Infant Antibiotic Exposure and Food Allergy Development

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Abstract

Background

Food allergy prevalence is steadily increasing in the developed world, for reasons that are still being investigated. Epidemiological evidence suggests that insufficient microbial exposure early in life may increase the risk of developing allergic diseases. Antibiotics, which are a significant source of microbial deprivation, may be a risk factor for developing food allergies.

Objective

The objective of this study was to characterize the association between antibiotic exposure in the first year of life and the subsequent development of food allergies by age five.

Methods

A cohort of 18,088 patients born between 01/01/2006 and 12/31/2010 was analyzed retrospectively. Poisson regression was used to analyze the time-weighted association between antibiotic prescriptions and food allergy diagnosis, while adjusting for sex and race/ethnicity.

Results

In both the unadjusted and adjusted analyses, the risk of developing a food allergy for the group exposed to antibiotics in the first year of life was more than double that of the unexposed group. In the unadjusted Poisson regression model, the relative risk was 2.53 [1.96, 3.26]. In the model adjusted for sex and race/ethnicity, the relative risk was 2.33 [1.19, 4.56]. Neither sex nor race/ethnicity was found to be significantly associated with the likelihood of a food allergy diagnosis.

Conclusion

There is a significant association between antibiotic exposure in the first year of life and food allergy development by age five. While the results of this study support an existing hypothesis that posits an antibiotic-allergy association mediated by reduced microbial exposure, they do not provide direct evidence of mediation. In order to more accurately characterize this association, additional studies will need to directly analyze the quantity and variety of intestinal microbiota in relation to food allergy prevalence.

Background

Over the past several decades, allergy-related disease prevalence has risen dramatically in the industrialized world while remaining relatively stable in underdeveloped nations (1). This phenomenon coincides both spatially and temporally with public health victories over infectious diseases in the 20th and 21st centuries. The times and places in which advancements in refrigeration, pasteurization, vaccination, and antibiotics have taken hold have seen notable reductions in infections. However, when and where infections declined, food, skin, and respiratory allergies flourished. Although the biological mechanism for the phenomenon has not been conclusively determined, epidemiological evidence suggests an inverse relationship between microbial exposure and allergy development risk.

The Hygiene Hypothesis

The hygiene hypothesis, first proposed by David Strachan in 1989, posits that individuals with insufficient microbial exposure in infancy have a greater risk of developing allergic diseases later in life (2). In a study on hay fever, hygiene, and household size, Strachan commented,

> "Over the past century declining family size, improvements in household amenities, and higher standards of personal cleanliness have reduced the opportunity for cross infection in young families. This may have resulted in more widespread clinical expression of atopic disease, emerging earlier in wealthier people, as seems to have occurred for hay fever" (2).

Since then, numerous studies have been conducted with the goal of establishing a relationship between hygiene factors and allergic diseases, such as asthma, eczema, and food allergies. In

the United States, food allergy prevalence among children aged 0-17 years increased from 3.4% in 1997-1999 to 5.1% in 2009-2011 (3). By 2012, the percentage of children with food allergies in the last 12 months had risen to 5.6% (4). Currently, most research identifies birth order, delivery method, number of siblings, childcare attendance, childhood infections, exposure to farming and cowsheds, endotoxin exposure, and antibiotic exposure as hygiene factors associated with allergic disease (1). Other possible risk factors include sex, race/ethnicity, genetics, vitamin D insufficiency, atopic comorbidity, diet, and obesity (5).

Biological Mechanism

One proposed biological mechanism suggests that when the Th-1 arm of the immune system lacks stimulation from microbial exposure, the Th-2 T-cell phenotype becomes overexpressed. This phenotype produces inflammatory cytokines associated with Immunoglobulin E antibody production, resulting in an increased immune response to harmless allergens (1). Antibiotics, which can reduce or delay bacterial colonization of the gastrointestinal tract early in life, could represent a significant source of microbial deprivation and may influence the expression of T cells at a critical point in development.

