Regional variation in epinephrine autoinjector prescriptions in Australia: more evidence for the vitamin D–anaphylaxis hypothesis

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Background: There is little information on the regional distribution of anaphylaxis in Australia.

Objective: To examine the influence of latitude (a marker of sunlight/vitamin D status) as a contributor to anaphylaxis in Australia, with a focus on children from birth to the age of 4 years.

Methods: Epinephrine autoinjector (EpiPen) prescriptions (2006–2007) in 59 statistical divisions and anaphylaxis hospital admission rates (2002–2007) in 10 regions were used as surrogate markers of anaphylaxis.

Results: EpiPen prescription rates (per 100,000 population per year) were higher in children from birth to the age of 4 years (mean, 951) than in the overall population (mean, 324). In an unadjusted model of children from birth to the age of 4 years, decreasing absolute latitude was associated with a decrease in EpiPen prescription rates, such that rates were higher in southern compared with northern regions of Australia (β, −44.4; 95% confidence interval, −57.0 to −31.8; $P < .001$). Adjusting for age, sex, ethnicity, indexes of affluence, education, or access to medical care (general, specialist allergy, or pediatric) did not attenuate the finding (β, −51.9; 95% confidence interval, −71.0 to −32.9; $P < .001$). Although statistical power was limited, anaphylaxis admission rates (most prominent in children aged 0–4 years) showed a similar south-north gradient, such that admission rates were higher in southern compared with northern regions of Australia.

Conclusions: EpiPen prescription rates and anaphylaxis admissions are more common in southern regions of Australia. These data provide additional support for a possible role of vitamin D in the pathogenesis of anaphylaxis.

Ann Allergy Asthma Immunol. 2009;103:488–495.

INTRODUCTION

Estimates of anaphylaxis incidence vary widely, from 3.2 to 60.0 per 100,000 patient-years.[1–7] Although these differences may arise from the definition of anaphylaxis used or from whether studies have been hospital or community based,[8,9] geographic variation is rarely considered. The strong north-south gradient in epinephrine autoinjector (EpiPen) prescription rates in the United States,[10] along with evidence linking vitamin D status with recurrent wheezing of childhood,[11] has contributed to growing interest in the potential role of sunlight/vitamin D status on allergic conditions.

The objective of the present study was to examine evidence for geographical variation in anaphylaxis in Australia by examining EpiPen prescription and hospital anaphylaxis admission rates. Australia was considered an ideal location in which to explore regional variation in detail, given its broad range of latitude (33° vs 24° in the United States), the relatively homogeneous ethnicity and socioeconomic distribution, the universal public health system,[12] the relatively high anaphylaxis hospital admission rates,[13–17] and access to national EpiPen prescription and hospital admissions data. On the basis of the vitamin D–anaphylaxis hypothesis,[10] we hypothesized that higher EpiPen prescription and anaphylaxis admission rates might be observed in southern regions (less year-round sunlight) than in sunnier northern Australian regions.

METHODS

Australian Regional Classification

Data derived from Australian postal areas (the smallest geographical unit used in this study) were mapped to statistical divisions using Australian Bureau of Statistics (ABS)–derived data.[18] Statistical divisions are the largest statistical

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Disclosures: Authors have nothing to disclose.

Funding Sources: This study was supported by the Massachusetts General Hospital Center for D-Receptor Activation Research, Boston, Massachusetts (Dr Camargo). Selected data were purchased with funds provided by CSL Australia and Alphapharm Australia. Dr Mullins received investigator-initiated funding from CSL Australia (Melbourne) and Alphapharm Australia (Sydney) for data purchase, the past and current distributors of EpiPen in Australia, respectively. Dr Clark has received consulting funds from Dey (Napa, USA). Dr Camargo has received investigator-initiated research grants from, and consulted for, Dey (Napa, USA).

Previous Presentation: Presented in part at the Annual Scientific Meeting of the Australasian Society for Clinical Immunology and Allergy; Melbourne; November 12 to 14, 2008.

Reprints not available from the authors.

Received for publication April 28, 2009; Received in revised form June 11, 2009; Accepted for publication July 8, 2009.

building blocks of states and territories, do not cross state or territory boundaries, and cover all of Australia without gaps or overlaps. Data from all the 56 and 4 statistical divisions of mainland Australia and Tasmania, respectively, were examined and detailed; online maps are available.[18]

Australian Population and Demographic Data

Australian population statistics and demographic data (age, annual income, sex distribution, birth origin, ethnicity, educational level, housing density, employment, population density, number of practicing medical practitioners, and pediatricians) for each statistical division were from 2006 ABS Census data.[19] The Australasian Society of Clinical Immunology and Allergy provided regional practicing allergy/immunology specialist data (Jill Smith, BSc, written communication, November 2008).[20]

Mapping of EpiPen Prescription Rates

Commonwealth Serum Laboratories Australia (Melbourne) and IMS Health Australia (Sydney) supplied EpiPen prescription sales data (including refills) for 2 years (November 2005–October 2007), during which there were no competitive self-injectable epinephrine products available in Australia. EpiPen data were mapped to the postal area where prescriptions were filled. The Federal Department of Health and Aging (DOHA) in Canberra supplied information on the proportion of EpiPens prescribed by age group (0–4, 5–14, 15–24, 25–65, and ≥65 years). The ABS supplied latitude and longitude data for the geographical center (centroid) and geographical size of each statistical division.

