

Letter to the Editor

The relationship of early-life antibiotic use with asthma in at-risk children

To the Editor:

As the prevalence of asthma has doubled in developed countries over the last 30 years, the concurrent increase in children's antibiotic use has led to speculation of a possible causal relationship.¹ Retrospective studies focused on the hygiene hypothesis have shown correlations with early antibiotic use.² These findings, however, may be due to reverse causation, or confounding by indication. Existing evidence is inconsistent, and there have been few prospective studies. Controlling for temporal confounders within a prospective study, we investigated the effects of antibiotic use in the first year of life with subsequent asthma diagnosis and wheezing in the third year of life within a high-risk urban cohort.

Three hundred mother-child pairs were included from the Peer Education in Pregnancy Study. This randomized education intervention examined the effect of educators working with pregnant women at risk for having children with asthma on the modification of factors in the home known to exacerbate the disease. From 1998 to 2004, pregnant women in 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 children were followed from age 4 weeks through 2009. The primary end points of the study were asthma diagnosis and wheezing in the third year of life. Secondary end points included other respiratory symptoms in the third year of life. Asthma was defined as ever having an asthma diagnosis by age 3 years. Wheezing and other respiratory symptoms were determined by any positive response within the year before their third-year visit. Early antibiotic use, excluding topical antibiotics or antifungal agents, was determined at 5 time points during the first year of life. Reason for antibiotic use was separated into respiratory infections versus nonrespiratory infections. If both infections occurred, the reason was considered respiratory. Otitis media without respiratory symptoms was considered nonrespiratory. Unadjusted and adjusted logistic regression models were used, and all statistical analyses were performed using SAS statistical

software, version 9.3 (SAS Institute, Inc, Cary, NC). The study was approved by the University of Illinois at Chicago Human Subjects Institutional Review Board.

Forty-four (15%) children had asthma and 65 (22%) had wheezing in the third year of life. Any smoking in pregnancy, antibiotic and ibuprofen use during pregnancy, and maternal asthma were significantly associated with an asthma diagnosis and reported wheezing. Most of the mothers in the study were of Mexican ethnicity (67%); this was protective of developing asthma and wheezing. Having low birth weight was predictive and being breast-fed was protective of wheezing, but neither was associated with the development of asthma. The prevalence of infections was high within the first year of life, with 96% having infections. Most of the children ($n = 162$, 54%) had taken antibiotics within their first year of life. After adjustment for significant predictors of asthma and wheezing, the number of courses of antibiotics remained significant for both asthma (adjusted odds ratio [aOR], 1.58; 95% CI, 1.27-1.96) and wheezing (aOR, 1.29; 95% CI, 1.07-1.55) (data not shown).

We examined the possibility of reverse causation between the end points and antibiotic use by separating out indication for use (Table I). Sixty-nine (23%) children took antibiotics for respiratory reasons, and 124 (41%) took antibiotics for nonrespiratory reasons. After adjustment for significant maternal and child characteristics, the significant relationships between asthma and other respiratory symptoms held only for antibiotics used for respiratory reasons. There was an association between antibiotics used for respiratory reasons and wheezing, but it did not reach significance (aOR, 1.33; $P = .08$). None of the outcomes was associated with antibiotics used for nonrespiratory reasons.

In our prospective study, we found a significant relationship between antibiotic use within the first year of life and incident asthma and wheezing in year 3, which has been identified consistently in retrospective studies.^{3,4} The hygiene hypothesis theorizes that antibiotic-related suppression of inflammatory responses may lead to a greater impairment of immune responses in early childhood.⁵ However, a recent meta-analysis found that early antibiotic use and asthma in children was unproven and may be the result of confounding.² Research into this association has resulted in mixed conclusions, with one study finding that

TABLE I. Adjusted* regression models to predict 3-year outcomes by indication for antibiotic use in the first year

Outcomes	Antibiotics for respiratory infections in the first year of life		Antibiotics for nonrespiratory infections in the first year of life	
	OR (95% CI)	P value	OR (95% CI)	P value
Asthma by year 3	2.53 (1.67-3.82)	<.01	1.11 (0.83-1.46)	.49
Wheezing in year 3	1.33 (0.97-1.84)	.08	1.10 (0.86-1.41)	.47
Other symptoms in year 3				
Exercise-induced wheezing	1.74 (1.20-2.51)	<.01	1.12 (0.83-1.50)	.46
Sleep-disturbed wheezing	1.74 (1.16-2.62)	<.01	1.06 (0.74-1.50)	.77
Wheezing without a cold	1.84 (1.24-2.73)	<.01	1.03 (0.73-1.44)	.88
ER visit for breathing problems	1.43 (1.02-2.00)	.04	0.91 (0.67-1.24)	.56

ER, Emergency room; OR, odds ratio.

*Adjusted analyses include study intervention and significant variables ($P < .10$) from univariate analysis. Asthma is adjusted for Mexican ethnicity, maternal smoking, antibiotics and ibuprofen during pregnancy, maternal asthma, and exposure to smoke in the home. Wheezing is adjusted for Mexican ethnicity, maternal smoking, antibiotics and ibuprofen during pregnancy, maternal asthma, low birth weight, breast-feeding, and exposure to smoke in the home.

antibiotic use in early life was not associated with asthma, but rather that frequent use is more common among asthmatic children.⁶ A birth cohort found that the effect of antibiotic exposure on the development of asthma between birth and 4 years may be due to confounding by chest infections at an early age when asthma may be indistinguishable from infection.⁷ In addition, respiratory infections in early childhood could contribute to the development of asthma by damaging the airways or, alternatively, severe respiratory infections could be an indicator of genetic predisposition for asthma.⁸

Our results indicate that the association between antibiotic use and subsequent asthma holds only in the case of respiratory infections, adding to the previous research suggesting that the relationship may be explained by reverse causation or confounding by indication. There are some limitations with our study, however. Asthma is a complex clinical disease that is difficult to assess before age 6 years.¹ Given that our study included diagnoses before age 3 years, the nature of the disease progression may still be unpredictable. Because there was a high rate of infections in this cohort, there may be a covariation effect between infections and antibiotic use that we were unable to separate. Also, the use of antibiotics and type of infections noted are based on parental recall and so are prone to recall bias. Another limitation is that we do not have access to the types of antibiotics used. Broad-spectrum antibiotics became more prevalent in the 1980s and may alter the microbiome more than the narrow-spectrum antibiotics used in the past.⁹

Despite the limitations inherent in this research, we conclude that the associations found between antibiotic use in young children and the subsequent development of asthma and wheezing may be due to confounding by respiratory infections.

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