This Th-1/Th-2 hypothesis has been supported by *in vivo* studies (6), and many observational studies appear to confirm a link between antibiotic exposure and allergic disease in humans (7, 8). Approaching microbial exposure from the opposite angle, several randomized controlled trials have attempted to supplement gut microbiota using prebiotics and probiotics. One meta-analysis found no significant difference in infant asthma in a review of two prebiotic studies, but did find a significant reduction in infant eczema in a review of four prebiotic studies

(9). Although far from conclusive, the current body of evidence points to an association between microbial exposure and increased allergic disease, likely mediated through the manipulation of Th-1 and Th-2 T-cell expression with antibiotics.

Epidemiology

Although the hygiene hypothesis has been well-documented in its application to other allergic diseases, food allergy studies have been less conclusive. This is likely due to the fact that childhood rates of asthma (8.4% in 2015), hay fever (8.4% in 2014), respiratory allergies (10.0% in 2014), and skin allergies (11.6% in 2014) are much higher than that of food allergies in the United States (10, 11). Because food allergies are comparatively rare, studies are limited and results vary.

A systematic review of the association between microbial exposure and food allergies examined 46 studies investigating environmental exposures such as Caesarean delivery, family size, probiotics, day-care attendance, and childhood infections (12). The results were inconclusive; only four out of 13 Caesarean delivery studies, two out of four family size studies, one out of 11 probiotics studies, one day-care study, and one Hepatitis A serology study demonstrated a significant difference in food allergy prevalence between exposure groups.

A 2016 electronic medical record-based case-control study found that children with three or more antibiotic orders had between 65% and 78% greater odds of food allergies compared to children with zero antibiotic orders, and that associations varied by age and antibiotic class (13). This observed association between the antibiotic dose and food allergy risk was corroborated by a 2013 matched case-control study, which examined both maternal and

childhood exposure to antibiotics as risk factors for infant allergy to cow's milk (14). Maternal use of antibiotics during pregnancy was found to be associated with an increased risk of milk allergy for children, with an odds ratio of 1.26 [1.20, 1.33]. The risk of developing a milk allergy was also significantly associated with an increasing number of infant antibiotic prescriptions ($p < 0.001$).

A 2016 survey-based cross-sectional study found a statistically significant unadjusted association between antibiotic exposure in the first year of life and asthma, but not with food allergy. That study acknowledged that "although this [hygiene] hypothesis has been well studied for asthma, it has not yet been extensively studied for food allergy", and suggested that "future studies should evaluate food allergy in more ethnically and socioeconomically diverse groups" (15). The source population for this study was chosen with these suggestions in mind.

Objective

This objective of this study was to use an electronic medical record (EMR)-based retrospective cohort design to explore the hygiene hypothesis as it applies to food allergy development in a racially/ethnically diverse and socioeconomically disadvantaged source population. It was designed to test the hypothesis that there is an association between antibiotic exposure in the first year of life and the subsequent development of food allergies by age five.

Public Health Relevance

Food allergy rates continue to climb in the United States and other developed countries, impacting the quality of life for an ever-increasing number of people. Identifying possible risk factors is an important first step toward establishing disease pathogenesis, and ultimately treatment and prevention. Epidemiological validation for the hygiene hypothesis can be used to justify experimental research to determine the precise biological mechanism behind allergic diseases.

The epidemiologic evidence itself may also be actionable, even in the absence of mechanistic proof. If insufficient microbial exposure is found to be a significantly associated with food allergies, health care providers and the public can take responsible steps to reduce infants' risk. Providers would be able to make more informed choices regarding the costs and benefits of prescribing antibiotics for infants, and parents could supplement the development of their children's microbiomes by incorporating more breastfeeding, prebiotics, and probiotics into their diets.

