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## Prenatal exposure to acetaminophen and respiratory symptoms in the first year of life

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### Abstract

**Background**—Prevalence of asthma in developed countries increased between the 1970s and the 1990s. One factor that might contribute to the trends in asthma is the increased use of acetaminophen vs aspirin in children and pregnant women.

**Objective**—To examine relationships between in utero exposure to acetaminophen and incidence of respiratory symptoms in the first year of life.

**Methods**—A total of 345 women were recruited in the first trimester of pregnancy and followed up with their children through the first year of life. Use of acetaminophen in pregnancy was determined by questionnaire and related to incidence of respiratory symptoms.

**Results**—Use of acetaminophen in middle to late but not early pregnancy was significantly related to wheezing (odds ratio, 1.8; 95% confidence interval, 1.1-3.0) and to wheezing that disturbed sleep (odds ratio, 2.1; 95% confidence interval, 1.1-3.8) in the first year of life after control for potential confounders.

**Conclusion**—This study suggests that use of acetaminophen in middle to late but not early pregnancy may be related to respiratory symptoms in the first year of life. Additional follow-up will examine relationships of maternal and early childhood use of acetaminophen with incidence of asthma at ages 3 to 5 years, when asthma diagnosis is more firmly established.

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## INTRODUCTION

Prevalence of asthma increased significantly in most developed countries between the 1970s and the mid-1990s. Increases in objective measures, such as prevalence of atopy and bronchial hyperreactivity, during the last several decades suggest that these trends cannot be attributed solely to improved detection. Several hypotheses have emerged, with no consistent evidence to support any specific cause. Circumstantial data are consistent with decreased exposures to selected infections early in life, skewing the immune system away from fighting infections and toward allergic responses, represented by a shift from T<sub>H</sub>1 to T<sub>H</sub>2 cytokine responses. This “hygiene hypothesis” is supported by lower asthma rates in developing countries, children attending daycare in the first 6 months of life, children with dogs at home in the first year, early exposure to farm animals, and early exposure to gram-negative bacteria.<sup>1-3</sup> Although this hypothesis is an appealing explanation for cross-cultural differences in asthma rates, it does not readily explain the trends in developed countries, where no obvious changes have occurred in exposures to infectious agents. Alternative explanations that have been proposed include increased use of antibiotics,<sup>4,5</sup> increased numbers of immunizations,<sup>6-8</sup> changes from aspirin to acetaminophen,<sup>9-19</sup> increased stress,<sup>20,21</sup> and changes in dietary patterns.<sup>22-26</sup> The possibility that acetaminophen use in utero or early childhood may contribute to the development of asthma is supported by ecologic studies, a few analytic studies of high-risk populations, and biologic plausibility.<sup>9,10</sup> Acetaminophen is thought to act via its metabolite, N-acetyl-p-benzoquinoneimine (NAPQ1), which in turn depletes the antioxidant glutathione.<sup>27-29</sup> The purpose of this article is to examine the association of exposure to acetaminophen in utero with the subsequent development of wheezing and allergic symptoms in the first year of life.

## METHODS

The Peer Education in Pregnancy Study is a randomized controlled trial examining the effect of community educators working with pregnant women at risk for having children with asthma (defined as the unborn child having a first-degree relative with asthma, hay fever, or eczema) on modification of factors in the home known to exacerbate the disease. The intervention did not include discussion of acetaminophen use. The primary end points of the study are wheezing and allergic symptoms in the first year of life, as well as wheezing, allergic symptoms, and diagnosed asthma in children 3 to 5 years of age. All women in the study received general health education. Half of the women, in addition, received a series of home visits from a community health educator to identify and decrease asthma triggers. Of a total of 5,443 women identified as being pregnant, 354 (6.5%) could not be located and 380 (7.0%) were not interested in participating. Of the remainder, 86% were not eligible (did not have a history of asthma or allergies, were more than 4 months pregnant, had a miscarriage, or did not live in the targeted area). A total of 483 women were initially enrolled. Of those, 100 dropped out before the second visit, at which time 383 were randomized into the trial. To date, all infants have reached 1 year of age: 11 families withdrew before year 1 (2.9% of women randomized). We have followed up 351 mother-child pairs (91.6%) to 1 year. Six women were excluded from analyses because of missing data on critical variables, leaving 345 (90.1%) available for this report. Demographic information of women initially enrolled, randomized, and followed up for 1 year are given in Table 1. The mean age of the mothers whose children were followed up to 1 year of age was 26 years, with 65% of Mexican background. For 38% of the women, this was the first pregnancy. Demographic variables were similar among the groups.

