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Prenatal and Infant Exposure to Acetaminophen and Ibuprofen and the Risk for Wheeze and Asthma in Children

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Abstract

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, 1) during pregnancy and 2) during the first year of life (infancy), with asthma-related outcomes, before and after controlling for early life respiratory infections.

Methods—We included 1490 mother-child pairs in Project Viva, a longitudinal pre-birth cohort study. We categorized prenatal acetaminophen exposure as the maximum intake (never, 1–9 or 10 times) in early or mid-pregnancy, and ibuprofen intake as presence or absence in early pregnancy. We expressed intakes of antipyretics in infancy as never, 1–5, 6–10, or >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 (3–5 y) (n= 1419) and mid-childhood (7–10 y) (n= 1220).

Results—Unadjusted models showed an elevated asthma risk in early childhood for higher infant acetaminophen (OR 1.21, 95% CI 1.04, 1.41) and ibuprofen (OR 1.35, 95% CI 1.19, 1.52) intake. Controlling for respiratory 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 but not mid-childhood.

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Conclusions—Adjustment for respiratory infections in early life substantially diminished associations between infant antipyretics and early childhood asthma. Respiratory infections should be accounted for in studies of antipyretics and asthma, to mitigate bias due to confounding by indication.

Keywords

Asthma; antipyretic; analgesic; respiratory infection

INTRODUCTION

Epidemiologic studies have documented an increase in the prevalence of asthma in the United States since the 1980s, especially among children under the age of five years.⁽¹⁾ Although it remains unclear why the prevalence of asthma has risen at such an alarming rate, a concomitant increase in acetaminophen and ibuprofen use among children was also observed during this time period, following reports of an association between aspirin use and Reye's Syndrome among children.⁽²⁾ While some aspirin-sensitive patients with asthma experience cross-reactivity with the use of acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs), these over-the-counter medications may play a role in the pathogenesis of asthma even among individuals without a known sensitivity to aspirin. Studies in both children and adults have suggested that acetaminophen intake may be associated with allergic disease, incident asthma and increased symptoms of asthma among known asthmatics.^(3–13) Prenatal exposure to acetaminophen has also been linked to increased childhood asthma risk in many^(14–18, 20), but not all⁽¹⁹⁾ reports. 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 among children less than 2 years of age.⁽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 may occur whenever those individuals 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 may occur if respiratory infections lead independently both to wheeze and to other symptoms such as fever, malaise or headache for which acetaminophen or ibuprofen are administered. Many studies of acetaminophen use and asthma fail to adequately address this potential source of confounding. Others do adjust for infection in early life, but 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 mid-childhood, after adjusting for respiratory infections in infancy. In light of the frequent co-existence 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 incidence of wheeze, asthma and allergen sensitization in children.

METHODS

This study involves 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 eight 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 prior to delivery of the infant and gestational age at 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 <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 (age 3–5) and mid-childhood (age 7–10)). Overall, our sample size for the current analysis was 1490 mother-infant pairs during infancy, 1419 (95%) at age 3–5 years and 1220 (82%) at age 7–10 years. Comparison of the 1490 participants in this analysis with the 593 excluded participants who delivered after 34 weeks showed some differences. For example, more of the included subjects were white (70% vs. 60%), highly educated (68% vs. 55% with a college education), and had household incomes \$70,000/y (63% vs. 56%) than excluded participants, but the two groups did not differ on mean maternal pre-pregnancy 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 of gestation. During the 1st trimester we gathered information regarding maternal age, pre-pregnancy 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 the administration of acetaminophen, ibuprofen, and multivitamins to the child and occurrence of ear infections, bronchiolitis, pneumonia, bronchitis, croup or other respiratory infections. The questionnaires also included questions regarding potential confounders such as exposure to passive smoking, duration of breastfeeding, number of children under the age of 12 years 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, 1–5 times, 6–10 times, and greater than 10 times. Each individual 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 greater than 10 times).

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

Exposures with more than two levels were analyzed as ordinal categorical variables, after a linear dose response was verified for each increasing intake category vs. 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 + infant) for both acetaminophen and ibuprofen. For the acetaminophen score, the maximum prenatal intake level (0=never, 1= 1 to 9 times during pregnancy, 2= greater than or equal to 10 times during pregnancy) was added to the infant intake level in the first year of life (0=never, 1=1 to 10 times, 2= greater than 10 times), to produce an ordinal cumulative exposure score (ranging from 0 to 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 to 10 times, 2= greater than 10 times) to produce an ordinal cumulative exposure score for ibuprofen (ranging from 0 to 3). These scores were entered into models for early and mid- childhood asthma, recurrent wheeze and sensitization outcomes, as described above.

Outcome Measures

The asthma-related outcomes at early childhood were: 1) *recurrent wheeze* 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 vs. no wheezing; 2) *Asthma* defined as mother's report of a doctor diagnosis of asthma, wheeze or reactive airway disease at anytime between birth and age 3; 3) *allergen sensitization* defined as any specific IgE level ≥ 0.35 IU/ml to common indoor (*Dermatophagoides farinae*, cat, dog, cockroach), mold (*Alternaria*, *Aspergillus*) or food (egg white) allergens, or total IgE ≥ 75.6 IU/ml (greater than or equal to the 75th percentile for IgE).

