

Antibiotic Exposure and the Risk of Food Allergy: Evidence in the US Medicaid Pediatric Population



Minghui Li, PhD^a, Z. Kevin Lu, PhD^b, David J. Amrol, MD^c, Joshua R. Mann, MD, MPH^d, James W. Hardin, PhD^e, Jing Yuan, PhD^b, Christina L. Cox, PharmD^b, and Bryan L. Love, PharmD, MPH^b *Memphis, Tenn; Columbia, SC; and Jackson, Miss*

What is already known about this topic? Antibiotic therapy could have a significant role in altering gastrointestinal microflora, which is thought to contribute to development of food allergies in children.

What does this article add to our knowledge? Antibiotic exposure early in life was significantly associated with faster development of food allergy in a large Medicaid pediatric population.

How does this study impact current management guidelines? The present study adds to the literature demonstrating an association between antibiotic exposure and food allergy diagnosis; however, it is not yet established whether this is a causal relationship or an incidental finding.

BACKGROUND: Food allergy is a significant public health concern in the United States, especially in the pediatric population. It places substantial clinical and economic burdens on the health care system. Exposure to antibiotics in early childhood is thought to increase the risk of subsequent food allergy.

OBJECTIVE: To examine the impact of exposure to antibiotics early in life on time to development of food allergy.

METHODS: We conducted a population-based matched cohort study using Medicaid data from 28 states. Antibiotic nonusers were matched 1:1 to antibiotic users on date of birth, sex, race, and state. A Cox proportional hazards regression model was used to evaluate the effect of antibiotic exposure on time to development of food allergy. Sensitivity analyses were performed to assess the robustness of study findings.

RESULTS: We matched 500,647 antibiotic nonusers to 500,647 antibiotic users in the Medicaid pediatric population. In the adjusted Cox proportional hazards regression analysis, antibiotic exposure was significantly associated with faster development of food allergy (hazard ratio, 1.40; 95% CI, 1.34-1.45). The

magnitude and significance of the association between antibiotic exposure and food allergy did not change in the sensitivity analyses. A significant association between antibiotic exposure and faster development of food allergy was found in 17 of 28 states. **CONCLUSION:** Compared with antibiotic nonusers, children with antibiotic prescription had an increased risk of food allergy. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:492-9)

Key words: Antibiotics; Food allergy; Health outcomes; Medicaid; Pediatric

INTRODUCTION

Food allergy is a significant public health concern in the United States, especially in the pediatric population. Recent estimates suggest that approximately 15 million Americans, 4% of children and 1% of adults, have food allergies.¹⁻³ The prevalence of food allergy among children has continued to grow over the last 20 years, placing substantial clinical and economic

^aDepartment of Clinical Pharmacy and Translational Science, College of Pharmacy, The University of Tennessee Health Science Center, Memphis, Tenn

^bDepartment of Clinical Pharmacy and Outcomes Sciences, College of Pharmacy, University of South Carolina, Columbia, SC

^cDivision of Allergy, Asthma and Immunology, Department of Internal Medicine, School of Medicine, University of South Carolina, Columbia, SC

^dDepartment of Preventive Medicine, School of Medicine and John D. Bower School of Population Health, University of Mississippi Medical Center, Jackson, Miss

^eDepartment of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC

This study was supported by a grant from the Maternal and Child Health Research Program, Maternal and Child Health Bureau (Title V, Social Security Act), Health Resources and Services Administration, Department of Health and Human Services (grant no. R40MC23628-01-00) and also by a grant from the University of South Carolina Office of Research Advanced Support for Innovative Research Excellence (ASPIRE) program (grant no. 11150-E404).

Conflicts of interest: M. Li and J. Yuan have received support from the University of South Carolina's Support to Promote Advancement of Research and Creativity (SPARC) grant. B. L. Love received research support from the University of South Carolina through an ASPIRE II grant. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication December 14, 2017; revised September 12, 2018; accepted for publication September 19, 2018.

Available online November 20, 2018.

Corresponding author: Bryan L. Love, PharmD, MPH, Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina College of Pharmacy, 715 Sumter St, Columbia, SC 29208. E-mail: loveb@cop.sc.edu.

2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2018.09.036>

Abbreviations used

GI-gastrointestinal

HR-hazard ratio

ICD-9-CM-International Classification of Diseases, Ninth Revision, Clinical Modification

MAX-Medicaid Analytic eXtract

NICU-neonatal intensive care unit

burdens on the health care system. Compared with children without food allergy, those with food allergy have more illness, hospitalizations, and medical costs.⁴

Adverse food reactions can be classified into food intolerance and food hypersensitivity. Food intolerance is nonimmunologic and indicates an adverse physiologic reaction to food. Food hypersensitivity is true allergy and is caused by both IgE-mediated and non-IgE-mediated immune mechanisms.⁵ Children with food allergy can have a range of symptoms, from localized hives to fatal anaphylaxis.^{5,6}

In animal models, the interaction between gastrointestinal (GI) microflora and the GI immune system plays an important role in the development of immunologic tolerance to potential food allergens. The immature development of this interaction has

been proposed as one hypothesis for the increased prevalence of food allergy in children.⁷ Antibiotics are common and account for more than 30% of total prescriptions dispensed to preschool children.⁸ However, indiscriminate use of antibiotics is associated with several complications. Short-term side effects of antibiotics include nausea, vomiting, diarrhea, and rash. Long-term use of antibiotics is associated with increased risks of obesity, inflammatory bowel disease, and allergic diseases.⁹⁻¹² We hypothesized that antibiotic therapy could have a significant role in altering GI microflora, which are believed to be important in the development of normal immune tolerance to food antigens.