Acetaminophen use was determined from 4 different questionnaires: (1) at enrollment (first trimester): “Since you became pregnant, which of the following nonprescription medications have you taken . . . acetaminophen (Tylenol)?”; (2) at the second visit (4-5 months of gestation); (3) at the third visit (7-8 months of gestation): “Since our last visit, which of the following

nonprescription medication have you taken . . . acetaminophen (Tylenol)?"; and (4) at the first postpartum visit (visit 4): "Between our last visit and delivery which of the following nonprescription medications did you take . . . acetaminophen (Tylenol)?" A total of 70% of women had used acetaminophen at least once in pregnancy: 40.1% in early pregnancy (first trimester); 38.1% in middle pregnancy, 49.0% in late pregnancy (after 4-5 months of gestation as determined from a positive response on either visit 3 or 4), and 59.9% in either middle or late pregnancy (after the first trimester).

Development of respiratory end points was determined by any positive response to the following questions at visit 4 (child 4 to 6 weeks old), at visit 5 (child 6 months old), at visit 6 (child 12 months old), or during telephone calls at 3 and 9 months: "During this time period has he/she had any wheezing (whistling in the chest)?"; "Did the wheezing ever disturb the baby's sleeping at night?"; "Have there been any times when he/she coughed frequently throughout the day or night, during this time period?"; "Did the coughing ever disturb the baby's sleeping at night?"; "Was your baby treated in the emergency room for breathing problems (coughing, congestion, runny nose, wheezing) during this time period?"; "Was your baby admitted to the hospital, other than the ER [emergency room], with breathing problems (coughing, congestion, runny nose, wheezing) during this time period?"; and "Has a doctor ever told you that your baby has asthma?"

Respiratory symptoms were common in the first year of life, with 33.0% reporting some wheezing, 21.5% reporting wheezing that disturbed sleep, 65.4% reporting coughing that disturbed sleep, 33.9% going to the emergency department for a respiratory problem, 10.1% being hospitalized for a respiratory problem, and 4.6% being diagnosed as having asthma.

Smoking in pregnancy was determined from the following questions: "Have you ever smoked?"; "Have you smoked any cigarettes in the last 7 days?"; If no, "How long ago did you stop smoking?" Exposure to passive smoke was determined from the following questions: "In an average week about how many hours are you exposed to other peoples' cigarette smoke at home, including by family members and visitors" and "In an average week, about how many hours are you exposed to other peoples' cigarette smoke outside the home?" (any positive answer was considered yes). Active smoking in pregnancy was rare (10.1% early in pregnancy and 5.2% later). Among Mexican women, it was particularly rare, with 18.2% born in the United States and 4.4% born in Mexico smoking early in pregnancy. Exposure to passive smoke, however, was common, with 31.9% being exposed in the home, 52.8% being exposed elsewhere, and 62.3% exposed to some passive smoke either at home or elsewhere.

Breastfeeding was determined on the first visit after delivery (when the infant was 4 to 6 weeks old): "Have you ever breastfed your baby since giving birth?" and "Are you still breastfeeding your baby?" Most women breastfed their infants (87.8%), with 68.7% breastfeeding for 4 or more weeks. Early use of formula was also common, with 70.1% starting at birth and another 14.8% beginning in the first month of life. Thus, most women fed their infants with a combination of breast milk and formula.

