
North-south differences in US emergency department visits for acute allergic reactions

Susan A. Rudders, MD*†; Janice A. Espinola, MPH†; and Carlos A. Camargo Jr, MD, DrPH†‡§

Background: In a previous study, latitude was positively associated with EpiPen prescription rates.

Objective: To determine whether a similar geographic difference exists for emergency department (ED) visits for acute allergic reactions (including anaphylaxis).

Methods: We combined National Hospital Ambulatory Medical Care Survey data for ED visits to noninstitutional hospitals from 1993 to 2005. Acute allergic reactions were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 995.0, 995.60-995.69, 995.1, 995.2, 995.3, 989.5, and 693.1, and visit rates were compared across standardized geographic divisions.

Results: Between 1993 and 2005, there were 17.3 million ED visits for acute allergic reactions, representing 1.3% (95% confidence interval [CI], 1.2%-1.3%) of all ED visits. Per 1000 population, the Northeast had 5.5 visits (95% CI, 4.7-6.2 visits) and the South had 4.9 visits (95% CI, 4.3-5.6 visits). In a multivariable model, the Northeast had a higher odds ratio (OR) than the South (1.13; 95% CI, 1.01-1.27; $P = .04$). The association was stronger when restricting the analysis to visits for food-related allergic reactions (OR, 1.33; 95% CI, 1.14-1.56; $P < .001$).

Conclusions: The ED visit rates for acute allergic reactions are higher in northeastern vs southern regions. These observational data are consistent with the hypothesis that vitamin D may play an etiologic role in anaphylaxis, especially food-induced anaphylaxis.

Ann Allergy Asthma Immunol. 2010;104:413-416.

INTRODUCTION

Anaphylaxis lies at the far end of a continuum of acute allergic reactions and is defined as a serious allergic reaction that is rapid in onset and that may cause death.¹ Recent studies²⁻⁴ from the United States, Canada, and the United Kingdom estimate that the prevalence of anaphylaxis ranges from 0.3% to 0.95%. Despite the emergent nature of acute allergic reactions, little is known about their geographic distribution. Historically, epidemiologic research on anaphylaxis has been complicated by several factors. First, the definition of anaphylaxis has been highly variable, and accepted diagnostic criteria were lacking until recently.¹ Furthermore, the presentations of anaphylaxis are varied and can mimic those of other disorders. In addition, when symptoms do not seem life-threatening, physicians are less likely to categorize even multisystem complaints as anaphylaxis.⁵

Affiliations: * Division of Allergy and Immunology, Children's Hospital Boston, Boston, Massachusetts; † Department of Emergency Medicine, Massachusetts General Hospital, Boston, Massachusetts; ‡ Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; § Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts.

Disclosures: Dr. Rudders is supported by NIH training grant NRSA T32-AI-007512 (Bethesda, USA). Dr Camargo is supported, in part, by the Massachusetts General Hospital Center for D-receptor Activation Research (Boston, USA).

Received for publication January 6, 2010; Received in revised form January 25, 2010; Accepted for publication January 29, 2010.

© 2010 American College of Allergy, Asthma & Immunology.

Published by Elsevier Inc. All rights reserved.

doi:10.1016/j.anai.2010.01.022

In 2007, Camargo et al⁶ described a north-south gradient of EpiPen prescriptions in the United States, with significantly higher dispensing rates in northeastern vs southwestern states. In this ecologic study, EpiPen prescriptions served as a surrogate marker for rates of anaphylaxis. The authors hypothesized that the north-south gradient could suggest a potential role for vitamin D in the etiology of anaphylaxis. Potential shortcomings of the study were acknowledged, including the possibility that the observed difference between geographic areas might represent practice discrepancies rather than a true divergence in disease risk. In support of this latitudinal trend, Sheehan et al⁷ recently reported a similar gradient when evaluating patient encounters for anaphylaxis at 24 US children's hospitals, with food-related anaphylaxis encounters occurring twice as often in the North as compared to the South. Furthermore, recent studies by Mullins et al have confirmed an ecologic association in Australia between latitude and food allergy-related prescriptions^{8,9} and anaphylaxis hospital admissions.⁸

Because studies have shown that most anaphylaxis cases are treated in the emergency department (ED),² we sought to determine whether a similar north-south gradient was observed when directly evaluating rates of ED visits for acute allergic reactions (including anaphylaxis). We hypothesized that the Northeast would have a higher frequency of ED visits for acute allergic reactions compared with the South. Furthermore, we hypothesized that this difference would be more pronounced when restricting the comparison to food-related allergic reactions, which, unlike stinging insect hypersensi-

tivity reactions, would be less affected by other climate-related factors.