Until now, few studies have examined the association between antibiotic exposure and food allergy at the population level.¹³⁻¹⁶ The objective of this study was to assess the relationship between antibiotic prescription early in life and time to development of food allergy in a diverse, multistate Medicaid population on the basis of our previous work.¹³

METHODS

Data sources

This study used data from the Medicaid Analytic eXtract (MAX) from 2006 to 2010 of 28 states: Arizona, California, Colorado, Connecticut, Florida, Georgia, Iowa, Illinois, Louisiana, Maryland, Massachusetts, Michigan, Mississippi, Montana, Nebraska, North Dakota, New Jersey, New Mexico, New York, Nevada, Ohio,

TABLE I. List of *ICD-9-CM* codes used to identify food allergy

Description	ICD-9-CM code	Total		Antibiotic users		Antibiotic nonusers	
		n*	%	n*	%	n*	%
Food allergy		14,812	1.48	9,193	1.84	5,619	1.12
Allergic rhinitis attributable to food	477.1	1,147	0.11	683	0.14	464	0.09
Allergic gastroenteritis and colitis	558.3	2,077	0.21	1,503	0.30	574	0.11
Contact dermatitis attributable to food in contact with skin	692.5	1,078	0.11	687	0.14	391	0.08
Dermatitis attributable to food taken internally	693.1	8,003	0.80	4,740	0.95	3,263	0.65
Toxic effect of fish and shellfish	988.0	52	0.01	24	<0.01	28	0.01
Anaphylactic shock attributable to adverse food reaction, specifically for							
Unspecified food	995.60	462	0.05	286	0.06	176	0.04
Peanuts	995.61	430	0.04	197	0.04	233	0.05
Crustaceans	995.62	36	<0.01	24	<0.01	12	<0.01
Fruits and vegetables	995.63	†	†	†	†	†	†
Tree nuts and seeds	995.64	86	0.01	58	0.01	28	0.01
Fish	995.65	124	0.01	41	0.01	83	0.02
Food additives	995.66	†	†	†	†	†	†
Milk products	995.67	†	†	†	†	†	†
Eggs	995.68	168	0.02	118	0.02	50	0.01
Other specified food	995.69	108	0.01	64	0.01	44	0.01
Other adverse food reactions, not elsewhere classified	995.7	1,228	0.12	731	0.15	497	0.10
General food allergy according to specific type of food							
Peanuts	V15.01	759	0.08	413	0.08	346	0.07
Milk products	V15.02	1,036	0.10	710	0.14	326	0.07
Eggs	V15.03	531	0.05	352	0.07	179	0.04
Seafood	V15.04	181	0.02	105	0.02	76	0.02
Other foods	V15.05	1,069	0.11	635	0.13	434	0.09

*A participant could have multiple food allergy codes in the individual rows at the same time.

†Data are not reported in these cells because of a small sample size.

