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Original Article

Urban/rural residence effect on emergency department visits arising from food-induced anaphylaxis

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ED, Emergency department; SID, State Inpatient Database; SEDD, State Emergency Department Database; HCUP, Healthcare Cost and Utilization Project; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; RUCA, Rural–Urban Commuting Area; NY, New York; FL, Florida

ABSTRACT

Background: Anaphylaxis is a severe and potentially fatal allergic response. Early-life exposure to rural environments may help protect against allergic reaction. This study assesses urban/rural differences by age and race/ethnicity in emergency department (ED) pediatric visit rates for food-induced anaphylaxis. **Methods:** This observational study examined 2009–2014 inpatient and ED data from New York and Florida, using ICD-9-CM diagnostic code (995.6) to identify food-induced anaphylaxis cases <18 y/o. Primary predictor of interest was urban/rural setting, with race/ethnicity and age also evaluated. Associations between ED visit rates and urban/rural setting were evaluated by multivariable hierarchical negative binomial regression with state and year fixed effects.

Results: ED visit rates (per 100,000) for food-induced anaphylaxis were 12.31 and 4.60 in urban and rural settings, respectively. Rates were highest among Blacks (15.26) younger urban children (17.29) and older rural children (6.99). Compared to rural, urban children had significantly higher anaphylaxis ED visit rates (IRR 2.77).

Conclusions: Food-induced anaphylaxis ED visit rates were highest among younger urban children and Black children, with a notable contrast in age distribution between urban and rural rates. Higher urban rates may be attributed to Hygiene Hypothesis, though racial, economic and emergency care access disparities may also influence these outcomes.

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Introduction

Anaphylaxis is a severe and potentially fatal allergic response. A nationwide survey estimated lifetime prevalence of anaphylaxis to be at least 1.6% in the United States.¹ Recent literature reports that healthcare utilization, i.e., emergency department (ED) visits and hospitalization due to anaphylaxis, is increasing.^{2,3} Over 2005–2014, Motosue *et al.*² identified increasing trends for ED visits due to anaphylaxis, particularly among pediatric patients. Dyer *et al.*³ reported increasing trends in ED and hospital visits

due to mostly IgE-mediated, food-induced hypersensitivity among Illinois pediatric patients,³ with highest rates in urban Chicago.³ An urban/rural association has been reported for certain allergic diseases, including food allergy, asthma, eczema, allergic rhinitis, and allergic conjunctivitis.^{4–9} Previous literature theorized that early life exposure to certain microbial agents associated with rural living may protect against allergic reaction,^{10,11} in accord with Hygiene Hypothesis originally reported by Strachan in 1989.¹² Following over 17,000 British children up to 23 y/o, and citing the number of older siblings as a strong predictor for development of hay fever and eczema, Strachan described preventive effects of infection in early childhood transmitted by unhygienic contact with older siblings, or acquired prenatally from a mother infected by contact with her older children.¹² Additional literature has since supported the Hygiene Hypothesis with epidemiological^{4–10,13,14} and molecular-level evidence.¹⁵

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The objective of our study, focused on the pediatric population, was to assess urban/rural differences in ED visit rates where food-induced anaphylaxis was the presenting symptom. Applying the “Hygiene Hypothesis” rationale, we hypothesized that urban residence predicted higher ED visit rates due to food-induced anaphylaxis than rural residence.

Methods

Data collection

This study utilizes New York (NY) and Florida (FL) State Inpatient Databases (SID) and Emergency Department Database (SEDD) from Healthcare Cost and Utilization Project (HCUP) 2009–2014. Both SID and SEDD provide discharge data and encompass all patients, regardless of payer, enabling us to conduct a population-based study. Of the 20 U.S. states with 5 consecutive years of recent SID and SEDD data available from HCUP, NY and FL were chosen based on their large population size, the affordability of the data, and the availability of specific variables needed for analyses.

Pediatric patients (<18 y/o) with a primary diagnosis of food-induced anaphylaxis were identified using International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM codes 995.60–995.69: anaphylactic reaction due to food). ED visits not resulting in hospitalization were identified by SEDD, while hospitalizations through ED visits were identified by SID. Patients visiting one hospital ED, but admitted to another hospital, were included in both SEDD and SID. Therefore, double-counting of patients was avoided by using admission type as a proxy for ED admission.