Source Population

The source population was drawn from eight federally qualified health centers (FQHC) in Chicago, IL: Alivio Medical Center, Erie Family Health Center, Friend Family Health Center, Heartland Health Centers, Heartland Health Outreach, Howard Brown Health Center, Near North Health Service Corporation, and TCA Health. All of these health centers are safety net organizations, which have a mandate to provide access to services regardless of patients' ability to pay, and deliver health care to uninsured, Medicaid, and other vulnerable patients. These

centers served a combined 544,796 patients in 2015, of whom 147,605 were unemployed and 2,698 were either homeless, living on the street/public place, living in an emergency/transitional shelter, or migrants. 252,647 patients identified as Hispanic/Latino (46.4%), 194,852 as non-Hispanic Black/African American (35.8%), 63,116 as non-Hispanic White (11.6%), and 34,181 as non-Hispanic Other/Unknown (6.3%).

Methods

De-identified data was extracted from electronic medical records maintained by the Alliance of Chicago Community Health Services, L3C, and analyzed using a retrospective cohort study design. Medical record data was extracted via SQL by an Alliance of Chicago employee who was not involved in the study. The data included the following variables: date of birth, sex, race, ethnicity, family size, family history of atopic disease, delivery method, BMI dates, BMI percentiles, visit dates, prescription dates, prescription codes, prescription brand names, prescription generic names, prescription route, prescription strength, diagnosis codes, diagnosis code descriptions, diagnosis start dates, and diagnosis stop dates. However, the majority of patients did not have data available for family size, family history of atopic disease, delivery method, and BMI percentile, and they were therefore excluded from the analysis.

Birthdates, visit dates, and prescription dates were shifted by an arbitrary but consistent number of days before the data was made available to the researchers, in order to obscure any potentially identifiable information while preserving the temporal relationship between the variables. Each patient was assigned a unique dummy ID and health center number unlinked to their actual patient ID number or health center. This study met the requirements for exemption

from human subjects review from the Northwestern University Institutional Review Board and the Chicago Department of Public Health Institutional Review Board.

Exposure

Children born between 01/01/2006 and 12/31/2010 with at least two visits at community health centers served by the Alliance of Chicago were included in the study and examined over a five-year period. Participants were excluded if they did not have a recorded medical visit in the first year of life or were missing basic demographic data. Infant antibiotic exposure was defined as, "having an antibiotic prescription in the first year of life." Because data on the filling or taking of medication was not available, antibiotic prescriptions were used as a proxy for antibiotic exposure. Infant antibiotic exposure was identified using Medi-Span Generic Product Identifier (GPI) codes for antibiotic prescriptions in the first year of life, excluding medication with routes unlikely to affect gut microbiota, such as topical creams, lotions, or ointments (Appendix 1).

Outcome

Food allergy development following antibiotic exposure was assessed using International Classification of Diseases, 9^{th} (ICD-9) and 10^{th} (ICD-10) Edition codes associated with both food allergy status and anaphylactic reactions due to food (Appendix 2). These ICD codes covered food allergies due to peanuts, milk products, eggs, seafood, other/unspecified food, and food additives, as well as anaphylactic reactions due to peanuts, shellfish, fish, fruits and vegetables, tree nuts and seeds, milk and dairy products, eggs, other/unspecified food, and

food additives. ICD code selection was based on a previous study conducted at Northwestern University by Dr. Ruchi Gupta, who was consulted for this study (15). Demographic information and potentially relevant covariates were identified using General Electric's Centricity EMR clinical observation terms. Food allergy development outcomes were compared between infant antibiotic exposure groups using chi-square tests, logistic regression models, and Poisson regression models. The adjusted logistic regression and Poisson models included sex and race/ethnicity as demographic covariates.

Statistical Analysis

The unadjusted association between antibiotic prescriptions in the first year of life and subsequent food allergy diagnosis was initially examined with the use of chi-square tests. Both the exposure and outcome were coded as binary variables, and a chi-square test and logistic regression model (Appendix 3) were used to determine the probability of association. A Poisson regression was then performed with the inclusion of a time-at-risk variable, defined by the number of days from date of birth to either food allergy diagnosis or last follow up visit within five years. A Pearson scale was then applied to the Poisson regression model to adjust for overdispersion of the data.