METHODS

The National Hospital Ambulatory Medical Care Survey (NHAMCS) is a 4-stage probability sample of visits to non-institutional general and short-stay hospitals, excluding federal, military, and Veterans Affairs hospitals, in the United States.¹⁰ NHAMCS is conducted annually and covers geographic primary sampling units located in the 50 states and the District of Columbia. At each sampled hospital, trained hospital staff collect data during a randomly assigned 4-week data period, and a US Census Bureau field supervisor reviews the data collection. A variety of quality control measures are performed to assess inconsistencies and to clarify ambiguous responses during this process. The nonresponse rate for most items was less than 5%, and error rates were less than 2% for items that required medical coding. Completed data collection forms are sent for coding using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*. National estimates are then obtained through use of a multistage estimation procedure and patient visit weights. A more detailed description of NHAMCS data collection and estimation procedures is available for review in the technical notes section of each year's NHAMCS Emergency Department Survey.¹¹ Institutional review board approval and informed consent were not applicable.

The NHAMCS data from 1993 to 2005 were combined for the current analysis. We identified cases of acute allergic reactions by the following *ICD-9-CM* codes in any of the 3 diagnosis fields: 995.0 (other anaphylactic shock), 995.6 (anaphylactic shock due to adverse food reaction), 995.1 (angioneurotic edema), 995.2 (unspecified adverse effect of drug, medicinal, and biological substance), 989.5 (toxic effect due to venom), 693.1 (dermatitis due to food), and 995.3 (allergy, unspecified). US visit rates were computed using midyear age, sex, race, ethnicity, metropolitan status, and region-specific population estimates from the US Census Bureau. All rates are reported per 1000 individuals per year for the US civilian population.¹²

We analyzed ED visit rates by age, sex, race, ethnicity, metropolitan status, and region (Northeast, Midwest, South, and West). Metropolitan statistical areas and US region categories represent standardized geographic divisions defined by the US Census Bureau.¹² We focused the analysis on northeastern vs southern states because these regions most clearly represent distinct zones with which to test a north-south latitudinal gradient. Analyses included multivariable logistic regression modeling for acute allergic reactions, with region as the main risk factor of interest. We performed sensitivity analyses to examine the effect of (1) using a more restricted set of *ICD-9-CM* codes previously determined to be relevant to the study of anaphylaxis (ie, 995.0, 995.6, 995.1, 995.2, and 995.3)¹³ and (2) using *ICD-9-CM* codes specific to food-related acute allergic reactions (ie, 995.0, 995.6, 693.1,

and 995.3).¹⁴ A 2-sided *P* < .05 was considered statistically significant.

RESULTS

From 1993 to 2005, there were 17.3 million ED visits in the United States for acute allergic reactions, representing 1.3% (95% confidence interval [CI], 1.2%-1.3%) of all ED visits. In the northeastern region, there were 5.5 visits (95% CI, 4.7-6.2 visits) for acute allergic reactions per 1000 individuals in the US population. In contrast, in the southern region, there were 4.9 visits (95% CI, 4.3-5.6 visits) per 1000 US population.

In a multivariable model, ED visits were analyzed by age, sex, race, ethnicity, metropolitan status, and region (Table 1). Overall, ED visits for acute allergic reactions had a nonlinear association with age, with visits being more common in adults than in children younger than 10 years. This relationship was not consistent for the oldest individuals, who were the least likely to have an ED visit for an acute allergic reaction. ED visits for acute allergic reactions were also more likely in females and in white patients. There were no significant differences between metropolitan and nonmetropolitan areas. Comparing ED visit rates by region, the Northeast

Table 1. Multivariable Model of Emergency Department Visits for Acute Allergic Reactions

	Odds ratio (95% CI)	P value
Age group (years)		
<10	1 [Reference]	
10-19	0.98 (0.85-1.14)	.81
20-29	1.07 (0.94-1.22)	.32
30-39	1.16 (1.01-1.34)	.04
40-49	1.15 (1.00-1.33)	.05
50-59	1.20 (1.02-1.41)	.03
60-69	1.10 (0.93-1.32)	.26
70-79	0.84 (0.68-1.02)	.08
≥80	0.44 (0.34-0.58)	<.001
Sex		
Female	1 [Reference]	
Male	0.72 (0.67-0.78)	<.001
Race		
White	1 [Reference]	
Black	0.82 (0.73-0.92)	.001
Other	1.09 (0.86-1.39)	.47
Ethnicity		
Non-Hispanic	1 [Reference]	
Hispanic	0.92 (0.81-1.06)	.24
Missing	0.98 (0.87-1.09)	.68
Metropolitan area		
Yes	1 [Reference]	
No	1.07 (0.94-1.21)	.31
US region		
South	1 [Reference]	
Northeast	1.13 (1.01-1.27)	.04
Midwest	0.92 (0.81-1.03)	.16
West	0.99 (0.88-1.11)	.89

Abbreviation: CI, confidence interval.

had a significantly higher odds ratio (OR) than the South (OR, 1.13; 95% CI, 1.01-1.27; $P = .04$). In contrast, the Midwest (OR, 0.92; $P = .16$) and West (OR, 0.99; $P = .89$) were not significantly different from the South. The Northeast-South difference remained consistently elevated when we used a narrower scope of diagnosis codes (OR, 1.18; 95% CI, 1.03-1.35; $P = .01$).