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

Potential confounders

We gathered data on infections in infancy by questionnaire. Mothers were asked to report any diagnosis of a respiratory infection (bronchiolitis, pneumonia, bronchitis, croup, other respiratory 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 sex, birth

weight (continuous), race/ethnicity (white, black, Hispanic, and other), maternal age, maternal body mass index (BMI), maternal history of asthma or eczema, paternal history of asthma or eczema, duration of breastfeeding (<9 months versus ≥9 months), household income (<\$40,000, \$40–70,000, and >\$70,000), exposure to passive smoking (hours per week of exposure), number of other children under 12 years in the home (≤1 versus >1), attendance at childcare, smoking during pregnancy and multivitamin use during the first year of life.

Statistical analysis

All statistical analyses were performed using SAS statistical software, version 9.3 (SAS Institute, Inc., Cary, NC). We first performed unadjusted logistic regression to investigate the association between each exposure and each of the 3 outcomes in early childhood. Then we constructed models that adjusted for respiratory and ear infections during infancy, to account for potential confounding by indication. Lastly, we adjusted for respiratory and ear infections plus those covariates that were of *a priori* interest or confounded the exposure – outcome associations. These multivariable models included child's sex and multivitamin, ibuprofen (4-level) and acetaminophen (4-level) intake during the first year of life; mother's age at enrollment, race/ethnicity, and pre-pregnancy BMI; acetaminophen intake during pregnancy (3-level) and ibuprofen intake during pregnancy (2-level); household income, number of children under 12 years of age living in the household, breastfeeding duration, passive exposure to smoking during the first year of life, smoking during pregnancy and childcare attendance; and maternal and paternal history of asthma.

Similar models were constructed for outcomes in mid-childhood. We performed logistic regression to examine the relationship between ibuprofen or acetaminophen (using the same variables for intake in pregnancy/infancy) and current asthma, controlling for the same *a priori* confounders as listed above.

RESULTS

Table 1 shows the sociodemographic, perinatal, familial and environmental characteristics of the mothers and infants enrolled in the study. Mean maternal age was 32 years. Seventy percent of the participants in the study were white, with 14% black and 7% Hispanic. Sixty three percent of women reported a household income >\$70,000 and only 7% reported exposure to any passive smoke. Characteristics of the mother- infant pairs at enrollment were very similar to the characteristics of those followed until early and mid-childhood. By early childhood (age 3–5), 18% of children had recurrent wheezing, 22% had a doctor's diagnosis of asthma or RAD, and 40% tested positive for allergen sensitization. By mid-childhood (age 7–10), 5.2% had persistent wheezing, 19% of children had current asthma, and 53% tested positive for allergen sensitization. Asthma diagnosis in early childhood showed a strong association with current asthma in mid-childhood (OR=17.21 (95% CI 11.7 to 25.3)) for current asthma at age 7–10, if wheeze or asthma was reported at age 3–5. Only 9% of current asthma cases in mid-childhood had no prior asthma diagnosis or report of recurrent wheeze in early life.

The distributions of acetaminophen and ibuprofen use during pregnancy and the first year are shown in Table 2. Although most mothers reported at least some acetaminophen use during pregnancy (70%), ibuprofen use during early pregnancy was uncommon (17%), and use after the first trimester was rare (3%). Ninety-five percent of children were given acetaminophen at least once the first year of life (29% 1–5 times, 24% 6–10 times, and 42% >10 times). Infant ibuprofen intake was more evenly distributed across categories (31% never, 28% 1–5, 17% 6–10, and 24% >10 times). Sixty six percent of infants (n=780) were exposed to both acetaminophen and ibuprofen during infancy. For infants in the highest acetaminophen exposure (>10) category (n=508), ibuprofen intakes were as follows: 44% for >10 times in the first year of life, 12% for 6–10 times, and 23% for 1–5 times (the remaining 21% reported no ibuprofen intake in infancy). For infants in the highest ibuprofen intake category (>10 times) (n=288), acetaminophen intakes were as follows: 77% for > 10 times, 10% for 6–10 times, and 10% for 1–5 times (the remaining 3% reported no acetaminophen intake in infancy).

The results of the analysis of acetaminophen intake during infancy and asthma-related outcomes are shown in Table 3. In the unadjusted analysis, increasing acetaminophen intake during infancy was associated with recurrent wheeze (OR 1.29, 95% CI 1.06, 1.56), and asthma (OR 1.21, 95% CI 1.04, 1.41) in early childhood. After adjustment for respiratory infections these associations became null (OR 1.05, 95% CI 0.85, 1.31 for recurrent wheeze, and OR 1.03, 95% CI 0.88, 1.22 for asthma). Higher acetaminophen intake during the first year was not associated with allergen sensitization in early childhood. For outcomes in mid-childhood (Table 3), acetaminophen intake in the first year of life was associated with persistent wheeze (OR 1.28, 95% CI 0.95, 1.74) and current asthma (OR 1.27, 95% CI 1.05, 1.54) in unadjusted models. Adjustment for respiratory infections reduced the odds ratio for persistent wheeze in later childhood (OR 1.06, 95% CI 0.76, 1.46). For current asthma, attenuation of the association from (OR 1.27, 95% CI 1.05, 1.54 in the unadjusted model) to (OR 1.21, 95% CI 1.00, 1.48) was observed after adjustment for potential confounders including respiratory infections during infancy. In the same set of multivariable models, respiratory infections themselves were associated with an increased risk of asthma in both early childhood (OR 3.82, 95% CI 2.69, 5.41) and mid-childhood (OR 2.27, 95% CI 1.44, 3.57).