Using 2010–2014 data from the United States Census Bureau, the pediatric population at each zip code of FL and NY were estimated, stratified by age group, race, and year. ED visit rates for 2009 were based on 2010 population estimates, since stratified population estimates were unavailable. Only patients residing in FL or NY were included in the study.

Dichotomized to *urban* or *rural*, the primary predictor of interest was geographic setting, based on coding assignments from Rural–Urban Commuting Area (RUCA) code,¹⁶ corresponding to each patient's zip code (Supplementary Table 1). Detailed methods to define urban/rural are described elsewhere.¹⁷

Other variables of interest included race, age group, and year. Race was defined as non-Hispanic White, Black, and Other. Age group was broken into four categories: age in years (1) 0–4, (2) 5–9, (3) 10–14, and (4) 15–17 in order to match the categories used in Census Bureau population estimates.¹⁸ We chose to stratify cases by age group because we expected that the association between geographic setting (rural vs urban) and anaphylaxis ED visit rates would be stronger for the younger age group. This prediction was based on the assumption that as a pediatric cohort ages, an increasing number would be expected to relocate from rural to urban areas, or vice versa, creating bias towards the null.

Statistical analysis

Demographic data was tabulated to compare urban and rural settings with variables of interest, including age, race, years, sex, state, emergency department disposition, and insurance status.

ED visit rates for anaphylaxis were calculated for each zip code separately by age, race, and year, using number of emergency visits and population estimates obtained from Census. Number of cases in each zip code, stratified by age, race, and year, were divided by total population estimates for each group and multiplied by 100,000 to represent cases per 100,000 children. Rates were then compared between urban and rural settings across race and age groups.

Year trends in ED visit rates for anaphylaxis were evaluated by state and urban/rural settings. The outcome, total cases, was offset by the log-transformed population size for each unit of analysis. Negative binomial was used in favor of Poisson model due to over-dispersion in data. An interaction term was included to assess differences in urban/rural by state.

Lastly, hierarchical negative binomial regression analyses were used to calculate whether urban/rural settings were associated with a greater rate of ED visits for anaphylaxis, while controlling for state of residence and year as fixed effects, and zip code as a random effect. The primary unit of analysis for these regression models is defined as zip code stratified by age, race, and year. As with year trend, assessments of outcome and total cases were offset by log-transformed population size for each unit of analysis. All analyses were performed with Stata 14.2.

Results

We identified 5850 pediatric patients (<18 y/o) with a primary diagnosis of food-induced anaphylactic reaction. Among these patients, three provided only a three-digit zip code, and eleven did not have a matching zip code, so zip codes were re-assigned using age, race, and first three zip code digits to determine most likely residence.

Results from descriptive characteristics of food-induced anaphylaxis cases (Table 1) show 177 cases with rural residence and 5673 cases with urban residence. The total number of children residing in rural areas is 3,849,377 and the total number residing in urban areas is 46,067,947, yielding ED visit rates of 4.60 and 12.31 per 100,000 children, respectively. In urban areas, younger children visit ED due to food-induced anaphylaxis at over double the rate of

Table 1
Descriptive statistics of cases of pediatric anaphylaxis in urban and rural areas.