Other potential confounders included family history of asthma evaluated at baseline by questionnaire history of a first-degree relative of the unborn child having a history of asthma, antibiotic use in pregnancy evaluated by questionnaire at 7 to 8 weeks of gestation and at 4 to 6 weeks of age (between the last visit and delivery), birth weight of the child evaluated by questionnaire when the child was 4 to 6 weeks of age, and antioxidant intake evaluated at 7 to 8 months of gestation using the 1992 Block National Cancer Institute Health Habits and History Questionnaire in English and the Hispanic Food Frequency Questionnaire.<sup>30,31</sup> For analyses of potential confounders, in this article antioxidants were assumed to include vitamin A, vitamin C, vitamin E, lycopene, lutein, beta-carotene, alpha-carotene, and cryptoxanthin.

Except for the vitamins, no specific antioxidant intakes are recommended, especially for pregnancy.<sup>32</sup> Therefore, to evaluate for possible confounding by antioxidants, for each woman each of these vitamins or antioxidants was determined to be above or below the median intake, then summed to give an antioxidant score for each participant. Women were assumed to have high antioxidant intake if intakes were above the median for 5 or more of the 8 antioxidants; they were assumed to have low antioxidant intake if they had intakes above the median for 4 or fewer of the 8 antioxidants. Dietary data were available for only 312 of the 345 women included in this analysis. Final analyses, therefore, were performed with and without adjustment for level of antioxidant intake.

Statistical analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina). The  $\chi^2$  statistic tested the significance of differences between potential confounding variables and both acetaminophen use and respiratory end points. Logistic regression models were used to estimate the effect of acetaminophen use during pregnancy on the child's respiratory symptoms in the first year of life. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented. Multivariate models controlled for maternal age, child's sex, home environment intervention group, maternal Mexican ethnicity, child breastfed for 4 or more weeks, active smoking in middle to late pregnancy, exposure to passive smoke during pregnancy, low birth weight (<2,500 g), antibiotic use in late pregnancy, age at which formula introduced (categorized by birth, <4 weeks, 4-12 weeks, and >12 weeks), and family history of asthma. Additional analysis also controlled for infections during pregnancy and low intake of antioxidants during pregnancy. The study was approved by the University of Illinois at Chicago Human Subjects Institutional Review Board.

## RESULTS

Associations of potential confounders identified in the literature with acetaminophen use are given in Table 2. Mexican women and women without infections used less acetaminophen than women not of Mexican ethnicity and women with infections early in pregnancy. Associations of potential confounders identified in the literature with respiratory end points are given in Table 3. Incidence of respiratory end points was generally higher in boys; in those whose mothers were not Mexican, who smoked after the first visit (middle to late pregnancy), or who were exposed to passive smoke in pregnancy; whose birth weight was less than 2,500 g; who began using formula early; and whose mothers breastfed for fewer than 4 weeks. Infants whose mothers had used antibiotics between the second nurse visit and the end of pregnancy were also at higher risk of respiratory symptoms, with the differences for any wheezing and wheezing that disturbed sleep reaching statistical significance.

Incidence of respiratory end points in relation to acetaminophen use with and without control for potential confounders is given in Table 4. The results suggest that acetaminophen use in middle to late but not early pregnancy may increase risk of respiratory symptoms, with acetaminophen use in middle to late but not early pregnancy significantly increasing risk of wheezing (OR, 1.8; 95% CI, 1.1-3.0) and wheezing that disturbed sleep (OR, 2.1; 95% CI, 1.1-3.8) after control for maternal age, child's sex, intervention group, Mexican ethnicity, the child being breastfed for 4 or more weeks, exposure to maternal smoke in middle to late pregnancy, exposure to passive smoke in pregnancy, low birth weight, antibiotic use in late pregnancy, age of introduction of formula, and family history of asthma.

The small numbers of women who used aspirin or ibuprofen without acetaminophen precluded separate analyses. Nine women used aspirin; of those, 7 also used acetaminophen. Eleven women used ibuprofen and did not use acetaminophen. After control for potential confounders with exclusion of any women who used ibuprofen in pregnancy (n = 50), use of acetaminophen

in middle to late pregnancy remained significantly associated with any wheezing (OR, 2.0; 95% CI, 1.1-3.5) and with wheezing that disturbed sleep (OR, 2.3; 95% CI, 1.2-4.5).