Ibuprofen intake during the first year of life was associated with increased odds of recurrent wheeze (OR 1.38, 95% CI 1.19, 1.60), and asthma (OR 1.35, 95% CI 1.19, 1.52) in unadjusted models for early childhood outcomes. These associations were attenuated (OR 1.17, 95% CI 0.99, 1.40 for recurrent wheeze) and (OR 1.19, 95% CI 1.05, 1.36 for asthma), after adjustment for respiratory infections. (Table 3) Odds ratios for the effect of infant ibuprofen intake on persistent wheeze and current asthma at school age were substantially lower than those for wheeze and asthma outcomes in early childhood. Negative associations of borderline significance were observed for ibuprofen intake in infancy and allergen sensitization both in early childhood (OR=0.85, 95% CI 0.71, 1.01) and mid-childhood (OR= 0.87, 95% CI 0.72, 1.05).

Acetaminophen intake during pregnancy was associated with increased risk of early childhood recurrent wheeze and asthma outcomes in both the unadjusted and multivariable

analysis (Table 4). Adjustment for potential confounders lowered effect estimates for recurrent wheeze and asthma outcomes by 10 to 25%. Prenatal acetaminophen exposure was not associated with allergen sensitization in early or mid- childhood. Ibuprofen intake during early pregnancy was associated with early childhood asthma in the unadjusted analysis (OR 1.55, 95% CI 1.12, 2.14) but the association did not remain in the multivariable analysis (OR 1.17, 95% CI 0.78, 1.76) (Table 4).

For cumulative exposure models, trends appeared to mirror the strongest effect estimate seen for either prenatal or infant exposure to a given antipyretic, although, comparatively, odds ratios were higher overall for cumulative exposures (Table 5). Acetaminophen and ibuprofen cumulative exposure scores were associated with a 17 to 50% increased odds of asthma related outcomes. Attenuation of these effects was observed for early (but not mid) childhood asthma, after adjustment for potential confounders, including respiratory infections in infancy. Although cumulative exposure to acetaminophen did not appear to be linked to allergen sensitization in our data, we did observe lower odds of allergen sensitization for infants with higher cumulative exposure scores for ibuprofen.

DISCUSSION

In this study, we found that controlling for respiratory infections in infancy diminished the associations observed for infant antipyretic intake and asthma-related outcomes. The most substantial attenuation of risk estimates occurred in models of early childhood wheeze and asthma. Adjustment for respiratory infections considerably reduced risk estimates, rendering the association between infant acetaminophen intake and early childhood asthma null. A substantial decrease in the associations between infant ibuprofen and early childhood wheeze and asthma was also observed after accounting for respiratory infections in infancy (although some increased risk remained after adjustment). In contrast, confounding by respiratory infections had a smaller impact on associations for mid-childhood asthma, and some suggestion of increased risk remained in adjusted models both for infant and cumulative (prenatal + infant) acetaminophen exposure. This may be due to the fact that the early outcomes were more proximal to the exposure and confounder than the mid-childhood outcomes. None of the exposures studied were associated with an increased risk of allergen sensitization, suggesting that if any true relationship between antipyretic exposure in infancy and asthma incidence does exist, it is unlikely to operate through an IgE-mediated allergic disease pathway.

Our findings make an important contribution to the growing body of literature on the relationship between acetaminophen intake and asthma-related outcomes. One of the earliest epidemiologic studies to suggest a link between acetaminophen and asthma was a population-based ecological study of European countries that reported positive associations between increased sales of acetaminophen and rates of both asthma-related symptoms among 13 to 14 year-olds and asthma/bronchial hyper-responsiveness among adults.⁽²⁸⁾ A report from the Nurse's Health Study indicated that frequency of acetaminophen use was prospectively associated with an increased risk of adult-onset asthma⁽⁴⁾, and a subsequent cross-sectional analysis of the Third National Health and Nutrition Examination Survey

(NHANES III) revealed a dose-response association between acetaminophen use and asthma, as well as an inverse association with lung function.⁽⁶⁾

Unfortunately, none of these studies adjusted for common illnesses that might have led to increased use of acetaminophen among those with respiratory symptoms. A recent meta-analysis of cross-sectional, case-control and cohort study results⁽²⁹⁾ also concluded that acetaminophen use is linked to increased risk of asthma in children and adults. However, only unadjusted odds ratios were included in the analysis, so that even this systematic review is prone to confounding by indication.

In addition to the data presented here, other studies have adjusted for respiratory infections in analyses of early life acetaminophen use and asthma. In an Australian birth cohort, the initial association observed between acetaminophen use in the first two years of life and childhood asthma was no longer present in models controlling for early life respiratory infections.⁽²⁵⁾