Variables	Total (n = 5850) n (%)	Rural (n = 177) n (%)	Urban (n = 5673) n (%)	p-value
Inpatient	1122 (19.18%)	12 (6.78)	1110 (19.57)	<0.01
Age Group				
0–4	2194 (37.50%)	41 (23.16)	2153 (37.95%)	<0.01
5–9	1340 (22.91%)	42 (23.73)	1298 (22.88%)	0.79
10–14	1255 (21.45%)	44 (24.86)	1211 (21.35%)	0.26
15–17	1061 (18.14%)	50 (28.25)	1011 (17.82%)	<0.01
Race Group				
White	2408 (41.35%)	126 (71.59%)	2282 (40.41%)	<0.01
Black	1485 (25.50%)	21 (11.93%)	1464 (25.93%)	<0.01
Other	1930 (33.14%)	29 (16.48%)	1901 (33.66%)	<0.01
Sex				
Female	2388 (40.82%)	74 (41.81%)	2314 (40.79%)	0.79
Male	3462 (59.18%)	103 (58.19%)	3359 (59.21%)	0.79
Insurance				
Public	2011 (34.38%)	59 (33.33%)	1952 (34.41%)	0.77
Private	3253 (55.61%)	91 (51.41%)	3162 (55.74%)	0.25
Other	586 (10.02)	27 (15.25%)	559 (9.85%)	0.02
ED Disposition				
Routine or discharged alive	4598 (78.60%)	159 (89.83%)	4439 (78.25%)	<0.01
Hospital Admit	1239 (21.18%)	18 (10.17%)	1221 (21.52%)	<0.01
Other	13 (0.22%)	0 (0.00%)	13 (0.23%)	0.99
State				
NY	4140 (70.77%)	141 (79.66%)	3999 (70.49%)	<0.01
FL	1710 (29.23%)	36 (20.34%)	1674 (29.51%)	<0.01
Year				
2009	641 (10.96%)	11 (6.21%)	630 (11.11%)	0.04
2010	735 (12.56%)	9 (5.08%)	726 (12.80%)	<0.01
2011	860 (14.70%)	27 (15.25%)	833 (14.68%)	0.83
2012	1061 (18.14%)	25 (14.12%)	1036 (18.26%)	0.16
2013	1181 (20.19%)	52 (29.38%)	1129 (19.90%)	<0.01
2014	1372 (23.45%)	53 (29.94%)	1319 (23.25%)	0.04

older children (38.0% of 0–4 y/o versus 17.8% of 15–17 y/o). This trend does not transcend to rural areas, where cases are more equally dispersed from infancy to early adolescence, abruptly increasing around mid-adolescence.

When stratified by age and race (Table 2), results show Blacks to have higher incidence of anaphylaxis-related ED visits across all age groups, largely driven by those residing in urban regions. Furthermore, for each race, incidence of anaphylaxis increases in older age groups in rural areas, whereas incidence rates are highest among younger children in urban regions.

Time trend by state and urban/rural region (Table 3) demonstrated higher ED visit rates in NY than FL, and urban than rural regions, with no statistically significant differences between states in total and urban year trends ($p = .53$ and 0.61). However, the increasing trend in ED visit rates in rural areas of NY was significantly more pronounced than in FL ($p = .02$).

Overall, results from hierarchical negative binomial regression (Table 4) suggest an association between urban settings and higher incidence rate of food-induced anaphylaxis compared to rural

settings (Incidence Rate Ratio: 2.77; 95% Confidence Interval: 2.32, 3.31), which remains significant across all age groups and races. Among Black and *Other* race categories, this significance appears largely driven by children ages 0–4. Race and age stratified results shows non-Hispanic Whites of all ages to have significantly higher rates of food-induced anaphylaxis in urban areas, yet this relationship is less apparent among older children of Black and *Other* races. Still, the general trend and direction of incidence rate ratios appear mostly consistent, however, low numbers of rural cases may have significantly underpowered this study.

Discussion

This population-based study established that 2009–2014 ED visit rates due to food-induced anaphylaxis were 11.72 per 100,000 children, on average, among the pediatric population in FL and NY, with a higher rate in NY (16.00) than FL (7.11). Rates increased over time in both states, with rates consistently higher in urban than rural areas.

Our ED visit rates are comparable to previous studies. Dyer *et al.*³ reported a food-induced anaphylaxis ED visit rate of 10.9 per 100,000 children in Illinois between 2008 and 2012, with an increasing trend. Our 2009–2014 study period included later years with higher rates, resulting in slightly higher estimates overall. Harduar-Morano *et al.*¹⁹ reported 2005–2006 food-induced anaphylaxis ED visit rates of 8.2 per 100,000 children under five years old in FL, closely reflecting our under-five estimates for FL.