A total of 91.3% women had possible infections in pregnancy (defined by history of cold, flu, cough, fever, or other infection). Of these, 70.9% had infections in early pregnancy, 57.7% in middle pregnancy, 63.1% in late pregnancy, and 86.5% in middle or late pregnancy (data not shown). Control for any infections, as well as control for upper respiratory tract infections (cough, cold, or sore throat), at any time during pregnancy did not change associations of acetaminophen use during those periods with respiratory symptoms in the children (data not shown). The associations of acetaminophen with respiratory symptoms were also unchanged after control for maternal education, number of previous live births (parity), acetaminophen use in the first year of life, gestational age younger than 36 weeks, or separate measures of exposure to passive smoke in early, middle, or late pregnancy, and the magnitude of the associations was not changed after control for low antioxidant intake in pregnancy for the subset of 312 women with complete dietary data, although the *P* values became of borderline statistical significance with the reduction in numbers available for analysis (data not shown).

## DISCUSSION

The results of this study suggest that acetaminophen use in middle to late pregnancy may increase risk of respiratory symptoms in the first year of life. The findings of a differential effect with ingestion later in pregnancy is consistent with the one other study that looked at effects of in utero exposure.<sup>16,17</sup> The overall association is also consistent with results of other ecologic, case-control, and cohort studies.<sup>11-15,18-19</sup> General use of acetaminophen vs aspirin began in the early 1980s in response to concern over aspirin-induced Reyes syndrome, around the time the increase in asthma prevalence was first noted. An ecologic analysis of International Study of Asthma and Allergies in Childhood data<sup>11</sup> noted that acetaminophen sales are particularly high in English-speaking countries with the highest rates of asthma. A cross-sectional survey of parents of 6- to 7-year-old children in New Zealand showed increased risk of current wheezing and asthma among both children who had used acetaminophen in the first year of life and those who had used it in the previous year.<sup>12</sup> Another cross-sectional survey of 7,649 adults and children in Ethiopia found significant associations of frequency of acetaminophen use with wheezing and other allergic symptoms.<sup>18</sup> Examination of 13,492 adults in the National Health and Nutrition Examination Survey III similarly showed significant associations of acetaminophen use with asthma, chronic obstructive lung disease, and decreased pulmonary function.<sup>19</sup> A case-control study of 664 adults with asthma and 910 without the disease in the United Kingdom reported ORs for asthma compared with never users of 1.06, 1.22, 1.79, and 2.38 in infrequent, monthly, weekly, and daily users, respectively.<sup>13</sup> These studies are consistent with the decreased asthma morbidity in children who received ibuprofen vs acetaminophen for febrile episodes.<sup>14</sup> To date, 2 prospective studies have shown increases in asthma incidence in users of acetaminophen. The Nurses Health Study of 121,700 adult women in whom 346 developed asthma after baseline examination showed a rate ratio of 1.63 (95% CI, 1.11-2.39) for asthma among women who used acetaminophen more than 14 days a month.<sup>15</sup> The Avon Longitudinal Study of Parents and Children (ALSPAC), the only previous study to examine the effect of in utero exposure in pregnant women on subsequent risk of asthma, in a cohort of 8,511 children, also found that use of acetaminophen in late but not early pregnancy was positively associated with asthma in children of mothers who took it sometimes and most days or daily (OR, 1.22, 95% CI, 1.06-1.41; OR, 1.62; 95% CI, 0.86-3.04; respectively).<sup>16,17</sup>

The biologic plausibility of a causal relationship of acetaminophen primarily rests on its depletion of glutathione, which in turn mitigates against oxidative stress from free radicals or reactive oxygen species.<sup>9,33</sup> Reactive oxygen species have a variety of toxic effects, one of