Furthermore, the authors noted that acetaminophen taken for non-respiratory causes did not show a relationship with asthma or wheeze in unadjusted models. In the Italian arm of the ISAAC study, although they were unable to control for confounding by respiratory infections directly, Rusconi et al concluded, based on logistic regression analyses and directed acyclic graphs, that the association between acetaminophen exposure in infancy and childhood asthma ‘might fully or in part, be due to confounding’.⁽³⁰⁾ An analysis by Schnabel et al, also suggests that underlying respiratory infections may explain the association between acetaminophen intake and asthma development.⁽²⁶⁾ In contrast, an Ethiopian prospective birth cohort study reported a link between acetaminophen in early life and increased risk of allergic disease in childhood after taking into account possible confounding by indication. However, this analysis controlled for possible symptoms of respiratory infections, rather than diagnosis of the infections themselves; therefore adjustment for this potential source of bias may have been incomplete.⁽⁹⁾ A prospective birth cohort study in Oslo, in which a relatively low proportion of infants (83 out of 1016) received acetaminophen by 6 months, reported that respiratory infections did not confound the association between infant acetaminophen intake and asthma in girls.⁽³⁴⁾ Lastly, in the COPSAC2000 study, an independent association was observed between infant acetaminophen intake and early childhood asthma after adjusting for respiratory infections, however the authors acknowledge that there could be some residual confounding by indication.⁽²⁴⁾

Because we have demonstrated attenuation of associations between early life acetaminophen intake and asthma-related outcomes in childhood following adjustment for respiratory infections, our study offers evidence for confounding by indication in any analysis that does not adjust for respiratory infections. This conclusion is further supported by the fact that similar patterns were observed for intake of ibuprofen. Thus, it appears that confounding by indication is likely to be a generalized phenomenon that is not specific to a given analgesic or antipyretic, but rather may play a role in any study of widely available over-the-counter medications.

Although results for acetaminophen exposure in infancy and early childhood asthma outcomes were clearly null once respiratory infections and other confounders were adjusted for, odds ratios for infant acetaminophen intake and mid-childhood asthma showed some suggestion of increased risk. Infant ibuprofen intake was also associated with an increased risk of early childhood asthma in adjusted models (although controlling for respiratory infections did decrease the crude measure of association considerably). Residual confounding by uncomplicated upper respiratory infections (unaccounted for in our analysis) may explain the increase in asthma risk observed in adjusted models. Alternatively, acetaminophen and ibuprofen intake in infancy could have underlying biological effects that increase the risk of asthma. For instance, acetaminophen may deplete antioxidant capacity⁽³¹⁾, thereby increasing generation of reactive oxygen species that may contribute to asthmatic airway inflammation.⁽³²⁾ Ibuprofen is an inhibitor of cyclooxygenase (COX)-1, which may result in upregulation of leukotrienes, which are thought to play a role in asthma.⁽³³⁾ While ibuprofen exposure was associated with increased asthma risk, odds ratios for allergen sensitization (in infant and cumulative exposure models) went in the opposite direction, demonstrating a negative association between ibuprofen and atopy. Further studies with more detailed information on indications for antipyretic use in early life are needed to ensure a more complete adjustment for confounding by indication.

While the majority of studies on antipyretics and asthma have focused on antipyretic use in infancy and childhood, other reports have examined the potential effects of prenatal exposures. An early report from a large birth cohort study found that maternal intake of acetaminophen between 20 and 32 weeks of gestation was associated with increased wheeze at age 30–42 months.⁽¹⁵⁾ A subsequent analysis of the same cohort suggested that intake of acetaminophen during this period was associated with both asthma and wheeze at age 69–81 months.⁽¹⁴⁾ A Swedish birth cohort study reported similar findings for prenatal acetaminophen exposure and wheeze using a more refined phenotype (ICS-treated wheeze not resulting from viral illness).⁽¹⁸⁾

In addition to asthma-related outcomes, maternal acetaminophen use during pregnancy has also been linked to increased odds of allergic rhinitis in school aged children.⁽³⁴⁾ Prenatal acetaminophen exposure has been hypothesized to induce oxidative stress in utero, possibly precipitating epigenetic changes that increase the offspring's susceptibility to asthma. In support of this hypothesis, prenatal acetaminophen exposure studies have shown evidence for effect modification by genetic polymorphisms in oxidative stress pathways. In a population-based New York birth cohort, children with functional polymorphism in *GSTP1* had an increased risk of wheeze in response to prenatal acetaminophen.⁽¹⁶⁾ Findings from the Avon Longitudinal Study of Parents and Children demonstrated potential modification of response to prenatal acetaminophen by maternal polymorphisms in *Nrf2* and *GSTT1*.⁽³⁵⁾

In the present work, we observed a 40 to 50% increased odds of wheeze and asthma in early childhood for those children exposed to higher levels of prenatal acetaminophen, which was attenuated to 30 to 40% after multivariable adjustment. These findings suggest that there may be some increased risk of childhood asthma with prenatal acetaminophen intake. However, we did not have information on maternal indication for acetaminophen intake, and therefore could not adjust for confounding by maternal indication in these analyses. As

result, we were unable to rule out the possible influence of maternal viral infection, or other indications that may be associated with acetaminophen intake. In future studies, information on maternal indication for antipyretic use should be gathered. Finally, the aim of this analysis was to investigate the effects of early life antipyretic intake and the role of respiratory infections in the first year. Future studies should also investigate antipyretic intake and respiratory infections throughout childhood.

The current study has several strengths. Project Viva is a large, prospective pre- birth cohort study that enrolled women early in pregnancy. Due to the large amount of information gathered prospectively, we were able to control for multiple potential confounders simultaneously in all of our analyses. Most notably, we adjusted for the presence of respiratory infections during infancy, in models for infant antipyretic intake and asthma outcomes. In contrast to other studies, we were able to examine both ibuprofen and acetaminophen (prenatal and early life) in multiple regression models.