Once the unadjusted exposure-outcome association was characterized through univariate Poisson regression, multivariate Poisson regression was applied to adjust for sex and race/ethnicity. Sex was coded as a binary variable with female as the reference group, and race/ethnicity was coded as a categorical variable with four levels: non-Hispanic White (reference group), non-Hispanic Black/African American, non-Hispanic Other/Unknown, and

Hispanic/Latino. All statistical analyses were conducted using a SAS 9.4 software package (Cary, NC).

Results (Table 1)

The total sample size of patients born between 2006 and 2010 with at least two Alliance of Chicago health center visits (one of which occurred in the first year of life) over five years was 18,088 patients. Sample patients were 49.4% female. Non-Hispanic White patients made up 34.0% of the sample, non-Hispanic Black/African American patients made up 28.0%, non-Hispanic Other/Unknown patients made up 19.8%, and Hispanic/Latino patients made up 19.3%.

There were 2,288 patients with at least one antibiotic prescription of interest in the first year of life (12.7%). The distribution of antibiotic prescriptions by sex matched the expected Chi-square distribution ($p = 0.612$). In contrast, the distribution of antibiotic prescriptions was found to be independent of race/ethnicity ($p < 0.0001$). Non-Hispanic White patients were significantly overrepresented in the exposed group (54.1% exposed vs. 34.0% overall), while non-Hispanic Other/Unknown patients were significantly underrepresented (2.8% exposed vs. 19.8% overall). The prevalence of food allergy diagnoses in patients age five or younger was 1.5% (270 patients).

Results (Table 2)

In the unadjusted Poisson regression model, the relative risk of developing a food allergy by age five was found to be 2.53 [1.96, 3.26] times as great for those who had been

prescribed an antibiotic by age one compared to those who had not. In the Poisson regression model adjusted for sex and race/ethnicity, the relative risk of developing a food allergy by age five was found to be 2.33 [1.19, 4.56] times as great for those who had been prescribed an antibiotic by age one than those who had not. Neither sex ($p = 0.630$) nor race/ethnicity ($p = 0.578$) was found to be significantly associated with the likelihood of a food allergy diagnosis overall. Despite the Type III sum of squares for race/ethnicity not reaching global significance, non-Hispanic Other/Unknown patients did have a significantly reduced risk compared to non-Hispanic White patients. However, because this categorization is so broad, it is difficult to draw any meaningful conclusions from this observation, especially because neither non-Hispanic Black/African-American patients nor Hispanic/Latino patients differed significantly from non-Hispanic White patients in terms of relative risk.

Discussion

The adjusted results indicate that exposure to antibiotics in the first year of life more than doubled the risk of developing a food allergy, controlling for sex and race/ethnicity. This finding is significant in that it corroborates an understudied aspect of the hygiene hypothesis. This hypothesis, while strongly supported in the scientific literature in its application to asthma and skin allergies, has not yet been established with the same weight of evidence with respect to food allergies. The results of this study support the notion that food allergies, skin allergies, respiratory allergies, and asthma share common environmental risk factors and pathologies. This may allow hypotheses and results to be shared between branches of allergic disease investigation, accelerating the pace of research.

Interestingly, the food allergy prevalence in this study was far lower than the rates reported by the CDC or other food allergy studies. While the literature describes food allergy prevalence in the 5-8% range, a mere 1.5% of the subjects in this study had a food allergy diagnosis or recorded anaphylactic reaction to food. A possible explanation for this discrepancy is the nature of the patient population at the community health centers served by the Alliance of Chicago. Because many of these health centers serve economically disadvantaged populations for whom medical coverage may be inconsistent, their patient attrition rates are likely much higher than those of traditional hospitals. A smaller average follow-up window for each patient would be expected to diminish the likelihood of capturing an already rare outcome.