which involves oxidation of phospholipids with subsequent effects on prostaglandins and leukotrienes, inflammatory mediators for asthma. Acetaminophen is metabolized through 3 pathways: glucuronidation, sulfation, and via specific cytochrome P450 enzymes to a highly reactive arylating metabolite (NAPQ1), which in turn depletes the antioxidant glutathione.<sup>27-29</sup> Evidence indicates that, although the fetal liver may not be able to metabolize to reactive intermediates early in gestation, by 16 to 23 weeks the cytochrome P450 is at least partially functional,<sup>34,35</sup> consistent with the findings from ALSPAC.<sup>16,17</sup> The importance of glutathione as an etiologic factor in the development of asthma is supported by research showing increased lung function<sup>36</sup> but decreased lung function growth<sup>37</sup> in children with glutathione transferase geno-types GSTM1 null and GSTP1 val<sup>105</sup>/val<sup>105</sup> and greater pulmonary effects of ozone and modulation of these effects in children with GSTM1 null.<sup>26</sup> Other suggested mechanisms resulting from glutathione depletion involve decreased removal of toxic metabolites and damage to alveolar macrophages, as well as altered expression of T cells toward the T<sub>H</sub>2 phenotype.<sup>9,38,39</sup>

Thus, the findings in the current study are consistent with previous literature showing increases in asthma symptoms from acetaminophen exposure. In addition, the findings have biologic plausibility. The study, however, has several limitations. Use of acetaminophen, but not frequency of use or dosage, was ascertained. ALSPAC previously suggested that frequency may also be important.<sup>16,17</sup> We controlled for many potential confounders, including mother's age and ethnicity, child's sex, history of breastfeeding and formula initiation, antibiotic use, low birth weight, and exposure to smoke, as well as summary measures of infections. Nevertheless, greater detail about infections and types of antibiotics used both in pregnancy and in the first year of life would have strengthened the analysis. In addition, although wheezing is a cause of morbidity in the child and parental report of wheezing in infancy is highly correlated with clinical evaluation,<sup>40</sup> wheezing in infancy itself may be a poor predictor of subsequent asthma.<sup>41</sup> Current follow-up of the children to 3 and 5 years of age should provide more precise estimates of asthma incidence. Finally, use of acetaminophen may reflect exposure to undetected infections in the mother requiring acetaminophen that in turn could affect the development of respiratory symptoms in the child. Nevertheless, this is the second study suggesting that exposure to acetaminophen late in pregnancy may affect the subsequent development of allergic symptoms in the child. Confirmation of these findings in additional cohorts would have substantial public health implications in both defining factors that could be contributing to asthma trends and developing subsequent intervention strategies.

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**Table 1**  
Peer Education in Pregnancy Study Demographic Variables

| Variable  | Women initially enrolled<br>(n = 483) | Women randomized (n =<br>383) | Women followed up to 1 y<br>(n = 345) |
|---|---------------------------------------|-------------------------------|---------------------------------------|
| Maternal age, mean (range), y   | 25.6 (14-45)                          | 25.6 (15-43)                  | 25.8 (15-43)                          |
| Race/ethnicity, %   |                                       |                               |                                       |
| Mexican   | 60.0                                  | 62.7                          | 65.2                                  |
| Puerto Rican  | 16.8                                  | 15.4                          | 14.5                                  |
| Other/mixed Hispanic  | 10.6                                  | 11.0                          | 10.7                                  |
| African American  | 6.4                                   | 6.0                           | 5.8                                   |
| Other   | 6.2                                   | 5.0                           | 3.8                                   |
| US born, %  | 41.7                                  | 39.2                          | 38.0                                  |
| Time in United States of those born outside the<br>United States, mean (range), y | 8.6 (0.2-39.0)                        | 8.4 (0.2-39.0)                | 8.4 (0.2-39.0)                        |
| Language, %   |                                       |                               |                                       |
| English   | 42.7                                  | 39.7                          | 38.0                                  |
| Spanish   | 46.2                                  | 48.8                          | 50.7                                  |
| English and Spanish   | 11.2                                  | 11.5                          | 11.3                                  |
| Education completed, %  |                                       |                               |                                       |
| <High school  | 42.0                                  | 41.2                          | 42.3                                  |
| High school graduate  | 32.9                                  | 33.9                          | 34.2                                  |
| Some college  | 20.4                                  | 20.1                          | 18.3                                  |
| College graduate  | 4.8                                   | 4.7                           | 5.2                                   |
| Works outside home, %   | 32.6                                  | 31.3                          | 29.6                                  |
| Married, %  | 44.0                                  | 46.5                          | 47.3                                  |
| No. of previous live births, %  |                                       |                               |                                       |
| 0   | 38.5                                  | 37.9                          | 37.7                                  |
| 1   | 26.2                                  | 27.2                          | 27.3                                  |
| 2   | 21.9                                  | 22.4                          | 22.9                                  |
| ≥3  | 13.4                                  | 12.8                          | 12.2                                  |
| Health care site, %   |                                       |                               |                                       |
| 1   | 56.9                                  | 57.4                          | 57.4                                  |
| 2   | 25.3                                  | 26.9                          | 27.8                                  |
| 3   | 17.8                                  | 15.7                          | 14.8                                  |