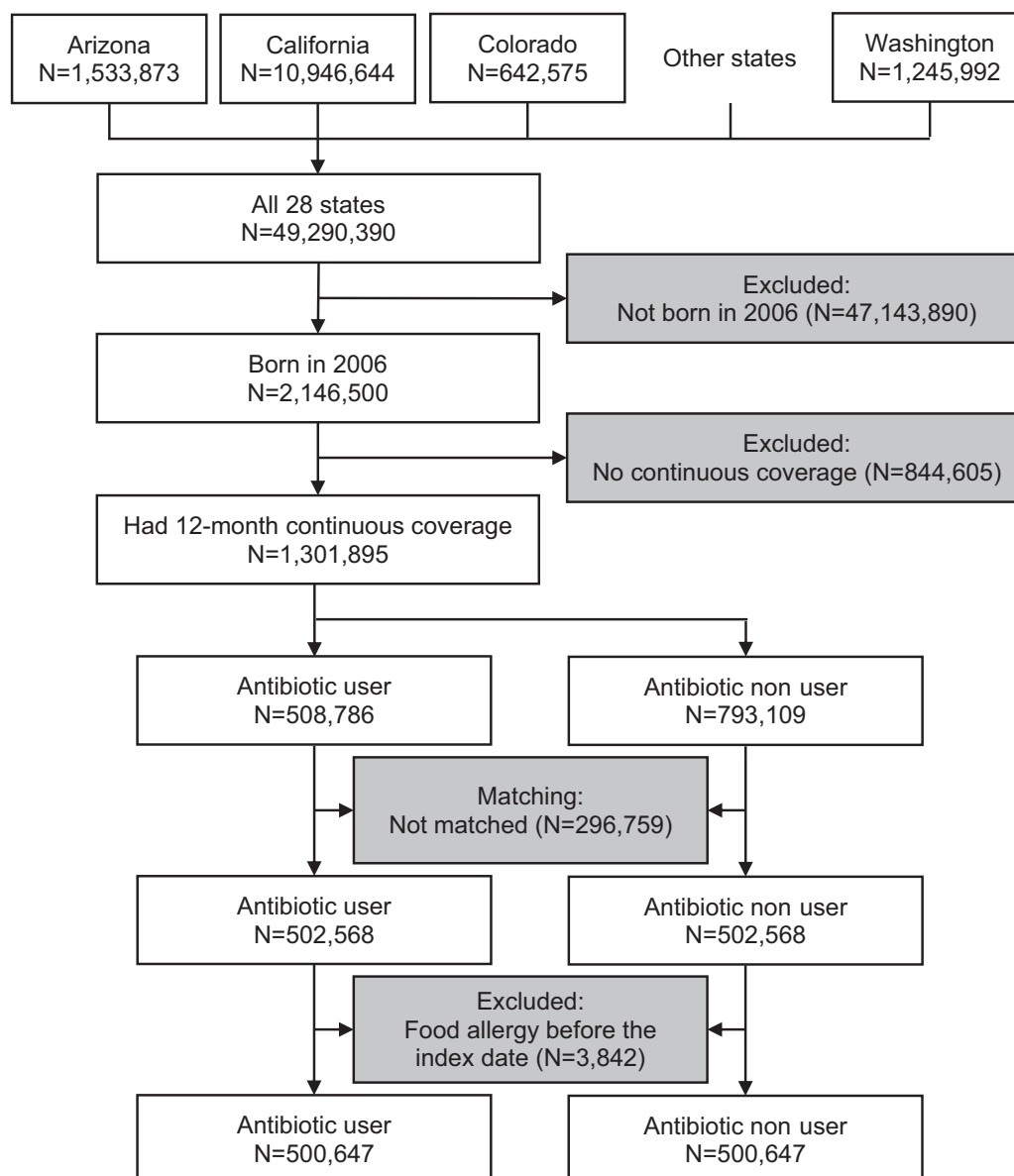


FIGURE 1. Consolidated Standards of Reporting Trials flow diagram of study participants.

Oregon, Pennsylvania, South Carolina, Tennessee, Texas, Virginia, and Washington. These states cover a large geographic area with highly diverse populations in the United States. Each state reports individual-level Medicaid enrollment and claims data to the Center for Medicare & Medicaid Services on a quarterly basis.¹⁷ MAX data are appropriate for this study because there is rich information on Medicaid enrollment, demographic characteristics, socioeconomic, diagnosis, health service utilization, and prescription drug utilization. MAX data have been widely used in health outcome assessments in the pediatric population.¹⁸⁻²⁰

Study design

We conducted a population-based matched cohort study to examine the association between childhood antibiotic exposure and time to development of food allergy. We examined time to

development of food allergy because lengths of follow-up differed significantly between antibiotic users and nonusers. A cohort study design has advantages compared with other types of observational study designs, such as case control studies in which the outcome is ascertained before exposure is determined. An exact match between antibiotic users and nonusers was performed to assign an appropriate index date to each antibiotic nonuser. Antibiotic nonusers were matched 1:1 to antibiotic users on date of birth, sex, race, and state. The index date for an antibiotic user was the date of the first antibiotic prescription, and the index date for an antibiotic nonuser was assigned as the same index date from the matched antibiotic user. Antibiotic users and nonusers were followed until they developed food allergy, died, left the Medicaid program, or until the end of the study period on December 31, 2010. This study received approval from the University of South Carolina Institutional Review Board review committee.

TABLE II. Baseline characteristics of study subjects in the Medicaid pediatric population (N = 1,001,294)

Characteristic	Antibiotic users (n = 500,647) (%)	Antibiotic nonusers (n = 500,647) (%)	P value
Age at index (d), mean ± SD	198.80 ± 88.94	198.80 ± 88.94	1.0000
Sex			1.0000
Male	53.28	53.28	
Female	46.72	46.72	
Race			1.0000
Non-Hispanic white	33.08	33.08	
Non-Hispanic black	18.88	18.88	
Hispanic	38.41	38.41	
Other	9.63	9.63	
Season of birth			1.0000
Spring	24.63	24.63	
Summer	25.98	25.98	
Fall	25.13	25.13	
Winter	24.26	24.26	
Geographic region			1.0000
Northeast	12.36	12.36	
Midwest	12.35	12.35	
South	51.76	51.76	
West	23.53	23.53	
Residence area			<.0001
Metropolitan area	92.94	91.89	
Nonmetropolitan area	7.06	8.11	
Managed care			<.0001
Yes	90.58	90.85	
No	9.42	9.15	
SCHIP			<.0001
Yes	0.70	0.83	
No	99.30	99.17	
Atopic dermatitis			<.0001
Yes	7.65	5.58	
No	92.35	94.42	
Asthma/wheeze			<.0001
Yes	18.03	7.06	
No	81.97	92.94	
Preterm/LBW			<.0001
Yes	9.97	9.16	
No	90.03	90.84	
Cesarean section			<.0001
Yes	20.64	18.75	
No	79.36	81.25	
NICU			<.0001
Yes	6.28	5.76	
No	93.72	94.24	

LBW, Low birth weight; SCHIP, State Children's Health Insurance Program.