Regional differences between NY and FL also mirrored previous studies reporting greater prevalence of anaphylaxis in higher versus lower latitudes.²⁰ Previous literature cited latitudinal differences in exposure to sunlight as influencing the role of vitamin D in regulation of immune function.²¹

Our findings uncovered statistically significant urban/rural differences in pediatric ED visit rates due to food-induced anaphylaxis. Stratified analyses by race demonstrated that this difference remains across racial groups. The pervasive influence of urban/rural settings aligns with Aligne *et al.*⁴ who demonstrated that all urban children had a higher risk of asthma, regardless of race or family income. If anaphylaxis was tracked from all sources, general consensus would likely cite air quality as a large factor in urban vs. rural anaphylaxis. For that reason, our study focused only on rates of food-induced anaphylaxis. The effects of urban air pollution cannot be totally dismissed, however, since combined exposure to air pollutants and allergens may have a synergistic effect on asthma and allergy symptoms.²²

Stratified analyses by age and race consistently presented an association between urban residence and higher anaphylaxis rates among the 0–4 y/o group. Other age groups failed to exhibit statistically significant differences between urban and rural areas across all races, though non-significant results could be due to the smaller sample size in older age groups.

The U.S. Census Bureau estimates that the average 18-year-old in the U.S. will have moved twice.²³ As a pediatric cohort ages, an increasing number would be expected to relocate from rural to urban areas, or vice versa. This transposition means some children who spent early childhood in urban areas moved, and were included in rural groups without exposure to a rural environment in early childhood. Conversely, others who received the protective effects of rural living in early childhood moved and were included in urban groups. Given that the Hygiene Hypothesis predicts a preventive effect of environmental factors on allergic response in “early childhood,”¹² moving between urban and rural areas would create bias toward the null. Our study demonstrated that the magnitude of association attenuated as children aged, i.e., Incidence Rate Ratio comparing urban to rural for 0–4 year olds was

Table 2
Incidence rate of anaphylaxis per 100,000 children stratified by geographic location.

	Total (n = 49,917,324)	Rural (n = 3,849,377)	Urban (n = 46,067,947)
Total by Age			
Total	11.67	4.60	12.31
0–4	16.28	3.95	17.29
5–9	9.92	4.06	10.41
10–14	8.88	4.06	9.29
15–17	11.74	6.99	12.15
White			
Total	10.00	4.23	10.82
0–4	15.09	3.82	16.68
5–9	8.63	3.25	9.39
10–14	7.01	4.11	7.42
15–17	9.68	6.31	10.17
Black			
Total	15.26	7.90	15.47
0–4	19.88	4.12	20.34
5–9	13.88	8.63	14.02
10–14	11.96	6.78	12.11
15–17	15.60	13.90	15.65
Other			
Total	9.21	3.49	9.44
0–4	15.85	4.40	16.31
5–9	9.49	6.02	9.62
10–14	9.93	2.50	10.21
15–17	12.57	7.42	12.76

Table 3
Time trend by state and urban/rural region.

	Total	2009	2010	2011	2012	2013	2014	p value
Total [†]								
Total	11.72	7.70	8.83	10.30	12.75	14.23	16.54	<0.01
Urban	12.31	8.20	9.45	10.82	13.50	14.73	17.20	0.02
Rural	4.60	1.70	1.39	4.14	3.88	8.20	8.48	<0.01
Total [†]								
NY	16.00	10.82	11.91	14.45	18.39	19.06	21.46	<0.01
FL	7.11	4.32	5.50	5.79	6.67	9.06	11.32	<0.01
Interaction term								0.53
Urban [†]								
NY	17.11	11.79	12.99	15.43	19.86	20.04	22.66	0.04
FL	7.37	4.50	5.80	6.03	6.93	9.30	11.65	<0.01
Interaction term								0.61
Rural [†]								
NY	5.62	1.90	1.90	5.39	4.77	9.92	10.08	<0.01
FL	2.69	1.34	0.45	1.77	2.23	4.98	5.50	<0.01
Interaction term								0.02

[†] Values expressed as incidence rates per 100,000 population.

