows: (1) *persistent wheeze*, which was defined as mother's report of wheezing in the first 3 years and wheezing between 6 and 7 years of life (year 7 questionnaire); (2) *current asthma*, which was defined as mother's report of a doctor's diagnosis of asthma since birth reported on the midchildhood questionnaire plus report of current wheeze or asthma medication at midchildhood (comparison group had no asthma diagnosis, no wheeze, or no asthma medication use); and (3) *allergen sensitization*, which was defined as any specific IgE level of 0.35 IU/mL or greater (to common indoor allergens and mold, as listed above), food allergens (egg white, milk, and soy bean), outdoor allergens (rye grass and ragweed), or total IgE level of 100 IU/mL or greater.

Potential confounders

We gathered data on infections in infancy by questionnaire. Mothers were asked to report any diagnosis of a respiratory tract infection (bronchiolitis, pneumonia, bronchitis, croup, or other respiratory tract infection) or ear infection by a health care professional in the first year of the child's life. Other potential confounders considered in the analysis included child's sex, birth weight (continuous), race/ethnicity (white, black, Hispanic, and other), maternal age, maternal BMI, maternal history of asthma or eczema, paternal history of asthma or eczema, duration of breast-feeding (<9 vs ≥9 months), household income (<$40,000, $40,000-$70,000, and >$70,000), exposure to passive smoking (hours per week of exposure), number of other children less than 12 years old in the home (≤1 vs >1), child care attendance, smoking during pregnancy, and multivitamin use during the first year of life.

Statistical analysis

All statistical analyses were performed with SAS statistical software, version 9.3 (SAS Institute, Cary, NC). We first performed unadjusted logistic regression to investigate the association between each exposure and each of the 3 outcomes