**Table 2**Percentage of Women Who Reported Acetaminophen Use in Pregnancy by Other Exposure Variables<sup>a</sup>

| Variable   | Any acetaminophen (n = 343) |                   | Early acetaminophen <sup>b</sup> (n = 344) |                   | Middle to late acetaminophen <sup>c</sup> (n = 342) |                   |
|--|-----------------------------|-------------------|--|-------------------|---|-------------------|
|  | Other exposure              | No other exposure | Other exposure                             | No other exposure | Other exposure                                      | No other exposure |
| Smoking in middle to late pregnancy <sup>d</sup> | 88.9                        | 68.9              | 38.9                                       | 40.2              | 77.8  | 59.0              |
| Any passive smoke in pregnancy <sup>e</sup>      | 73.4                        | 64.3              | 42.5                                       | 36.2              | 61.2  | 57.8              |
| Antibiotic use in late pregnancy <sup>f</sup>    | 72.6                        | 69.5              | 39.2                                       | 40.3              | 66.7  | 58.8              |
| Low antioxidant intake in pregnancy <sup>g</sup> | 71.7                        | 71.5              | 44.2                                       | 37.4              | 60.0  | 62.1              |
| Mexican ethnicity                                | 65.9                        | 77.5 <sup>m</sup> | 38.0                                       | 44.2              | 57.7  | 64.2              |
| Family history of asthma <sup>h</sup>            | 72.3                        | 66.4              | 41.8                                       | 37.7              | 61.5  | 57.7              |
| Child's sex male (vs female)                     | 72.5                        | 67.3              | 40.5                                       | 39.8              | 63.1  | 56.4              |
| Low birth weight <sup>i</sup>                    | 74.1                        | 69.6              | 33.3                                       | 40.7              | 63.0  | 60.0              |
| Breastfed for $\geq 4$ weeks <sup>j</sup>        | 67.2                        | 75.9              | 38.1                                       | 44.4              | 56.8  | 67.0              |
| Age formula started <sup>k</sup>                 | 69.6                        | 76.0              | 41.1                                       | 32.0              | 59.8  | 64.0              |
| Infections <sup>l</sup>                          | 72.0                        | 50.0 <sup>m</sup> | 45.1                                       | 30.8 <sup>m</sup> | 61.9  | 54.3              |

<sup>a</sup> Values are percentages of those with a positive or negative response to the stated exposure question.

<sup>b</sup> Acetaminophen use early in pregnancy defined as use before enrollment in the study.

<sup>c</sup> Acetaminophen use in middle to late pregnancy defined as use between enrollment and delivery of the newborn.

<sup>d</sup> Mothers smoked in pregnancy between enrollment and the end of pregnancy.

<sup>e</sup> Mothers exposed during pregnancy to passive smoke either at home or elsewhere.

<sup>f</sup> Antibiotics used between the second nurse visit and the end of pregnancy.

<sup>g</sup> Defined as 4 or more of 8 antioxidants below the median.

<sup>h</sup> First-degree relative of child has asthma.

<sup>i</sup> Low birth weight defined as less than 2,500 g.

<sup>j</sup> Breastfed 4 or more weeks defined as breastfeeding the child until 4 weeks of age or longer.

<sup>k</sup> *P* value for trend with age formula started coded for the analysis as birth, during first month, at 1 to 3 months, and at older than 3 months.

<sup>l</sup> Any infections during specified periods.

<sup>m</sup> *P* < .05 by  $\chi^2$  test.

