



## Relationship between prenatal antibiotic use and asthma in at-risk children



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### ABSTRACT

**Background:** Asthma prevalence has doubled in developed countries during the past 30 years. Pre- and perinatal events are essential in shaping the development of the immune system and systemic antibiotic use during this time could alter the maternal or placental microbiome, leading to an increase in the child's risk of developing asthma.

**Objective:** To determine whether prenatal antibiotic use is associated with asthma and wheezing in children at risk for asthma.

**Methods:** Using data from a randomized education intervention of families at risk for asthma from 1998 followed through 2009 in urban Chicago, asthma was defined as ever having a physician asthma diagnosis by year 3 and wheezing in the third year. Logistic regression models controlling for confounders investigated the effect of antibiotic use during pregnancy on these outcomes.

**Results:** After adjustment, prenatal antibiotic use was a risk factor for asthma (odds ratio 3.1, 95% confidence interval 1.4–6.8) but was only weakly associated with wheezing (odds ratio 1.8, 95% confidence interval 0.9–3.3). Analyses of the effects of timing of prenatal antibiotic use on asthma and wheezing showed the relation remained consistent for antibiotic use later in pregnancy, but the outcomes were not associated with antibiotic use in the first trimester.

**Conclusion:** This study suggests prenatal antibiotic use might be associated with the development of asthma in children at risk for asthma. Although the relation with prenatal antibiotics does not hold for wheezing in this study, there might be a trend that could be delineated further within a larger cohort study.

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### Introduction

Prevalence of asthma has doubled in developed countries during the past 30 years.<sup>1</sup> The factors causally driving these temporal increases remain essentially unknown, with poor and minority children in the United States presenting with a disproportionately

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greater burden of asthma morbidity.<sup>2</sup> Concurrent increases in antibiotic use to treat infections in children have led to speculation of a causal relation. Retrospective studies have shown strong correlations between early antibiotic use and asthma, but the findings suggest the possibility of reverse causation or confounding by indication.<sup>3,4</sup> Conversely, prenatal antibiotics have been found to be associated with the development of asthma and wheezing in early life.<sup>5–11</sup> The hygiene hypothesis suggests that birth into an environment with fewer microbial exposures can alter development of the immune system, leading to a greater risk of atopy.<sup>12</sup> Data have suggested that antibiotics in utero could change the maternal or placental microbiome and increase the child's risk of developing allergic disease.<sup>13,14</sup> Factors that modify microbial exposure pre- and perinatally could have a long-term impact on the risk of developing subsequent atopic disease.<sup>7,15,16</sup> Research using prospective birth cohorts has been limited, especially in impoverished urban residents.

Controlling for maternal and child confounders within a prospective study, the authors investigated the effects of prenatal antibiotic use with the subsequent development of asthma by year 3 and wheezing in the third year within a high-risk urban cohort. Because this relation could be confounded by maternal asthma or by antibiotic use in the child, the authors investigated the associations within subsets of mothers without asthma and within children who did not use antibiotics. They also investigated the impact of antibiotics during different trimesters of pregnancy.

## Methods

The Peer Education in Pregnancy Study is a randomized education intervention examining the effect of community educators working with pregnant women at risk for having children with asthma on modification of factors in the home known to exacerbate the disease. From 1998 to 2004, at-risk families living in disadvantaged areas of urban Chicago were identified to participate in the study if the unborn child had a first-degree relative with asthma, hay fever, or eczema. Mothers were followed and surveyed in each trimester of pregnancy and soon after delivery, and 301 children were followed from 4 weeks through 3 years of age. The intervention did not address antibiotic usage. All women in the study received general health education. Half the women also received a series of home visits from a community health educator to identify and decrease in-home asthma triggers. The complete outline of participant flow through the study has been published elsewhere.<sup>17,18</sup>