This disadvantage was likely exacerbated by the fact that food allergy documentation is typically reliant on initiation by patients or their parents. If patients new to the Alliance of Chicago had already participated in a food allergy consultation with their previous health provider, parents may not consider it necessary to bring it up during a routine visit. This would further diminish the reported food allergy prevalence at the Alliance of Chicago health centers and other providers experiencing a high rate of patient churn, and could help to explain the low capture rate.

Limitations

A significant limitation of this study was the fact that data on the filling or taking of the prescribed medication was unavailable. Characterization of antibiotic exposure was therefore reliant on antibiotic prescription data as an imperfect proxy. Patients who were prescribed

antibiotics in the first year of life but did not fill or take them could have been a potential source of misclassification. This would have artificially inflated the exposed group and deflated the unexposed group, biasing results toward the null hypothesis of no association between antibiotic exposure and food allergies.

Similarly, patients who were prescribed antibiotics through a provider outside of the Alliance of Chicago electronic medical record system could have also biased results toward the null hypothesis. If antibiotic prescriptions were not captured in the data set, patients who may have been exposed to antibiotics as infants would have been misclassified in the unexposed group, artificially deflating the exposed group and inflating the unexposed group. One possible solution would have been to supplement the prescription data with a survey to determine whether the prescriptions were filled and taken as prescribed, although this would have been extremely resource-intensive and itself vulnerable to recall bias.

Another constraint introduced by high patient attrition rates was the poor capture of covariates. Ideally the analysis would have involved adjusting for known atopic covariates, including BMI percentile, family size, family history of atopic diseases, and birth method. However, there was insufficient data to adjust for these variables while maintaining a reasonable sample size. Even BMI percentile, a standard measurement in any normal pediatric visit, was only present for approximately 50% of the sample. The other covariates were available considerably less frequently.

It is important to note that only association, not causality, should be inferred from these results. Although temporality can be reasonably established from retrospective cohort designs, several other factors limit causal inference. One major factor is the lack of genetic and medical

covariates available in the study, which could plausibly confound or mediate the exposure-outcome relationship. Another is the lack of a demonstrated dose-response relationship in this study, as the number, type, and strength of antibiotic prescriptions was not considered, nor were the number and severity of food allergies developed per patient. This demonstrated association should serve to support further observational and experimental investigation of the hygiene hypothesis.

Strengths

The study benefitted greatly from its large sample size, the racial/ethnic diversity and socioeconomic distribution of its source population, and its use of existing electronic medical record data. A study population of over 18,000 patients made it possible to conduct a sufficiently powered study despite the extreme rarity of the outcome of interest, and the racial/ethnic diversity of the source population allowed for greater generalizability to the population of the United States. In conjunction with other studies with samples drawn from predominantly upper-income populations, this study makes a strong case for antibiotic exposure as a risk factor for food allergies across socioeconomic strata as well.

The use of electronic medical record data limited opportunities for the introduction of sampling bias. Because this study was retrospective and did not rely on voluntary enrollment of participants, it was not vulnerable to the healthy participant bias, which describes the tendency for research volunteers to be healthier, more concerned for their health, and more predisposed to follow medical advice than those who do not participate. If anything, this study may have suffered from an opposite effect because both those in need of an antibiotic prescription and

those with food allergies would be more likely to seek care than their healthy counterparts, possibly increasing their inclusion in the study sample. However, because all infants and young children require vaccinations and checkups over the course of their first few years regardless of health status, it can be reasonably assumed that the medical record data captured a non-biased sample for this age group.

Reliance on medical record data also reduced the study's vulnerability to information bias. Unlike survey-based studies, this study was not affected by recall or interviewer bias. Exposure status was based on prescription records and did not rely on parents' memory of their children's medications before age one, which could have been influenced by their knowledge of their child's outcome status. Exposure status also did not depend on interviews, in which interviewers' knowledge of outcome status could have consciously or subconsciously influenced parents' responses. However, as mentioned previously, classification of exposure status via medical record data had its own limitations, as there was no way to know whether prescriptions were actually filled and taken as prescribed.