Our study also has several potential limitations. Although we were able to capture antipyretic intake within a certain exposure range, we did not have information on exact dose. As mentioned above, incomplete adjustment for uncomplicated upper respiratory infections may have resulted in residual confounding by indication in models for antipyretic use in infancy. We did not account for common indications for antipyretic use in pregnancy, which may confound associations for prenatal antipyretic exposures. Lastly, because administration of a medication must be linked in time with a given indication in order for confounding by indication to occur, an additional limitation of the current study was our inability to determine the relative timing of administration of medication compared with that of respiratory illness, and the continued use of antipyretics throughout childhood. While our analyses did show a potential link between prenatal exposure to acetaminophen and asthma outcomes in early childhood, these associations did not persist in models for mid-childhood asthma. Further studies with detailed information on timing and dose of antipyretics during pregnancy, as well as maternal indication for antipyretic use are required to better understand these relationships.

In conclusion, crude estimates showing increased childhood wheeze and asthma risk with infant antipyretic intake were decreased after controlling for respiratory infections in early life. The most substantial attenuation of risk estimates was observed in models for recurrent wheeze and asthma in early childhood; the effect of respiratory infections as a confounder was less pronounced in models of mid-childhood asthma and persistent wheeze. Our results suggest that respiratory infections, a major cause of fever in infancy, should be considered in all studies of infant antipyretic use and childhood asthma, in order to mitigate bias due to confounding by indication.

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References

1. Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma--united states, 1980–1999. *MMWR Surveill Summ*. 2002 Mar 29; 51(1):1–13.
2. Arrowsmith JB, Kennedy DL, Kuritsky JN, Faich GA. National patterns of aspirin use and reye syndrome reporting, united states, 1980 to 1985. *Pediatrics*. 1987 Jun; 79(6):858–863. [PubMed: 3588140]
3. Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics*. 2002 Feb; 109(2):E20. [PubMed: 11826230]
4. Barr RG, Wentowski CC, Curhan GC, Somers SC, Stampfer MJ, Schwartz J, et al. Prospective study of acetaminophen use and newly diagnosed asthma among women. *Am J Respir Crit Care Med*. 2004 Apr 1; 169(7):836–841. [PubMed: 14711794]
5. Cohet C, Cheng S, MacDonald C, Baker M, Foliaki S, Huntington N, et al. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. *J Epidemiol Community Health*. 2004 Oct; 58(10):852–857. [PubMed: 15365112]
6. McKeever TM, Lewis SA, Smit HA, Burney P, Britton JR, Cassano PA. The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med*. 2005 May 1; 171(9):966–971. [PubMed: 15735054]
7. Davey G, Berhane Y, Duncan P, Aref-Adib G, Britton J, Venn A. Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in butajira, ethiopia. *J Allergy Clin Immunol*. 2005 Oct; 116(4):863–868. [PubMed: 16210062]
8. Amberbir A, Medhin G, Hanlon C, Britton J, Venn A, Davey G. Frequent use of paracetamol and risk of allergic disease among women in an ethiopian population. *PLoS One*. 2011; 6(7):e22551. [PubMed: 21811632]
9. Amberbir A, Medhin G, Hanlon C, Britton J, Davey G, Venn A. Effects of early life paracetamol use on the incidence of allergic disease and sensitization: 5 year follow-up of an ethiopian birth cohort. *PLoS One*. 2014 Apr 9; 9(4):e93869. [PubMed: 24718577]
10. Kurukulaaratchy RJ, Raza A, Scott M, Williams P, Ewart S, Matthews S, et al. Characterisation of asthma that develops during adolescence; findings from the isle of wight birth cohort. *Respir Med*. 2012 Mar; 106(3):329–337. [PubMed: 22212639]
11. Beasley RW, Clayton TO, Crane J, Lai CK, Montefort SR, Mutius E, et al. Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: International study of asthma and allergies in childhood phase three. *Am J Respir Crit Care Med*. 2011 Jan 15; 183(2):171–178. [PubMed: 20709817]
12. Shaheen SO, Sterne JA, Songhurst CE, Burney PG. Frequent paracetamol use and asthma in adults. *Thorax*. 2000 Apr; 55(4):266–270. [PubMed: 10722764]
13. Shaheen S, Potts J, Gnatiuc L, Makowska J, Kowalski ML, Joos G, et al. The relation between paracetamol use and asthma: A GA2LEN european case-control study. *Eur Respir J*. 2008 Nov; 32(5):1231–1236. [PubMed: 18579547]
14. Shaheen SO, Newson RB, Henderson AJ, Headley JE, Stratton FD, Jones RW, et al. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy*. 2005 Jan; 35(1):18–25. [PubMed: 15649261]
15. Shaheen SO, Newson RB, Sherriff A, Henderson AJ, Heron JE, Burney PG, et al. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax*. 2002 Nov; 57(11):958–963. [PubMed: 12403878]
16. Perzanowski MS, Miller RL, Tang D, Ali D, Garfinkel RS, Chew GL, et al. Prenatal acetaminophen exposure and risk of wheeze at age 5 years in an urban low-income cohort. *Thorax*. 2010 Feb; 65(2):118–123. [PubMed: 19850963]
17. Rebordosa C, Kogevinas M, Sorensen HT, Olsen J. Pre-natal exposure to paracetamol and risk of wheezing and asthma in children: A birth cohort study. *Int J Epidemiol*. 2008 Jun; 37(3):583–590. [PubMed: 18400839]