Study population

The study population was selected from children born in 2006 with 12-month continuous Medicaid coverage after birth. Children who had at least 1 prescription of antibiotics during the first 12 months after birth were classified as antibiotic users. Children

without any antibiotic prescriptions during the first 12 months after birth were classified as antibiotic nonusers. To ensure that the exposure (antibiotic prescription) preceded the outcome (diagnosis of food allergy) among study participants, children diagnosed with food allergy before the index date were excluded from the study.

Measurement

The outcome of interest was the time to first food allergy-related claim, defined as the time between the index date and the incidence of food allergy. The diagnosis of food allergy was based on relevant *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes from Medicaid claims. Published studies identified various *ICD-9-CM* codes for food allergy diagnosis.²¹⁻²³ On the basis of systematic and comprehensive literature reviews and consultations with clinicians, we decided to use codes for case ascertainment as presented in Table I. A recent study showed that using only food-specific *ICD-9-CM* codes might miss up to 50% of true food allergy cases.²⁴ Antibiotic exposure was identified using prescription drug events from Medicaid claims. The fills of antibiotics were based on relevant national drug codes.

Antibiotic users and nonusers were matched on date of birth, sex, race, and state in this study. Other factors, however, might confound the association between antibiotic exposure and time to development of food allergy. Potential confounding factors considered in the study included residence area, managed care enrollment, State Children's Health Insurance Program enrollment, comorbidities, delivery-related diagnosis, and neonatal intensive care unit (NICU) admission. All potential confounding factors were measured at baseline (a 12-month period since birth). Residence area, managed care enrollment, and State Children's Health Insurance Program enrollment were identified on the basis of Medicaid enrollment information. Food allergy often coexists with other allergic diseases, including asthma, atopic dermatitis, and wheeze.^{25,26} These comorbidities were measured on the basis of *ICD-9-CM* codes from Medicaid claims. Although a consistent effect has not been observed, delivery-related diagnoses, including low birth weight and cesarean section, have been found to increase the risk of food allergy in some studies.^{27,28} These diagnoses were identified using *ICD-9-CM* codes from Medicaid claims. Children who were admitted to NICU may have additional comorbidities that may predispose them to receive antibiotics, which is of interest for this study. NICU admission was identified using procedure codes from Medicaid claims.

Statistical analysis

Baseline characteristics of antibiotic users and nonusers were compared using chi-square or the Fisher exact test for categorical variables and *t* test for continuous variables. Differences in medians were measured using the Kruskal-Wallis test. A Cox proportional hazards regression model was used to evaluate the effect of antibiotic exposure on the time to development of food allergy. In this model, the dependent variable was time to diagnosis of food allergy, the main independent variable was antibiotic exposure, and covariates included significant baseline characteristics. Hazard ratios (HRs) with 95% CIs were calculated to assess the impact of antibiotic exposure on time to development of food allergy. We performed subgroup analyses to fit the Cox proportional hazards regression model to each state and region individually.

Several sensitivity analyses were performed to assess the robustness of study findings. First, we developed a restricted model by excluding some *ICD-9-CM* codes (rhinitis, dermatitis, toxic effect, and other adverse food reactions) that might lead to misclassification