Research Implications

An area of focus for additional research should be to establish a more fundamental relationship between microbial exposure and food allergy development. While the results of this study imply that the antibiotic-allergy association is mediated by microbial exposure, they do not provide direct evidence. It is possible that a property of antibiotics other than their depletion of gastrointestinal flora, or a property of the illnesses that prompted the use of antibiotics, is the true exposure of interest. Perhaps by very nature of being sick, infants tend to

be isolated from other people and are less likely to be allowed outdoors, reducing their exposure to environmental microbes. Ideally, future studies will directly analyze the quantity and variety of microbiota in relation to food allergy outcomes in order to more accurately characterize this association.

For studies limited to electronic medical record data, there are still many avenues of inquiry to pursue. Additional research could consider the dose-response relationship between the strength/quantity of antibiotic prescriptions and the timing/severity/number of food allergies developed in order to investigate causality. When available, covariates such as birth order, delivery method, number of siblings, childcare attendance, and childhood infections should be included as proxies for microbial exposure. Studies based in several countries with varying levels of economic development could explore the ecological aspect of the hygiene hypothesis, and longitudinal studies based in rapidly developing countries could explore the temporal relationship between the reduction in infectious diseases and the increase in allergic diseases.

Public Health Implications

The results of this study have significant implications for the use of antibiotics in modern medicine, which impacts intestinal microbiotic composition and can induce antibiotic resistance in dangerous pathogens. Inappropriate prescription of antibiotics is a significant issue, independent its association with allergic disease (16). Further research in this field may encourage more responsible use of antibiotics overall, improving their effectiveness and reducing unwanted side-effects. If physicians become more aware of the potential risks of

indiscriminate antibiotic use, they may be more willing to wait for a definitive diagnosis before prescribing antibiotics.

For cases in which antibiotics are necessary, physicians may consider complementing the medication with prebiotics, probiotics, or even fecal transplants as a means of restoring gut bacteria. While not the only source of microbial exposure, intestinal flora has a uniquely symbiotic relationship with human biology that may amplify its impact. Parents can further aid microbiotic development by breastfeeding and providing food rich in dietary fiber. These measures have potential benefits beyond reducing food allergy risk factors. Microbiota play a key role in digestion: fermenting dietary fiber, synthesizing vitamins, and metabolizing bioactive compounds. They act as an endocrine organ, producing hormone-like short-chain fatty acids, which regulate inflammation and immune response (17). Although the human microbiome is still the subject of intense study, the current body of knowledge suggests that restoring microbiotic diversity in the gastrointestinal tract can provide significant health benefits with little to no downside.

This research could be used to develop public health programs to educate physicians about the risks inherent in infant antibiotic use, as well as ways to mitigate that risk in cases that necessitate the use of antibiotics. It could also inform programs that promote nutrition for infants and support the development of healthy intestinal microbiota. These applications would reduce the risk of developing food allergies through the promotion of evidence-based practices with a range of health benefits.

Conclusion

This study identified infant antibiotic exposure as a significant risk factor for the development of childhood food allergies, which is consistent with the prevailing hypotheses regarding allergic disease. This finding may help to explain the increasing prevalence of food allergies in the developed world and justify further investigation of the hygiene hypothesis. Based on this information, physicians can take steps to limit the overuse of antibiotics, and parents can make more informed dietary choices on behalf of their children.

Table 1: Demographic Characteristics by Exposure to Antibiotics in the First Year of Life

		N = 18088						
		Exposed		Unexposed		p-value*	Overall	
		N	%	N	%		N	%
Sex								
	Female	1118	(48.86%)	7810	(49.43%)	p = 0.6123	8928	(49.36%)
	Male	1170	(51.14%)	7990	(50.57%)		9160	(50.64%)
Race/Ethnicity								
	Non-Hispanic White	1237	(54.06%)	4910	(31.08%)	p < 0.0001	6147	(33.98%)
	Non-Hispanic Black/ African American	542	(23.69%)	4336	(27.44%)		4878	(26.97%)
	Non-Hispanic Other/Unknown	63	(2.75%)	3516	(22.25%)		3579	(19.79%)
	Hispanic/Latino	446	(19.49%)	3038	(19.23%)		3484	(19.26%)