18. Goksor E, Thengilsdottir H, Alm B, Norvenius G, Wennergren G. Prenatal paracetamol exposure and risk of wheeze at preschool age. *Acta Paediatr.* 2011 Dec; 100(12):1567–1571. [PubMed: 21767300]
19. Kang EM, Lundsberg LS, Illuzzi JL, Bracken MB. Prenatal exposure to acetaminophen and asthma in children. *Obstet Gynecol.* 2009 Dec; 114(6):1295–1306. [PubMed: 19935033]
20. Persky V, Piorkowski J, Hernandez E, Chavez N, Wagner-Cassanova C, Vergara C, et al. Prenatal exposure to acetaminophen and respiratory symptoms in the first year of life. *Ann Allergy Asthma Immunol.* 2008 Sep; 101(3):271–278. [PubMed: 18814450]
21. Signorello LB, McLaughlin JK, Lipworth L, Friis S, Sorensen HT, Blot WJ. Confounding by indication in epidemiologic studies of commonly used analgesics. *Am J Ther.* 2002 May-Jun;9(3): 199–205. [PubMed: 11941379]
22. Rothman, K., editor. *Epidemiology: An introduction.* New York: Oxford University Press; 2002.
23. Bakkeheim E, Mowinckel P, Carlsen KH, Haland G, Carlsen KC. Paracetamol in early infancy: The risk of childhood allergy and asthma. *Acta Paediatr.* 2011 Jan; 100(1):90–96. [PubMed: 21143295]
24. Kreiner-Moller E, Sevelsted A, Vissing NH, Schoos AM, Bisgaard H. Infant acetaminophen use associates with early asthmatic symptoms independently of respiratory tract infections: The copenhagen prospective study on asthma in childhood 2000 (COPSAC(2000)) cohort. *J Allergy Clin Immunol.* 2012 Dec; 130(6):1434–1436. [PubMed: 23102919]
25. Lowe AJ, Carlin JB, Bennett CM, Hosking CS, Allen KJ, Robertson CF, et al. Paracetamol use in early life and asthma: Prospective birth cohort study. *BMJ.* 2010 Sep 15;341:c4616. [PubMed: 20843914]
26. Schnabel E, Heinrich J. LISA Study Group. Respiratory tract infections and not paracetamol medication during infancy are associated with asthma development in childhood. *J Allergy Clin Immunol.* 2010 Nov; 126(5):1071–1073. [PubMed: 20888627]
27. Gillman MW, Rich-Edwards JW, Rifas-Shiman SL, Lieberman ES, Kleinman KP, Lipshultz SE. Maternal age and other predictors of newborn blood pressure. *J Pediatr.* 2004 Feb; 144(2):240–245. [PubMed: 14760269]
28. Newson RB, Shaheen SO, Chinn S, Burney PG. Paracetamol sales and atopic disease in children and adults: An ecological analysis. *Eur Respir J.* 2000 Nov; 16(5):817–823. [PubMed: 11153577]
29. Etminan M, Sadatsafavi M, Jafari S, Doyle-Waters M, Aminzadeh K, Fitzgerald JM. Acetaminophen use and the risk of asthma in children and adults: A systematic review and metaanalysis. *Chest.* 2009 Nov; 136(5):1316–1323. [PubMed: 19696122]
30. Rusconi F, Gagliardi L, Galassi C, Forastiere F, Brunetti L, La Grutta S, et al. Paracetamol and antibiotics in childhood and subsequent development of wheezing/asthma: Association or causation? *Int J Epidemiol.* 2011 Jun; 40(3):662–667. [PubMed: 21262745]
31. Nuttall SL, Khan JN, Thorpe GH, Langford N, Kendall MJ. The impact of therapeutic doses of paracetamol on serum total antioxidant capacity. *J Clin Pharm Ther.* 2003 Aug; 28(4):289–294. [PubMed: 12911681]
32. Dworski R. Oxidant stress in asthma. *Thorax.* 2000 Oct; 55(Suppl 2):S51–S53. [PubMed: 10992559]
33. Levy S, Volans G. The use of analgesics in patients with asthma. *Drug Saf.* 2001; 24(11):829–841. [PubMed: 11665870]
34. Bakkeheim E, Mowinckel P, Carlsen KH, Haland G, Carlsen KC. Paracetamol in early infancy: The risk of childhood allergy and asthma. *Acta Paediatr.* 2011 Jan; 100(1):90–96. [PubMed: 21143295]
35. Shaheen SO, Newson RB, Ring SM, Rose-Zerilli MJ, Holloway JW, Henderson AJ. Prenatal and infant acetaminophen exposure, antioxidant gene polymorphisms, and childhood asthma. *J Allergy Clin Immunol.* 2010 Dec;126(6):1141, 8.e7. [PubMed: 21051083]

Key Messages

- Respiratory infections may confound the relationship between infant antipyretic intake and early childhood asthma
- Confounding by indication should be considered in studies of antipyretics and asthma to mitigate this bias

