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The Relationship of Early-Life Antibiotic Use with Asthma in At-Risk Children

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Summary

Asthma prevalence has increased with the reason remaining unknown. Antibiotics early in life have been hypothesized as playing a role in the development of asthma; however, we have found the relationship may be due to confounding by respiratory infections and may not be causally related.

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Keywords

Childhood asthma; antibiotics; respiratory infections; wheezing; hygiene hypothesis

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 4 weeks of age through 2009. The primary endpoints of the study are asthma diagnosis and wheezing in the third year of life. Secondary endpoints include other respiratory symptoms in the third year of life. Asthma was defined as ever having an asthma diagnosis by 3 years of age. Wheezing and other respiratory symptoms were determined by any positive response within the year prior to 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 non-respiratory infections. If both infections occurred, the reason was considered respiratory. Otitis media without respiratory symptoms was considered non-respiratory. Unadjusted and adjusted logistic regression models were utilized and all statistical analyses were performed using SAS statistical software, version 9.3 (SAS Institute Inc, Cary, North Carolina). 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. The majority of 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. The majority of 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 (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 endpoints 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 non-respiratory 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=0.08). None of the outcomes were associated with antibiotics used for non-respiratory 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 three 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 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 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). Additionally, 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 the association between antibiotic use and subsequent asthma holds only in the case of respiratory infections, adding to the previous research suggesting 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 which is difficult to assess before age 6 (1). Given that our study included diagnoses prior to age 3, the nature of the disease progression may still be unpredictable. Since there was a high rate of infections in this cohort, there may be a co-variation 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 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 the associations found between antibiotic use in young children and subsequent development of asthma and wheezing may be due to confounding by respiratory infections.

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Abbreviations

aOR adjusted Odds Ratio

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Table I

Adjusted regression models to predict three-year outcomes by indication for antibiotic use in the first year.

	Antibiotics for Respiratory Infections In the First Year of Life		Antibiotics for Non-Respiratory Infections In the First Year of Life	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Outcomes				
Asthma by Year 3	2.53 (1.67, 3.82)	<i>italic</i> >0.01	1.11 (0.83, 1.46)	0.49
Wheezing in Year 3	1.33 (0.97, 1.84)	0.08	1.10 (0.86, 1.41)	0.47
Other Symptoms in Year 3				
Exercise Induced Wheezing	1.74 (1.20, 2.51)	bold >0.01	1.12 (0.83, 1.50)	0.46
Sleep Disturbed Wheezing	1.74 (1.16, 2.62)	<0.01	1.06 (0.74, 1.50)	0.77
Wheezing without a Cold	1.84 (1.24, 2.73)	<0.01	1.03 (0.73, 1.44)	0.88
ER Visit for Breathing Problems	1.43 (1.02, 2.00)	0.04	0.91 (0.67, 1.24)	0.56

OR=Odds Ratio; CI=Confidence Interval; ER=Emergency Room

Adjusted analyses include study intervention and significant variables ($p < 0.10$) 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.