Table 4

Results from regression models to evaluate the association between emergency department visit rates due to food-related anaphylaxis and urban/rural setting.

	Total				White				Black				Other			
	IRR [†]	SE [‡]	95%CI [§]	P	IRR [†]	SE [‡]	95%CI [§]	P	IRR [†]	SE [‡]	95%CI [§]	P	IRR [†]	SE [‡]	95%CI [§]	P
Total																
Urban	2.77	0.25	[2.32, 3.31]	<0.01	2.79	0.3	[2.25, 3.43]	<0.01	1.86	0.46	[1.15, 3.02]	0.01	2.56	0.52	[1.72, 3.81]	<0.01
Rural	Reference				Reference				Reference				Reference			
0–4 yo																
Urban	4.7	0.79	[3.38, 6.53]	<0.01	5.08	1.03	[3.41, 7.56]	<0.01	6.01	4.3	[1.48, 24.36]	0.01	4.18	1.62	[1.96, 8.93]	<0.01
Rural	Reference				Reference				Reference				Reference			
5–9 yo																
Urban	2.82	0.47	[2.04, 3.91]	<0.01	3.37	0.72	[2.22, 5.12]	<0.01	1.99	1.01	[0.74, 5.40]	0.17	1.62	0.54	[0.84, 3.10]	0.15
Rural	Reference				Reference				Reference				Reference			
10–14 yo																
Urban	2.44	0.39	[1.78, 3.34]	<0.01	2.06	0.39	[1.42, 3.00]	<0.01	1.51	0.68	[0.62, 3.67]	0.37	3.95	2.00	[1.46, 10.65]	<0.01
Rural	Reference				Reference				Reference				Reference			
15–17 yo																
Urban	1.86	0.29	[1.38, 2.52]	<0.01	1.81	0.34	[1.25, 2.63]	<0.01	1.04	0.44	[0.46, 2.39]	0.92	1.64	0.64	[0.77, 3.51]	0.20
Rural	Reference				Reference				Reference				Reference			

[†] Incidence rate ratio.[‡] Standard error.[§] Confidence interval.

4.70, whereas the ratio for 15–17 year olds was 1.86. Further study using detailed histories of patients with anaphylaxis is needed to explore the association between a history of living in rural areas and ED visits due to anaphylaxis.

To our knowledge, this is the first study to report differences in U.S. emergency department visit rates, in an age- and race-stratified pediatric population, due to food-induced anaphylaxis, based on childhood residence in urban or rural settings. A Polish study that included adult populations supports our results, indicating a large difference in the prevalence of anaphylaxis between rural and urban areas (13.1 vs. 0.8 per 100,000).²⁴ Prior studies have shown allergic diseases to be less prevalent in immigrants than non-immigrants,^{25,26} with immigrants usually from low-to-middle-income (developing, and non-affluent) countries, migrating to high-income (industrialized and affluent) countries. It is noteworthy to point out that these results could be due to a “healthy migrant effect”, that is, those with relatively lower morbidity are more likely to migrate.^{13,26} Sakai Bizmark *et al.*²⁷ studied Japanese immigrants in Thailand, and demonstrated that children living in developing countries before five years of age had a lower rate of asthma later in life, even when controlling for healthy migrant effect. This lower rate of allergic disease among immigrants also supports the Hygiene Hypothesis.

The association between living in farming areas during childhood and lower prevalence of allergic disease has been frequently reported.^{7,9–11,15} Braun-Fahrlander *et al.*¹⁰ also demonstrated an association between higher endotoxin levels and significantly decreased risk of allergic disease in childhood, independent of experiences living in farm settings. Kramer *et al.*¹⁴ reported that among children from small families, prevalence of atopy was higher among children who started attending day nursery at an older age than those starting at a younger age. Kramer *et al.*¹⁴ argued that this phenomenon was due to early exposure to cross infections at the nursery.

Our study showed that, similar to other allergic diseases, the Hygiene Hypothesis could be applied to anaphylaxis, a potentially fatal condition. This study could not specify which environmental exposures in rural or urban settings were associated with the development of anaphylaxis. For example, early-life exposure to nature and certain microbial agents associated with rural living may better protect individuals prone to developing atopic disease than exposure to ambient pollutants or increased indoor time in urban areas.^{7,9–11} Further research into the differences between urban and rural settings may lead to more strategies in prevention and treatment of anaphylaxis.