Table 1

Characteristics of mother-infant pairs participating in Project Viva

	Total (n=1490)	Follow up in early childhood (n=1419)	Follow up in mid- childhood (n=1220)
	Mean (SD)		
Maternal age	32.2 (5.2)	32.3 (5.0)	32.2 (5.2)
Maternal pre-pregnancy BMI, kg/m ²	24.8 (5.3)	24.7 (5.2)	24.7 (5.2)
	N (%)		
Race/Ethnicity			
Black	213 (14.3)	181 (12.8)	183 (15.0)
Hispanic	98 (6.6)	88 (6.2)	75 (6.2)
White	1036 (69.7)	1015 (71.7)	846 (69.5)
Other	139 (9.4)	132 (9.3)	113 (9.3)
Household Income			
<\$40,000	193 (14.2)	168 (12.8)	160 (14.3)
\$40,000-\$70,000	314 (23.1)	301 (23.0)	251 (22.5)
>\$70,000	853 (62.7)	839 (64.1)	706 (63.2)
Maternal History of Asthma			
No	1290 (86.9)	1236 (87.3)	1067 (87.7)
Yes	195 (13.1)	179 (12.7)	149 (12.3)
Infant Sex			
Male	765 (51.3)	728 (51.3)	611 (50.1)
Female	725 (48.7)	691 (48.7)	609 (49.9)
Birth Weight, kg, mean (SD)	3.51 (0.52)	3.51 (0.52)	3.52 (0.51)
Exposure to Passive Smoking			
No	1214 (92.6)	1187 (92.7)	1014 (92.6)
Yes	97 (7.4)	94 (7.3)	81 (7.4)
Multivitamin Use during First Year			
No	1130 (81.8)	1095 (81.8)	925 (81.1)
Yes	251 (18.2)	244 (18.2)	215 (18.9)
Duration of Breastfeeding			
<9 months	847 (61.1)	816 (60.7)	681 (59.2)
9 months	540 (38.9)	528 (39.3)	469 (40.8)
Attendance at Childcare			
No	681 (56.3)	667 (56.2)	565 (55.1)
Yes	529 (43.7)	520 (43.8)	460 (44.9)
Respiratory Illnesses during First Year			
No	889 (73.6)	870 (73.4)	758 (74.1)
Yes	319 (26.4)	315 (26.6)	265 (25.9)
Ear Infections during First Year			
No	529 (43.9)	519 (43.9)	457 (44.8)

	Total (n=1490)	Follow up in early childhood (n=1419)	Follow up in mid- childhood (n=1220)
	Mean (SD)		
Yes	677 (56.1)	664 (56.1)	564 (55.2)

Table 2

Distribution of acetaminophen and ibuprofen intake in pregnancy and during the first year (N=1490)

Acetaminophen Intake		N (%)
During pregnancy		
	Never	430 (30.2)
	1–9 times	648 (45.6)
	10 times	344 (24.2)
During the first year		
	Never	54 (4.5)
	1–5 times	347 (28.9)
	6–10 times	292 (24.3)
	>10 times	508 (42.3)
Ibuprofen Intake		N (%)
During pregnancy		
	Never	1222 (83.2)
	1 time	247 (16.8)
During the first year		
	Never	375 (31.4)
	1–5 times	333 (27.9)
	6–10 times	197 (16.5)
	>10 times	288 (24.1)

Table 3

Early life acetaminophen and ibuprofen intake and wheeze, asthma and allergic sensitization in early and mid-childhood. Data from mother –infant pairs participating in Project Viva.

Exposure in Infancy	Early Childhood (Age 3 to 5) Outcomes							
	Recurrent Wheeze OR (95% CI)		Asthma OR (95% CI)		Allergen Sensitization OR (95% CI)		Adj. (All covars) ²	Adj. (All covars) ²
	Unadjusted	Adj. (Infection) ¹	Unadjusted	Adj. (Infection) ¹	Unadjusted	Adj. (Infection) ¹		
Acetaminophen	1.29 (1.06, 1.56)	1.05 (0.85, 1.31)	1.21 (1.04, 1.41)	1.03 (0.88, 1.22)	0.86 (0.72, 1.01)	0.90 (0.76, 1.08)	0.97 (0.78, 1.19)	
Ibuprofen	1.38 (1.19, 1.60)	1.17 (0.99, 1.40)	1.35 (1.19, 1.52)	1.19 (1.05, 1.36)	0.84 (0.73, 0.97)	0.88 (0.76, 1.02)	0.85 (0.71, 1.01)	
Exposure in Infancy	Mid-childhood (Age 7 to 10) Outcomes							
	Persistent Wheeze OR (95% CI)		Current Asthma OR (95% CI)		Allergen Sensitization OR (95% CI)		Adj. (All covars) ²	Adj. (All covars) ²
	Unadjusted	Adj. (Infection) ¹	Unadjusted	Adj. (Infection) ¹	Unadjusted	Adj. (Infection) ¹		
Acetaminophen	1.28 (0.95, 1.74)	1.06 (0.76, 1.46)	1.27 (1.05, 1.54)	1.21 (1.00, 1.48)	1.02 (0.85, 1.22)	1.05 (0.87, 1.27)	1.10 (0.88, 1.39)	
Ibuprofen	1.13 (0.89, 1.43)	0.95 (0.74, 1.23)	1.10 (0.95, 1.28)	1.05 (0.90, 1.23)	0.82 (0.70, 0.96)	0.85 (0.72, 1.00)	0.87 (0.72, 1.05)	

¹ Model includes analgesic exposure and adjustment for respiratory and ear infections in the first year of life

² Model includes all 4 analgesic exposures (acetaminophen in infancy, ibuprofen in infancy, prenatal acetaminophen, prenatal ibuprofen), respiratory and ear infections, covariates for child's sex and multivitamin intake, mother's age at enrollment, race/ethnicity, pre-pregnancy BMI, household income, number of children under 12 years of age in the home, breastfeeding duration, passive smoking exposure, smoking during pregnancy, childcare attendance, maternal and paternal history of asthma

Prenatal intake of acetaminophen and ibuprofen and wheeze, asthma and allergen sensitization in children in early and mid-childhood. Data from mother–infant pairs participating in Project Viva.