*p-values comparing exposed and unexposed groups were calculated using a chi-square test

Table 2: Poisson Regression Model for the Prevalence of Food Allergy by Age Five

		Unadjusted		Adjusted		
		RR	95% CI	RR	95% CI	p-value*
Antibiotic Prescription in the First Year of Life		2.53	[1.96, 3.26]	2.33	[1.19, 4.56]	p = 0.0191
Sex (reference is female)						
	Male			1.16	[0.63, 2.16]	p = 0.6303
Race/Ethnicity (reference is non-Hispanic White)						
	Non-Hispanic Black/ African American			1.11	[0.53, 2.31]	p = 0.5782
	Non-Hispanic Other/Unknown			0.47	[0.13, 1.75]	
	Hispanic/Latino			0.89	[0.38, 2.10]	

*p-values were calculated from the type 3 sum of squares

Appendix 1: Antibiotic Prescription GPI Codes

GPI	Frequency	Percent
1100020001810	1	0.03
1100030001820	1	0.03
1100040100310	2	0.07
1100040100315	1	0.03
1100040102105	16	0.56
1100040102110	58	2.02
120001010	5	0.17
1200010100105	2	0.07
1200010100110	1	0.03
1200010100303	12	0.42
1200010100315	16	0.56
1200010100510	3	0.1
1200010101910	4	0.14
1200010101913	76	2.64
1200010101915	170	5.91
1200010101924	1092	37.94
1990002101825	2	0.07
1990002200310	1	0.03
1990002200340	1	0.03
1990002200515	1	0.03
1990002200535	2	0.07
1990002201910	1	0.03
1990002201915	9	0.31
1990002201920	45	1.56
1990002201935	195	6.78
1990002201960	119	4.13
210002000	1	0.03
2100020000110	1	0.03
2100020000310	8	0.28
2100020001910	4	0.14
2100020001915	77	2.68
3100030301910	3	0.1
3400010000320	3	0.1
3400010001920	67	2.33
3400010001930	40	1.39
3400010003020	1	0.03
3500010001910	1	0.03
5000020001920	2	0.07
5000020001930	2	0.07
7000070002520	1	0.03

7000070102034	1	0.03
1600003500	1	0.03
1622002010	1	0.03
16220020100105	5	0.17
16220020100110	1	0.03
1622002022	1	0.03
16220020222120	307	10.67
1699000230	1	0.03
16990002300310	2	0.07
16990002301810	17	0.59
5250006000	1	0.03
53000050001810	12	0.42
5510001810	1	0.03
8610102310	5	0.17
86101023102010	201	6.98
86101023104210	6	0.21
86101025004210	10	0.35
86101038102020	1	0.03
86101047002020	18	0.63
8610107000	9	0.31
86101070002005	14	0.49
86101070004205	11	0.38
8610201010	1	0.03
8610990260	7	0.24
8610990310	5	0.17
86109903104220	8	0.28
86309902801820	1	0.03
86309903321810	1	0.03
87100012102020	9	0.31
87100060002010	2	0.07
8799100236	1	0.03
87991002361820	59	2.05
8799100240	1	0.03
87991002401820	1	0.03
8799100310	6	0.21
87991003101807	2	0.07
87991003102010	22	0.76
90051010104005	2	0.07
90051010104105	1	0.03
90051020004010	1	0.03
9010980310	16	0.56
90109803104200	58	2.02
90109903103710	1	0.03