Our study showed higher ED visit rates in the Black population (15.26) than non-Hispanic White (10.00) and Other Races (9.21). This disparity was still observed when stratified by urban/rural settings, and mirrors findings from previous studies.^{15,28} Since recommended management, such as food restriction, is rarely expected with undiagnosed food allergy, lower diagnostic rates in the Black population may lead to higher ED visit rates. Some studies argued that food-related allergy differences across race may be due to differences in food introduction practices, as well as familial and cultural differences in diets.²⁸ With further research in racial disparity, more strategies for management of allergic diseases can be developed.

Several limitations of this study should be acknowledged. First, the study employed an ecological design using zip-code level ED visit rates as the outcome. This approach suffers from ecological fallacy. Second, ED visit rates reported in this study could be underestimated for three reasons: 1) we were unable to verify cases by medical record review, 2) underuse of anaphylaxis codes has been reported, and 3) we were unable to include patients visiting hospitals outside NY or FL. Third, socioeconomic disparities in reporting and treating food allergies have been reported. Third, socioeconomic disparities in reporting and treating food allergies have been reported.²⁹ However, we were not able to adjust the models by socioeconomic factors. Fourth, due to lack of information on admission source, we were unable to identify patients admitted through the emergency department, and therefore used admission type as a proxy. Fifth, zip code level population was obtained from Factfinder,¹⁸ which is based on Zip Code Tabulation Areas (ZCTAs), whereas RUCA used in this study is assigned based on zip code. Although ZCTAs were assigned based on zip code, there could be some discrepancy between zipcode and ZCTAs.¹⁶ Sixth, although the study focused on food-induced allergies, some patients will cross the allergic threshold only after cumulative exposure to offending foods, often combined with other irritants, such as seasonal airborne allergens. Therefore, higher incidence rate in urban areas could be due to urban air quality.³⁰ Finally, this study utilized convenience sampling, i.e., only data from NY and FL were included, therefore, generalizability of the results is unclear.

We demonstrated that ED visit rates due to food-induced anaphylaxis are higher in urban settings, particularly among children 0–4. Rural settings have much lower rates that only begin to rise in mid-adolescence. Higher ED visit rates in the Black population than non-Hispanic White and Other Races were also observed. Further research in the influence of urban vs. rural settings, along with a more comprehensive examination of the effect

of racial disparities on atopic disease management, could lead to more targeted strategies in management of food-induced anaphylaxis. However, cumulative synergistic effects of air quality on management of atopic disease, and disparities in race, economic status, or access to emergency medical care, may also hinder medical response to potentially fatal anaphylaxis.

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The Institutional Review Board at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center confirmed that this study does not meet the Department of Health and Human Services (DHHS) definition of human subjects research, as defined in 45 CFR 46.102(f), and approved the study under the “exempt” category.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2018.12.007>.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

RSB conducted literature searches, conceptualized and designed the study, developed the models, performed data analyses, contributed to data interpretation, drafted the initial manuscript and revised the manuscript. SMIF and EJW obtained and cleaned the data, performed data analyses, created the tables, contributed to data interpretation, and reviewed and revised the manuscript. KO conducted literature searches, contributed to the discussion section, and reviewed and revised the manuscript. LAM and EHM conducted literature searches, contributed to the discussion section, and reviewed and revised the manuscript. YO supervised the study overall, confirmed the interpretation of the results, critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Supplementary Table 1. Urban/rural Assignments from Rural-Urban Commuting Area (RUCA) code

Urban										
	1.0	1.1	2.0	2.1	3.0	4.1	5.1	7.1	8.1	10.1
Rural										
	4.0	4.1	5.0	5.2	6.0	6.1	7.0	7.2	7.3	7.4
	8.0	8.2	8.3	8.4	9.0	9.1	9.2			
	10.0	10.2	10.3	10.4	10.5	10.6				