Table 4

	Early Childhood (Age 3 to 5) Outcomes					
	Recurrent Wheeze OR (95% CI)		Asthma OR (95% CI)		Allergen Sensitization OR (95% CI)	
	Unadjusted	Adjusted ¹	Unadjusted	Adjusted ¹	Unadjusted	Adjusted ¹
Prenatal Intake						
Acetaminophen	1.53 (1.23, 1.90)	1.41 (1.06, 1.89)	1.36 (1.14, 1.61)	1.26 (1.02, 1.58)	1.06 (0.87, 1.30)	1.04 (0.81, 1.34)
Ibuprofen	1.49 (0.98, 2.27)	1.10 (0.62, 1.93)	1.55 (1.12, 2.14)	1.17 (0.78, 1.76)	1.08 (0.72, 1.61)	0.85 (0.52, 1.39)
Mid-childhood (Age 7 to 10) Outcomes						
	Persistent Wheeze OR (95% CI)		Current Asthma OR (95% CI)		Allergen Sensitization OR (95% CI)	
	Unadjusted	Adjusted ¹	Unadjusted	Adjusted ¹	Unadjusted	Adjusted ¹
Prenatal Intake						
Acetaminophen	1.22 (0.87, 1.72)	1.03 (0.66, 1.60)	1.21 (0.98, 1.48)	1.25 (0.94, 1.65)	1.00 (0.80, 1.25)	0.90 (0.68, 1.19)
Ibuprofen	1.15 (0.59, 2.25)	0.78 (0.31, 1.95)	1.36 (0.93, 2.01)	1.16 (0.69, 1.95)	1.09 (0.72, 1.66)	0.95 (0.58, 1.57)

¹Model includes all 4 analgesic exposures (acetaminophen in infancy, ibuprofen in infancy, prenatal acetaminophen, prenatal ibuprofen), and covariates for child's sex and multivitamin intake, mother's age at enrollment, race/ethnicity, pre-pregnancy BMI, household income, number of children under 12 years of age in the home, breastfeeding duration, passive smoking exposure, smoking during pregnancy, childcare attendance, maternal and paternal history of asthma

Cumulative Exposure to acetaminophen and ibuprofen, and wheeze, asthma and allergen sensitization in children in early and mid-childhood. Data from mother –infant pairs participating in Project Viva.

Table 5

Cumulative Exposure Score	Early Childhood (Age 3 to 5) Outcomes							
	Recurrent Wheeze OR (95% CI)		Asthma OR (95% CI)		Allergen Sensitization OR (95% CI)		Adj. (All covars) ²	Adj. (All covars) ²
	Unadjusted	Adj. (Infection) ¹	Unadjusted	Adj. (Infection) ¹	Unadjusted	Adj. (Infection) ¹		
Acetaminophen	1.55 (1.29,1.87)	1.39 (1.13, 1.71)	1.40 (1.21, 1.62)	1.27 (1.08, 1.49)	0.92 (0.78, 1.09)	0.97 (0.82, 1.15)	1.01 (0.83, 1.22)	
Ibuprofen	1.54 (1.24, 1.91)	1.24 (0.97, 1.60)	1.52 (1.28, 1.80)	1.31 (1.10, 1.58)	0.82 (0.67, 0.99)	0.86 (0.70, 1.05)	0.78 (0.61, 0.99)	

Cumulative Exposure Score	Mid-childhood (Age 7 to 10) Outcomes							
	Persistent Wheeze OR (95% CI)		Current Asthma OR (95%CI)		Allergen Sensitization OR (95% CI)		Adj. (All covars) ²	Adj. (All covars) ²
	Unadjusted	Adj. (Infection) ¹	Unadjusted	Adj. (Infection) ¹	Unadjusted	Adj. (Infection) ¹		
Acetaminophen	1.37 (1.02,1.83)	1.26 (0.92, 1.73)	1.37 (1.14, 1.64)	1.34 (1.11, 1.62)	0.96 (0.80, 1.15)	0.97 (0.80, 1.17)	0.93 (0.74, 1.16)	
Ibuprofen	1.12 (0.81, 1.55)	0.92 (0.64, 1.31)	1.17 (0.96, 1.44)	1.12 (0.91, 1.39)	0.84 (0.68, 1.04)	0.88 (0.71, 1.09)	0.94 (0.73, 1.22)	

¹Model includes cumulative exposure score, and adjustment for respiratory and ear infections in the first year of life

²Model includes both cumulative exposure scores (acetaminophen score, ibuprofen score), and covariates for child’s sex and multivitamin intake, mother’s age at enrollment, race/ethnicity, pre-pregnancy BMI, household income, number of children under 12 years of age in the home, breastfeeding duration, passive smoking exposure, smoking during pregnancy, childcare attendance, maternal and paternal history of asthma