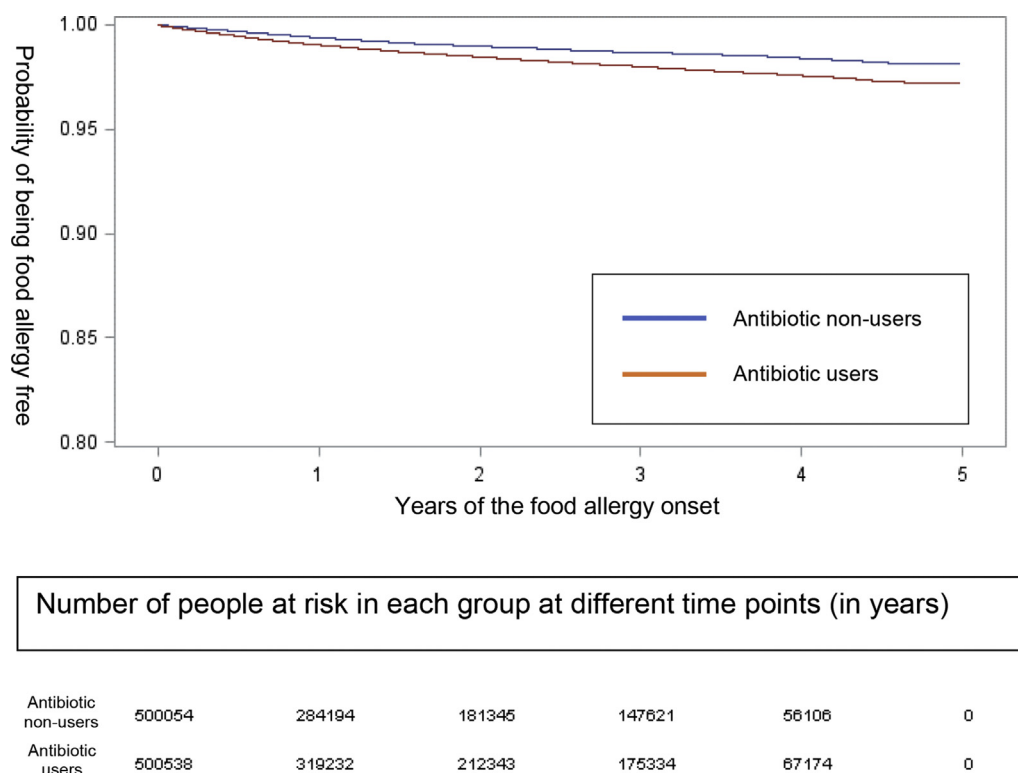


FIGURE 2. Survival curve for the development of food allergy by antibiotic exposure.

of true IgE-mediated food allergy. Second, we considered a model that restricted the outcome to children with at least 1 epinephrine prescription in addition to a food allergy diagnosis. Third, we considered an epinephrine model that was restricted to having at least 1 epinephrine prescription within 30 days of food allergy diagnosis. We also performed a subgroup analysis on different numbers of antibiotic prescriptions. Specially, we examined the effects of using (1) 1 antibiotic prescription and (2) 2 or more antibiotic prescriptions on the time to development of food allergy. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

After applying the inclusion and exclusion criteria, 500,647 antibiotic nonusers were matched to 500,647 antibiotic users (Figure 1). Except for matching factors, all other baseline characteristics were significantly different between antibiotic users and nonusers (Table II). Median follow-up time was 1.20 years (interquartile range, 0.65-3.44) in the antibiotic nonuser group as compared with 1.48 years (interquartile range, 0.75-3.68) in the antibiotic user group ($P < .001$). During the follow-up period, more antibiotic users developed food allergy than antibiotic nonusers (1.84% vs 1.12%; Table I).

In the unadjusted Cox proportional hazards regression analysis, antibiotic exposure was significantly associated with faster development of food allergy (HR, 1.56; 95% CI, 1.50-1.62; Figure 2). After controlling for covariates in the adjusted Cox proportional hazards regression analysis, antibiotic exposure remained significantly associated with faster development of food allergy (HR, 1.40; 95% CI, 1.34-1.45;

Table III). Compared with nonusers, antibiotic users had a 40% higher risk of food allergy at any time during the follow-up period. Other significant factors associated with development of food allergy included nonmetropolitan area (HR, 0.80; 95% CI, 0.74-0.87), managed care (HR, 1.08; 95% CI, 1.01-1.15), comorbidity of atopic dermatitis (HR, 3.72; 95% CI, 3.56-3.89), comorbidity of asthma or wheeze (HR, 1.57; 95% CI, 1.50-1.64), and preterm or low birth weight (HR, 1.33; 95% CI, 1.25-1.42).

The magnitude and significance of the association between antibiotic exposure and food allergy did not change in the sensitivity analyses (Table IV). After excluding ICD-9-CM codes of rhinitis, dermatitis, toxic effect, and other adverse food reactions, in the restricted model (model 2), antibiotic exposure was still significantly associated with faster development of food allergy (HR, 1.46; 95% CI, 1.38-1.55). If we only consider food allergy with epinephrine prescription (model 3), there was a significant association between antibiotic exposure and food allergy (HR, 1.37; 95% CI, 1.30-1.44). Further restricting the diagnosis of food allergy to those with an epinephrine prescription within 30 days of food allergy diagnosis (model 4), we still observed a significant association between antibiotic exposure and food allergy (HR, 1.42; 95% CI, 1.15-1.77). In the subgroup analysis, the magnitude and significance of the association between antibiotic exposure and food allergy were similar. Using 1 antibiotic prescription was significantly associated with faster development of food allergy (HR, 1.49; 95% CI, 1.41-1.58). Similarly, there was a significant association between using 2 or more antibiotic prescriptions and food allergy (HR, 1.31; 95% CI, 1.24-1.39).

TABLE III. Adjusted Cox proportional hazards regression model on food allergy in the Medicaid pediatric population

Factor	HR	95% CI
Antibiotics		
Yes	1.40	1.34-1.45
No	Reference	
Residence area		
Metropolitan area	Reference	
Nonmetropolitan area	0.80	0.74-0.87
Managed care		
Yes	1.08	1.01-1.15
No	Reference	
SCHIP		
Yes	0.90	0.71-1.12
No	Reference	
Atopic dermatitis		
Yes	3.72	3.56-3.89
No	Reference	
Asthma/wheeze		
Yes	1.57	1.50-1.64
No	Reference	
Preterm/LBW		
Yes	1.33	1.25-1.42
No	Reference	
Cesarean section		
Yes	0.97	0.92-1.01
No	Reference	
NICU		
Yes	0.97	0.89-1.05
No	Reference	

LBW, Low birth weight; SCHIP, State Children's Health Insurance Program.

TABLE IV. Sensitivity analysis of adjusted Cox proportional hazards regression model

Model*	HR	95% CI
Model 1: Original model	1.40	1.34-1.45
Model 2: Restricted model†	1.46	1.38-1.55
Model 3: Epinephrine model‡	1.37	1.30-1.44
Model 4: Epinephrine 30-d model§	1.42	1.15-1.77

LBW, Low birth weight; SCHIP, State Children's Health Insurance Program.