Appendix 2: Food Allergy Diagnosis ICD Codes

Diagnosis	ICD-9	ICD-10
Anaphylactic reaction due to food	995.6	T78.0
Anaphylactic reaction due to unspecified food	995.60	T78.00
Anaphylactic reaction due to peanuts	995.61	T78.01
Anaphylactic reaction due to shellfish	995.62	T78.02
Anaphylactic reaction due to fish	995.65	T78.03
Anaphylactic reaction due to fruits and vegetables	995.63	T78.04
Anaphylactic reaction due to tree nuts and seeds	995.64	T78.05
Anaphylactic reaction due to additives	995.66	T78.06
Anaphylactic reaction due to milk and dairy products	995.67	T78.07
Anaphylactic reaction due to eggs	995.68	T78.08
Anaphylactic reaction due to other food products	995.69	T78.09
Food allergy status	995.7	Z91.01
Allergy to peanuts	v15.01	Z91.010
Allergy to milk products	v15.02	Z91.011
Allergy to eggs	v15.03	Z91.012
Allergy to seafood	v15.04	Z91.013
Allergy to other foods	693.1	Z91.018
Food additives allergy status	v15.05	

Appendix 3: Logistic Regression Model for the Prevalence of Food Allergy by Age Five

		Unadjusted		Adjusted		
		RR	95% CI	RR	95% CI	p-value*
Antibiotic Prescription in the First Year of Life		3.49	[2.70, 4.52]	3.02	[2.32, 3.94]	p < 0.0001
Sex (reference is female)						
	Male			1.16	[0.91, 1.48]	p = 0.2249
Race/Ethnicity (reference is non-Hispanic White)						
	Non-Hispanic Black/ African American			1.01	[0.76, 1.34]	p = 0.0003
	Non-Hispanic Other/Unknown			0.35	[0.21, 0.58]	
	Hispanic/Latino			0.82	[0.59, 1.15]	

*p-values were calculated from the type 3 sum of squares

References

1. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clinical and experimental immunology. 2010;160(1):1-9.
2. Strachan DP. Hay fever, hygiene, and household size. BMJ (Clinical research ed). 1989;299(6710):1259-60.
3. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. NCHS data brief. 2013(121):1-8.
4. Bloom B, Jones LI, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2012. Vital and health statistics Series 10, Data from the National Health Survey. 2013(258):1-81.
5. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. The Journal of allergy and clinical immunology. 2014;133(2):291-307; quiz 8.
6. Hormannsperger G, Clavel T, Haller D. Gut matters: microbe-host interactions in allergic diseases. The Journal of allergy and clinical immunology. 2012;129(6):1452-9.
7. Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM, et al. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. Chest. 2006;129(3):610-8.
8. Alm B, Goksor E, Pettersson R, Mollborg P, Erdes L, Loid P, et al. Antibiotics in the first week of life is a risk factor for allergic rhinitis at school age. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2014;25(5):468-72.

9. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergy. Cochrane Database Syst Rev. 2013(3):CD006474.

10. National Health Interview Survey, 2015: National Center for Health Statistics; [Available from: https://www.cdc.gov/asthma/nhis/2015/table4-1.htm.

11. National Health Interview Survey, 2014: National Center for Health Statistics; [Available from: https://www.cdc.gov/nchs/fastats/allergies.htm.

12. Marrs T, Bruce KD, Logan K, Rivett DW, Perkin MR, Lack G, et al. Is there an association between microbial exposure and food allergy? A systematic review. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2013;24(4):311-20.e8.

13. Hirsch AG, Pollak J, Glass TA, Poulsen MN, Bailey-Davis L, Mowery J, et al. Early-life antibiotic use and subsequent diagnosis of food allergy and allergic diseases. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2017;47(2):236-44.

14. Metsala 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 (Cambridge, Mass). 2013;24(2):303-9.

15. Gupta RS, Walkner MM, Greenhawt M, Lau CH, Caruso D, Wang X, et al. Food Allergy Sensitization and Presentation in Siblings of Food Allergic Children. The journal of allergy and clinical immunology In practice. 2016;4(5):956-62.

16. Livorsi D, Comer A, Matthias MS, Perencevich EN, Bair MJ. Factors Influencing Antibiotic-Prescribing Decisions Among Inpatient Physicians: A Qualitative Investigation. Infection control and hospital epidemiology. 2015;36(9):1065-72.

17. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science (New York, NY). 2013;341(6150):1241214.