Finally, we compared ED visit rates using *ICD-9-CM* codes specific for food-related allergic reactions (Table 2). ED visits for food-related acute allergic reactions were more likely in the younger age groups and in females. No significant differences were observed based on race, ethnicity, or metropolitan status in this population. Comparing food-related ED visits by region, we found a more robust difference between the Northeast and the South (OR, 1.33; 95% CI, 1.14-1.56; $P < .001$).

DISCUSSION

These nationally representative data reveal geographic variation in the rate of acute allergic reactions presenting to EDs in the United States, with significantly higher rates in the Northeast than in the South. When examining ED visits for allergic reactions due to food allergy, this difference was

even more clearly delineated. It is possible that these findings could reflect regional practice differences or, when specifically considering food-related allergic reactions, previously undescribed regional differences in food allergy risk factors. Given the paucity of known risk factors for food allergy,¹⁵ we suggest that these observational data could also add to an emerging body of evidence that vitamin D may be involved in the pathogenesis of food allergy.⁶ Consistent with this hypothesis, statistically significant differences in ED visit rates were not observed when comparing other US regions that do not represent areas of such divergent latitude.

Vitamin D is a vital nutrient that can be synthesized in the skin under the influence of UV-B or obtained from dietary intake. In humans, most vitamin D is obtained from exposure to the sun. Accordingly, studies have shown that blood levels are correlated with latitude, and in regions above 35°N, vitamin D-effective UV-B radiation is not produced for significant portions of the year.^{16,17} The importance of vitamin D in bone metabolism has long been established. However, the health impact of vitamin D deficiency is currently broadening, and many studies are exploring its effects on myriad disorders, including autoimmune diseases, cardiovascular disease, and cancer.¹⁶ Recently, it has been postulated that vitamin D may also play a role in allergic/immunologic disorders. Specifically, recent studies have shown correlations between low levels of vitamin D and increased rates of childhood wheezing,¹⁸ respiratory infections,^{19,20} and winter-related atopic dermatitis.²¹ In support of these clinical observations, the vitamin D receptor, which is present on a variety of immune cells, has been described to serve a variety of immunomodulatory functions. Specifically, vitamin D receptor agonists have recently been described to promote tolerogenic dendritic cells and to facilitate the induction of regulatory rather than effector T cells.²² These immunoregulatory functions could have direct implications for a protective role for vitamin D in the development of allergic disorders, including food allergy, through the promotion of immunologic tolerance.

Although an observed geographic trend in ED visit rates is insufficient to elucidate the precise role of vitamin D in allergic disease, these data, in conjunction with other epidemiologic studies, provide a foundation for further study. Possible areas of future research include replicating these findings in other regions of the world to confirm a latitudinal association irrespective of other regional, cultural, and practice-based differences. To evaluate the specific role of vitamin D, one would also need to perform prospective studies of vitamin D status and risk of allergic reactions (including anaphylaxis). In addition, birth cohort studies and randomized controlled trials could examine the clinical implications of vitamin D supplementation during pregnancy and early childhood on the development of allergic disorders. Vitamin D-related asthma prevention trials already are under way (eg, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00856947) NCT00856947).

Potential shortcomings of this and other studies that rely on diagnosis codes include the possibility of inaccurate coding.

Table 2. Multivariable Model of Emergency Department Visits for Food-Related Acute Allergic Reactions

	Odds ratio (95% CI)	P value
Age group (years)		
<10	1 [Reference]	
10-19	0.90 (0.74-1.10)	.31
20-29	0.91 (0.76-1.08)	.27
30-39	1.01 (0.83-1.22)	.94
40-49	0.96 (0.79-1.16)	.65
50-59	0.97 (0.78-1.19)	.75
60-69	0.70 (0.52-0.93)	.02
70-79	0.49 (0.35-0.68)	<.001
≥80	0.24 (0.14-0.41)	<.001
Sex		
Female	1 [Reference]	
Male	0.65 (0.59-0.72)	<.001
Race		
White	1 [Reference]	
Black	0.96 (0.82-1.14)	.67
Other	1.28 (0.95-1.72)	.11
Ethnicity		
Non-Hispanic	1 [Reference]	
Hispanic	1.11 (0.93-1.31)	.25
Missing	0.95 (0.81-1.11)	.51
Metropolitan area		
Yes	1 [Reference]	
No	0.95 (0.79-1.14)	.58
US region		
South	1 [Reference]	
Northeast	1.33 (1.14-1.56)	<.001
Midwest	0.84 (0.70-1.01)	.07
West	1.06 (0.89-1.25)	0.53

Abbreviation: CI, confidence interval.