**Table 3**  
 Percentage of Women Who Reported Respiratory Symptoms in Their Child by Other Exposure Variables<sup>a</sup>

| Variable   | Wheeze, %      |                   | Wheezes that disturbed sleep, % |                   | Cough that disturbed sleep, % |                   | Emergency department visit for respiratory problem, % |                   | Hospitalized for respiratory problem, % |                   | Asthma diagnosis, % |                   |
|--|----------------|-------------------|---------------------------------|-------------------|-------------------------------|-------------------|---|-------------------|---|-------------------|---------------------|-------------------|
|  | Other exposure | No other exposure | Other exposure                  | No other exposure | Other exposure                | No other exposure | Other exposure  | No other exposure | Other exposure                          | No other exposure | Other exposure      | No other exposure |
| Smoking in middle to late pregnancy <sup>b</sup> | 61.1           | 31.5 <sup>k</sup> | 38.9                            | 20.5              | 83.3                          | 64.4              | 55.6  | 32.7 <sup>k</sup> | 27.8                                    | 9.2 <sup>k</sup>  | 16.7                | 4.0 <sup>k</sup>  |
| Any passive smoke <sup>c</sup>                   | 38.1           | 24.6 <sup>k</sup> | 27.0                            | 12.3 <sup>k</sup> | 72.4                          | 53.9 <sup>k</sup> | 37.7  | 27.7              | 12.6                                    | 6.2               | 6.5                 | 1.5 <sup>k</sup>  |
| Antibiotic use in late pregnancy <sup>d</sup>    | 47.1           | 30.6 <sup>k</sup> | 35.3                            | 19.1 <sup>k</sup> | 66.7                          | 65.2              | 43.1  | 32.3              | 15.7                                    | 9.2               | 5.9                 | 4.4               |
| Low antioxidant intake <sup>e</sup>              | 37.2           | 26.6              | 25.0                            | 16.1              | 65.2                          | 65.3              | 35.1  | 30.7              | 10.1                                    | 9.7               | 5.3                 | 3.2               |
| Mexican ethnicity                                | 29.8           | 39.2              | 17.8                            | 28.3 <sup>k</sup> | 63.4                          | 69.2              | 29.3  | 42.5 <sup>k</sup> | 8.4                                     | 13.3              | 2.2                 | 9.2 <sup>k</sup>  |
| Family history of asthma <sup>f</sup>            | 35.4           | 29.5              | 25.7                            | 15.1 <sup>k</sup> | 69.3                          | 59.7              | 38.4  | 27.3 <sup>k</sup> | 12.6                                    | 6.5               | 5.8                 | 2.9               |
| Child's sex male (vs female)                     | 40.8           | 24.7 <sup>k</sup> | 25.1                            | 17.5              | 75.4                          | 54.6 <sup>k</sup> | 38.0  | 29.5              | 13.4                                    | 6.6 <sup>k</sup>  | 5.0                 | 4.2               |
| Low birth weight <sup>g</sup>                    | 59.3           | 30.8 <sup>k</sup> | 37.0                            | 20.1 <sup>k</sup> | 74.1                          | 64.7              | 55.6  | 32.1 <sup>k</sup> | 22.2                                    | 9.1 <sup>k</sup>  | 14.8                | 3.8 <sup>k</sup>  |
| Breastfed for ≥4 weeks <sup>h</sup>              | 28.7           | 42.6 <sup>k</sup> | 17.7                            | 29.6 <sup>k</sup> | 62.7                          | 71.3              | 31.2  | 39.8              | 8.0                                     | 14.8              | 3.4                 | 7.4               |
| Age formula started <sup>i</sup>                 | 34.7           | 12.0              | 21.1                            | 8.0               | 67.2                          | 36.0 <sup>k</sup> | 36.4  | 20.0              | 10.7                                    | 8.0               | 4.1                 | 0.0               |
| Infections <sup>j</sup>                          | 32.9           | 33.3              | 21.7                            | 16.7              | 65.5                          | 65.5              | 32.9  | 43.3              | 8.6                                     | 23.3 <sup>k</sup> | 4.5                 | 6.7               |

<sup>a</sup>Values are percentages of those with a positive or negative response to the stated exposure question. Sample size was 345.