*All models adjusted for residence area, managed care, SCHIP, atopic dermatitis, asthma/wheeze, preterm/LBW, cesarean section, and NICU.

†The outcome was food allergy excluding rhinitis, dermatitis, toxic effect, and other adverse food reactions.

‡The outcome was food allergy with epinephrine prescription.

§The outcome was food allergy with epinephrine prescription within 30 d of diagnosis.

The significant association between antibiotic exposure and faster development of food allergy was found in 17 of 28 states: Massachusetts, New York, Pennsylvania, Iowa, Illinois, Michigan, Florida, Georgia, Louisiana, Maryland, Mississippi, South Carolina, Tennessee, Texas, Virginia, Colorado, and New Mexico (Figure 3). Antibiotic exposure was not significantly associated with food allergy in 10 of 28 states: Connecticut, New Jersey, Nebraska, North Dakota, Ohio, Arizona, Montana,

Nevada, Oregon, and Washington. In California, however, antibiotic exposure was significantly associated with slower development of food allergy (HR, 0.87; 95% CI, 0.80-0.95). Antibiotic exposure was found to be associated with increased risk of food allergy in 3 regions: Northeast (HR, 1.45; 95% CI, 1.32-1.59), Midwest (HR, 1.90; 95% CI, 1.66-2.16), and South (HR, 1.81; 95% CI, 1.70-1.92). Antibiotic exposure was not significantly associated with food allergy in the West region (HR, 0.96; 95% CI, 0.90-1.03).

DISCUSSION

Early antibiotic exposure was significantly associated with development of food allergy. This significance remained after controlling for potential confounding variables, including atopic dermatitis. Antibiotics are known to affect the GI flora, which could change the GI mucosal barrier.⁷ Compared with adults, children have an immature GI mucosal barrier. Therefore, using antibiotics early in life is believed to affect the GI flora and the GI mucosal barrier and to increase the risk of food allergy.⁷ In future studies, it is of great importance to explore how antibiotics change the normal flora and to explore different strategies to prevent the development of food allergy in children.

Results of this study were consistent with previous findings. Our previous matched case control study was conducted in a South Carolina Medicaid pediatric population. We found that receipt of antibiotics within 12 months after birth was associated with increased risk of food allergy (odds ratio [OR], 1.21; 95% CI, 1.06-1.39).¹³ In another US-based case control chart review, antibiotics were not found to be associated with increased risk of food allergy.¹⁵ A population-based nested case control study in Finland found that a child's use of antibiotics was associated with increased risk of cow's milk allergy (OR, 1.71; 95% CI, 1.59-1.84).¹⁴

We also sought to explore whether the association between antibiotics and food allergy differed according to geography, because antibiotic utilization can vary by location.²⁹ State- and region-specific associations between antibiotic exposure and time to development of food allergy were consistent with the overall results. Associations in some states, however, were not significant, which may be due to the small sample size of matched antibiotic users and nonusers in some states (eg, Connecticut, North Dakota, Montana, Nevada, and Oregon). We may not have enough power to detect the actual difference in some states where sample sizes were small. Furthermore, antibiotic exposure was associated with slower development of food allergy in California. Previous research suggests that antibiotic prescribing rates in all age groups, including younger than 2 years, are lower in Western states compared with Southern states. Differences in antibiotic prescription patterns may result in confounding when looking at state-specific associations between antibiotics and food allergy. In addition to different antibiotic prescription patterns, different patterns of food allergy diagnoses or some unmeasured confounding variables in California may explain the differences observed in this study. It is also possible that the inverse association in California represents a type 1 error, given that 28 state-level analyses were performed.

Antibiotics are associated with several short-term and long-term adverse events, and many antibiotics are prescribed without compelling indications. One important long-term effect is antibiotic resistance. The prevalence of antibiotic resistance is