A total of 298 mother–child pairs from the Peer Education in Pregnancy Study had information concerning systemic antibiotic use and were followed through the child's third year of life. The primary end points of the study were asthma diagnosis by year 3 and reported wheezing in the third year of life. Asthma was defined as ever having an asthma diagnosis by a physician by 3 years of age based on the self-reported answer to the question, "Has a doctor ever told you that your child has asthma?" Secondary end points included eczema and other respiratory symptoms in the third year:

exercise-induced wheezing, sleep disturbed by wheezing, wheezing without a cold, and emergency department visits for breathing problems. Development of the primary end point of wheezing and the secondary end points of eczema and other respiratory symptoms were determined by a positive response within the year before their third-year visit based on the following questions: "Has your child's chest sounded wheezy or whistling?" "Has a physician ever told you that your child has eczema?" "Has your child's chest sounded wheezy or whistling during or shortly after vigorous exercise?" "Has your child been awakened at night by wheeze or by shortness of breath?" "Has your child had episodes of wheezing or whistling without a cold?" "Was your child treated in the emergency department for breathing problems (coughing, congestion, runny nose, wheezing)?" Prenatal risk factors during pregnancy, such as antibiotic use, infections, and smoking status, were evaluated by questionnaire at enrollment in the first trimester, at 4 to 5 months of gestation, and at 7 to 8 months of gestation. Other potential confounders, including history of asthma, maternal age, maternal ethnicity, and acetaminophen and ibuprofen use, were evaluated by questionnaire during pregnancy and 5 times throughout the child's first year of life. Information on the reason for antibiotic use in the child was separated into respiratory vs nonrespiratory infections. If the 2 infection types occurred, the reason was considered respiratory. Reason for prenatal antibiotic use was not captured, but only systemic antibiotics were noted. Antibiotic use during each trimester of pregnancy was investigated as early use in the first trimester or mid-to-late use in the second to third trimester. Information on type of delivery and antibiotic use during delivery was not available in this cohort.

The study was approved by the university's institutional review board. All enrolled participants provided written informed consent. Maternal characteristics during pregnancy, child characteristics through the first year, and third-year outcomes were compared across prenatal antibiotic uses. Frequency counts and percentages are shown for categorical variables and were compared using  $\chi^2$  or the Fisher exact test. Continuous variables are presented as mean with SD and were compared using *t* test. Multivariable logistic

**Table 1**  
Maternal and child characteristics by prenatal antibiotic use (N = 298)

	Total	Prenatal antibiotic use	No antibiotic use	P value
Total, n (%)	298	103 (34.6)	195 (65.4)	
Study intervention, n (%)	148 (49.7)	51 (49.5)	97 (49.7)	.97
Maternal characteristics during pregnancy				
Maternal age (y), mean (SD)	25.9 (5.9)	26.0 (6.3)	25.8 (5.7)	.78
Mexican ancestry, n (%)	201 (67.5)	66 (64.1)	135 (69.2)	.37
Any smoking, n (%)	30 (10.1)	13 (12.6)	17 (8.7)	.29
Any acetaminophen, n (%)	204 (68.7)	74 (71.8)	130 (67.0)	.39
Any ibuprofen, n (%)	42 (14.1)	12 (11.7)	30 (15.4)	.38
Any infections, n (%)	270 (90.6)	94 (91.3)	176 (90.3)	.78
Any respiratory infections, n (%)	258 (86.6)	87 (84.5)	171 (87.7)	.44
Any fevers, n (%)	148 (49.8)	58 (56.3)	90 (46.4)	.10
Vitamin use, n (%)	84 (28.6)	38 (36.9)	46 (24.1)	.020
Mother has asthma, n (%)	98 (32.9)	45 (43.7)	53 (27.2)	.004
Child characteristics, n (%)				
Firstborn child	108 (36.2)	39 (37.9)	69 (35.4)	.67
Boy	155 (52.0)	58 (56.3)	97 (49.7)	.28
Low birth weight (<2,500 g)	25 (8.4)	10 (9.7)	15 (7.7)	.55
Premature birth (<36 wk)	14 (4.7)	4 (3.9)	10 (5.1)	.63
Breast-fed	264 (88.6)	92 (89.3)	172 (88.2)	.77
First year of life exposures, n (%)				
Exposed to cigarette smoke in home	53 (17.8)	22 (21.4)	31 (15.9)	.24
Any antibiotics	161 (54.0)	61 (59.2)	100 (51.3)	.19
Any acetaminophen	284 (95.6)	96 (94.1)	188 (96.9)	.25
Any ibuprofen	108 (36.2)	45 (43.7)	63 (32.3)	.052
Any infections	285 (95.6)	101 (98.1)	184 (94.4)	.14
Ear infections	111 (37.3)	41 (39.8)	70 (35.9)	.51
Respiratory infections	276 (92.6)	99 (96.1)	177 (90.8)	.09
Any fevers	86 (28.9)	35 (34.0)	51 (26.2)	.16

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