<sup>b</sup>Mothers smoked in pregnancy between enrollment and the end of pregnancy.

<sup>c</sup>Mothers exposed during pregnancy to passive smoke either at home or elsewhere.

<sup>d</sup>Antibiotics used between the second nurse visit and the end of pregnancy.

<sup>e</sup>Defined as 4 or more of 8 antioxidants below the median (n = 312).

<sup>f</sup>First-degree relative of child has asthma.

<sup>g</sup>Low birth weight defined as less than 2,500 g.

<sup>h</sup>Breastfed for 4 or more weeks defined as breastfeeding until the child was 4 weeks old or longer.

<sup>i</sup>P value for trend with age formula started coded for the analysis as birth, during first month, at 1 to 3 months, and at older than 3 months.

<sup>j</sup>Any infections during pregnancy.

<sup>k</sup>P < .05 by  $\chi^2$  test.

**Table 4**  
Relationship of Acetaminophen Use in Pregnancy With Infant's Respiratory End Points by 1 Year

| Respiratory end point <sup>a</sup>                 | Acetaminophen during pregnancy |                           | Odds ratios (95% confidence intervals) <sup>b</sup><br>Acetaminophen during early pregnancy <sup>c</sup> |               | Acetaminophen during middle to late pregnancy <sup>d</sup> |               |
|--|--------------------------------|---------------------------|--|---------------|--|---------------|
|  | Univariate                     | Multivariate <sup>e</sup> | Univariate   | Multivariate  | Univariate   | Multivariate  |
| Any wheeze   | 2.0 (1.2-3.3)                  | 1.7 (1.0-3.0)             | 1.0 (0.6-1.6)  | 1.0 (0.6-1.6) | 2.0 (1.2-3.3)  | 1.8 (1.1-3.0) |
| Wheeze that disturbed sleep                        | 2.6 (1.4-5.2)                  | 2.3 (1.1-4.6)             | 1.4 (0.8-2.3)  | 1.4 (0.8-2.4) | 2.2 (1.2-3.9)  | 2.1 (1.1-3.8) |
| Cough that disturbed sleep                         | 1.4 (0.9-2.3)                  | 1.3 (0.8-2.1)             | 1.0 (0.6-1.6)  | 0.9 (0.6-1.5) | 1.4 (0.9-2.2)  | 1.3 (0.8-2.1) |
| Emergency department visit for respiratory problem | 1.1 (0.7-1.8)                  | 0.9 (0.5-1.5)             | 0.9 (0.5-1.3)  | 0.8 (0.5-1.3) | 1.1 (0.7-1.7)  | 0.9 (0.6-1.5) |
| Hospitalization for respiratory problem            | 1.1 (0.5-2.3)                  | 0.8 (0.4-1.9)             | 0.9 (0.4-1.8)  | 0.9 (0.4-1.8) | 1.1 (0.6-2.4)  | 1.0 (0.4-2.1) |
| Asthma diagnosis                                   | 1.9 (0.5-6.8)                  | 1.6 (0.4-6.4)             | 1.2 (0.4-3.2)  | 1.3 (0.5-3.8) | 2.1 (0.7-6.5)  | 2.0 (0.6-7.2) |

<sup>a</sup>Respiratory end point by the age of 1 year.

<sup>b</sup>Odds ratio (95% confidence interval) from logistic regression (n = 343).

<sup>c</sup>Acetaminophen use early in pregnancy defined as use before enrollment in the study (n = 344).

<sup>d</sup>Acetaminophen use in middle to late pregnancy defined as use between enrollment and delivery of the newborn (n = 342).

<sup>e</sup>Odds ratio after control for maternal age, child's sex, home environment intervention group, maternal Mexican ethnicity, child breastfed for 4 or more weeks, active smoking in middle to late pregnancy, exposure to passive smoke during pregnancy, low birth weight (<2,500 g), antibiotic use in late pregnancy, age at which formula introduced (categorized by birth, <4 weeks, 4-12 weeks, >12 weeks), and family history of asthma.