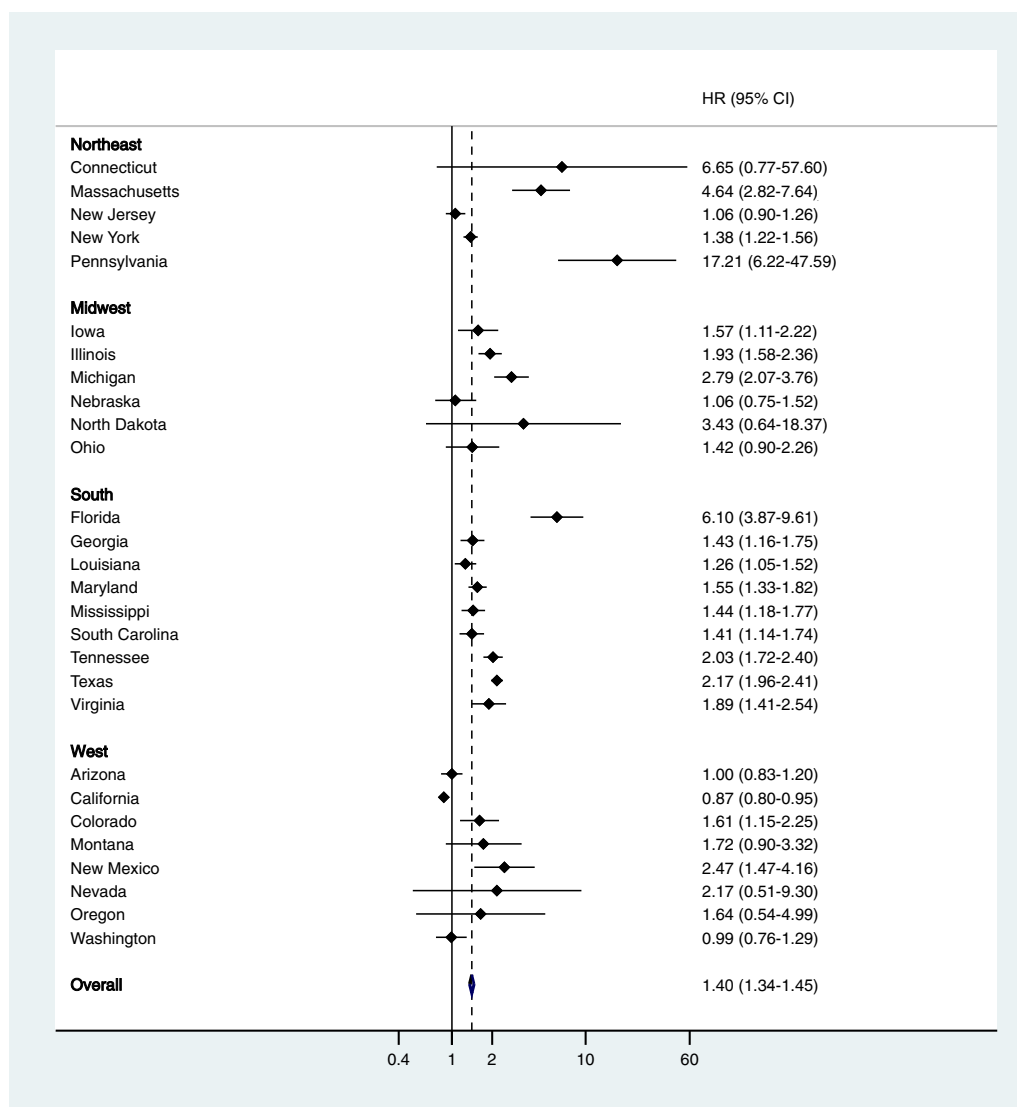


FIGURE 3. Forest plot of the association between antibiotic exposure and time to food allergy development in different regions and states.

high, and previous prescription of antibiotics is an important risk factor.³⁰ Resistance is a significant concern when prescribing antibiotics to children. Another important potential long-term effect suggested by the results of this study is subsequent food allergy. If true, it provides additional rationale to promote antibiotic stewardship.

This study had several strengths. First, MAX data were used as the data set in the study. MAX data included Medicaid enrollment and claims data from 28 states, which are representative of the US Medicaid population. In addition, MAX data allowed us to conduct subgroup analysis to explore the association between antibiotic exposure and time to development of food allergy in different states and regions. Second, the population-based matched cohort study was used in the study. By matching antibiotic nonusers to users, we were able to assign the same index date as the matched antibiotic users to nonusers. However, this study had some limitations. First, this study might be subject to residual confounding. Some unmeasured or unknown factors

(eg, family history of food allergy) might confound the association between antibiotic use and food allergy. In addition, confounding by indication might explain the association between antibiotic use and food allergy when antibiotics were prescribed for infections that were associated with food allergy.³¹ Second, using *ICD-9-CM* codes to identify food allergy might lead to misclassification of true IgE-mediated food allergy. However, we used a restricted definition of food allergy in the sensitivity analysis, and the sensitivity analysis results showed that the association between antibiotic use and food allergy was maintained. Third, this study did not measure antibiotic prescription patterns, which might differ by states, regions, age group, or provider type. Finally, there was an unexpectedly low incidence of food allergy observed in our study, which may have influenced the overall results. There are several possible explanations for lower than expected food allergy, including the following: (1) not all children were followed until age 4 years, (2) children with managed care may not have complete claims information, and

(3) some children with true food allergy may not have an *ICD-9-CM* code indicating food allergy because of inconsistencies in coding by providers. In addition, we excluded children diagnosed with food allergy before their first antibiotic prescription because we were interested in assessing the relationship between antibiotics and new-onset food allergy. However, excluding these patients with other potential causes of food allergy (eg, genetics) may limit the generalizability of findings.

Conclusions

Compared with antibiotic nonusers, children with antibiotic prescription early in life were at increased risk of food allergy. These findings are similar to other reports examining a relationship between antibiotics and food allergy; however, a prospective study is needed to determine whether this association is correctly attributed to antibiotics, potentially via changes to the microbiome.

Acknowledgment

We thank Dr Richard Schulz for his mentorship and encouragement throughout the project.