Anaphylaxis codes are widely underused, with physicians often assigning a diagnosis of “acute allergic reaction” for multisystem allergic complaints.⁵ Accordingly, we investigated a broad range of codes for acute allergic reactions to include more patients with anaphylaxis. The observed relationship was consistent regardless of the combination of codes investigated, including using a narrower scope of anaphylaxis diagnosis codes. Furthermore, the difference became more striking when exclusively examining visits for food-related allergic reactions. These findings support a true geographic trend in disease occurrence rather than regional differences in coding practices. Moreover, they suggest that the relation of vitamin D with anaphylaxis may be mediated through food allergy per se.

In summary, these nationally representative data support a north-south gradient in ED visits for acute allergic reactions and lend support to the novel hypothesis that vitamin D may play an etiologic role in anaphylaxis, especially food-induced anaphylaxis. Further study is warranted to evaluate the potential role of vitamin D in the development of these allergic conditions.

REFERENCES

1. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397.
2. Bohlke K, Davis RL, DeStafano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol*. 2004;113:536–542.
3. Simons FE, Peterson S, Black CD. Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. *J Allergy Clin Immunol*. 2002;110:647–651.
4. Peng MM, Jick H. A population-based study of the incidence, cause, and severity of anaphylaxis in the United Kingdom. *Arch Intern Med*. 2004;164:317–319.
5. Klein JS, Yocum MW. Underreporting of anaphylaxis in a community emergency room. *J Allergy Clin Immunol*. 1995;95:637–638.
6. Camargo CA Jr, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol*. 2007;120:131–136.
7. Sheehan WJ, Graham D, Ma L, Baxi S, Phipatanakul W. Higher incidence of pediatric anaphylaxis in northern areas of the United States. *J Allergy Clin Immunol*. 2009;124:850–852.
8. Mullins RJ, Clark S, Camargo CA Jr. Regional variation in EpiPen prescriptions in Australia: more evidence for the vitamin D-anaphylaxis hypothesis. *Ann Allergy Asthma Immunol*. 2009;103:488–495.
9. Mullins RJ, Clark S, Camargo CA Jr. Regional variation in infant hypoallergenic formula prescriptions in Australia. *Pediatr Allergy Immunol*. 2009. doi:10.1111/j.1399-3038.2009.00962.x.
10. McCaig LF, McLeMore T. Plan and operation of the National Hospital Ambulatory Medical Care Survey: series 1: programs and collection procedures. *Vital Health Stat 1*. 1994;(34):1–78.
11. Nawar EW, Niska RW, Xu J. National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. *Adv Data*. 2007;386:1–32.
12. United States Census 2000. US Census Bureau Web site. <http://www.census.gov/main/www/cen2000.html>.
13. Gaeta TJ, Clark S, Pelletier AJ, Camargo CA. National study of US emergency department visits for acute allergic reactions, 1993 to 2004. *Ann Allergy Asthma Immunol*. 2007;98:360–365.
14. 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.
15. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol*. 2008;121:1331–1336.
16. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–281.
17. Holick MF. Vitamin D: a D-lightful health perspective. *Nutr Rev*. 2008;66:S182–S194.
18. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr*. 2007;85:788–795.
19. Ginde AA, Mansbach JM, Camargo CA. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2009;169:384–390.
20. Laaksi I, Ruohola JP, Tuohimaa P, et al. An association of serum vitamin D concentrations <40 nmol/L with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr*. 2007;86:714–717.
21. Sidbury R, Sullivan AF, Thadhani RI, Camargo CA Jr. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *Br J Dermatol*. 2008;159:245–247.
22. Adorini L, Penna G. Dendritic cell tolerogenicity: a key mechanism in immunomodulation by vitamin D receptor agonists. *Hum Immunol*. 2009;70:345–352.

Reprint requests should be addressed to:
 Carlos A. Camargo Jr, MD, DrPH
 Massachusetts General Hospital
 326 Cambridge St, Ste 410
 Boston, MA 02114
 E-mail: ccamargo@partners.org