REFERENCES

- Jones SM, Burks AW. Food allergy. *N Engl J Med* 2017;377:1168-76.
- Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128:e9-17.
- Branum AM, Lukacs SL. Food allergy among children in the United States. *Pediatrics* 2009;124:1549-55.
- Mulla ZD, Simon MR. Hospitalizations for anaphylaxis in Florida: epidemiologic analysis of a population-based dataset. *Int Arch Allergy Immunol* 2007;144:128-36.
- Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. *J Allergy Clin Immunol* 2010;126:1105-18.
- Sampson HA. Food allergy. *J Allergy Clin Immunol* 2003;111:S540-7.
- Vighi G, Marcucci F, Sensi L, Di Cara G, Frati F. Allergy and the gastrointestinal system. *Clin Exp Immunol* 2008;153:3-6.
- Rossignoli A, Clavenna A, Bonati M. Antibiotic prescription and prevalence rate in the outpatient paediatric population: analysis of surveys published during 2000-2005. *Eur J Clin Pharmacol* 2007;63:1099-106.
- Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: an epidemiologic study. *Pediatr Allergy Immunol* 2004;15:421-7.
- Ajslev TA, Andersen CS, Gamborg M, Sorensen TI, Jess T. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *Int J Obes (Lond)* 2011;35:522-9.
- Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. *Am J Gastroenterol* 2010;105:2687-92.
- Foliaki S, Pearce N, Bjorksten B, Mallol J, Montefort S, von Mutius E. Antibiotic use in infancy and symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old: International Study of Asthma and Allergies in Childhood Phase III. *J Allergy Clin Immunol* 2009;124:982-9.
- Love BL, Mann JR, Hardin JW, Lu ZK, Cox C, Amrol DJ. Antibiotic prescription and food allergy in young children. *Allergy Asthma Clin Immunol* 2016;12:41.
- Metsälä J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM. Mother's and offspring's use of antibiotics and infant allergy to cow's milk. *Epidemiology* 2013;24:303-9.
- Dowhower Karpas K, Paul IM, Leckie JA, Shung S, Carkaci-Salli N, Vrana KE, et al. A retrospective chart review to identify perinatal factors associated with food allergies. *Nutr J* 2012;11:87.
- Mai XM, Kull I, Wickman M, Bergstrom A. Antibiotic use in early life and development of allergic diseases: respiratory infection as the explanation. *Clin Exp Allergy* 2010;40:1230-7.
- Sykes J, Verghese S. Medicaid Analytic Extract Date of Death (MAX DOD) master file, 2009 update. Mathematica Policy Research Reports. Princeton, NJ: Mathematica Policy Research; 2013.
- Kenyon CC, Rubin DM, Zorc JJ, Mohamad Z, Faerber JA, Feudtner C. Childhood asthma hospital discharge medication fills and risk of subsequent readmission. *J Pediatr* 2015;166:1121-7.
- Matone M, Localio R, Huang YS, dosReis S, Feudtner C, Rubin D. The relationship between mental health diagnosis and treatment with second-generation antipsychotics over time: a national study of US Medicaid-enrolled children. *Health Serv Res* 2012;47:1836-60.
- Rust G, Zhang S, Reynolds J. Inhaled corticosteroid adherence and emergency department utilization among Medicaid-enrolled children with asthma. *J Asthma* 2013;50:769-75.
- Trikha A, Baillargeon JG, Kuo Yf, Tan A, Pierson K, Sharma G, et al. Development of food allergies in patients with gastroesophageal reflux disease treated with gastric acid suppressive medications. *Pediatr Allergy Immunol* 2013;24:582-8.
- Patel DA, Holdford DA, Edwards E, Carroll NV. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. *J Allergy Clin Immunol* 2011;128:110-115.e5.
- Vassallo MF, Banerji A, Rudders SA, Clark S, Mullins RJ, Camargo CA. Season of birth and food allergy in children. *Ann Allergy Asthma Immunol* 2010;104:307-13.
- Clark S, Gaeta TJ, Kamarthi GS, Camargo CA. ICD-9-CM coding of emergency department visits for food and insect sting allergy. *Ann Epidemiol* 2006;16:696-700.
- Clark S, Bock SA, Gaeta TJ, Brenner BE, Cydulka RK, Camargo CA, et al. Multicenter study of emergency department visits for food allergies. *J Allergy Clin Immunol* 2004;113:347-52.
- Banerji A, Rudders SA, Corel B, Garth AP, Clark S, Camargo CA. Predictors of hospital admission for food-related allergic reactions that present to the emergency department. *Ann Allergy Asthma Immunol* 2011;106:42-8.
- Taylor B, Norman A, Orgel H, Turner M, Stokes C, Soothill J. Transient IgA deficiency and pathogenesis of infantile atopy. *Lancet* 1973;302:111-3.
- Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;121:1331-6.
- Hicks LA, Bartoces MG, Roberts RM, Suda KJ, Hunkler RJ, Taylor TH Jr, et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. *Clin Infect Dis* 2015;60:1308-16.
- Bryce A, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association with routine use of antibiotics in primary care: systematic review and meta-analysis. *BMJ* 2016;352:i939.
- Kummeling I, Thijs C. Reverse causation and confounding-by-indication: do they or do they not explain the association between childhood antibiotic treatment and subsequent development of respiratory illness? *Clin Exp Allergy* 2008;38:1249-51.