Australian Criteria for EpiPen Subsidy

EpiPen is subsidized under the Australian Pharmaceutical Benefits Scheme (at approximately one-fourth of the private prescription price) for the anticipated emergency treatment of acute allergic reactions with anaphylaxis in a patient evaluated to be at risk of anaphylaxis in consultation with an allergy/immunology specialist, pediatrician, or respiratory physician or after discharge from the hospital after anaphylaxis treatment with epinephrine (adrenaline).[21,22] Physicians need to obtain authorization from Medicare Australia before supplying "Authority" prescriptions. "In consultation" can be between an authorizing specialist and a patient or prescribing physician. Two EpiPens are currently subsidized for children younger than 18 years and one is subsidized for older individuals but can also be purchased privately without prescription (approximately Australian $110 vs $33 on Authority prescription vs $5.30 for those on low incomes). The proportion of Authority EpiPen prescriptions supplied with a PBS subsidy was supplied by DOHA.

Hospital Admissions Data

Australian National Hospital Morbidity Database Principal Diagnosis data were obtained from the Australian Institute of Health and Welfare for the following age groups: 0 to 4, 5 to 14, 15 to 24, 25 to 65, and 65 years and older. These data record primary and important secondary hospital discharge diagnoses classified using the *International Classification of Diseases, 10th Revision (ICD-10)*[23] for each financial year (July-June). Anaphylaxis discharges associated with food (code T78), serum (code T80.5), medication (code T88.6), and unclassified anaphylaxis (code T78.2) were examined for the 5 years from July 1, 2002, through June 30, 2007. Sting anaphylaxis was excluded, because it was not possible to distinguish anaphylaxis from other adverse reactions (eg, toxicity) using *ICD-10* codes. (National data pertaining to emergency department visits and treatment without admission were not available.) Admission analysis was restricted to 10 major regions (composed of ≥1 statistical division) to preserve patient anonymity and included only data related to patients resident in the same region. Population rates were calculated using the mean ABS national population estimates for the same period in these regions (north to south, composed of statistical divisions as listed): Far North Queensland (Far North/Northern/Mackay statistical divisions), Brisbane, Mid North Coast of New South Wales, southeast Western Australia (Perth/South West/Lower Great Southern), New South Wales/Victoria border (Murray/Ovens Murray), Sydney, Adelaide (including Adelaide and Outer Adelaide), Australian Capital Territory (ACT) (composed of the 2 statistical divisions of Canberra and the balance of the ACT), Melbourne (Melbourne/Barwon), and all Tasmania combined. Male and female admissions data were pooled to eliminate data suppression from small numbers. Discharge diagnoses were expressed as age-standardized rates per 100,000 population per year.

The study was approved by the Human Research and Ethics Committee (Calvary Bruce/Calvary John James private hospitals).

Statistical Analysis

Analyses were performed using commercially available software (STATA 10.0; StataCorp, College Station, Texas). To facilitate comparison between different statistical divisions, age-specific rates for EpiPen prescription and anaphylaxis admissions were expressed per 100,000 population per year for each age group in each statistical division. Means are presented with SDs and medians with interquartile ranges. The association between factors of interest was evaluated using the *t* test and the Kruskal-Wallis test, as appropriate. Multivariable linear regression was used to evaluate the association between statistical division–based demographic factors and EpiPen prescriptions. Multivariable linear regression was also used to evaluate the association between some regional demographic factors, latitude, and anaphylaxis admissions. Studentized residuals were used to identify outliers and to confirm the appropriateness of the selected models. These analytic techniques were also used to evaluate the association between statistical division characteristics and anaphylaxis admissions. All β coefficients are presented with 95% confidence intervals (CIs). $P < .05$ (2 sided) was considered statistically significant.

RESULTS

EpiPen Prescription Rates

From 2005 to 2007, 69,227 EpiPens prescriptions were filled (38,861 for 0.3 mg of EpiPen and 30,366 for 0.15 mg of EpiPen Jr), 87% with government subsidy. Prescriptions were more commonly filled in younger patients (0–4 years, 20% of sales; and 5–14 years, 38% of sales) than in older patients (15–24 years, 10% of sales; 25–64 years, 27% of sales; and ≥65 years, 5% of sales). EpiPen prescription rates (per 100,000 population per year) were higher for children from birth to the age of 4 years (n = 951) and for those aged 5 to 14 years (n = 1024), compared with those 15 years and older (n = 223) or the overall population mean (n = 324) (median, 297; interquartile range, 247–393) (Fig 1).

EpiPen prescription rates were higher in southern latitudes (less sunlight) compared with northern regions (Fig 1 and Fig 2) (unadjusted β, −11.4; 95% CI, −16.3 to −6.6; $P < .001$). Multivariable analysis controlling for median age, sex, citizenship, country of birth, median weekly household income, ethnicity, proportion of indigenous population, indexes of affluence, education, or access to medical care (general, specialist allergy, or pediatric) did not attenuate the relationship between absolute latitude and EpiPen prescription rates (β, −19.22; 95% CI, −26.71 to −11.73; $P < .001$).

Similar results were observed in each age group in unadjusted and multivariable analyses (controlling for median age, sex, citizenship, country of birth, median weekly household income, ethnicity, proportion of indigenous population, indexes of affluence, education, or access to medical care [general/specialist allergy/pediatric]) (Table 1 and Table 2). Regional differences in prescription rates were most prominent in children from birth to the age of 4 years, with a 6-fold difference between far southern Australia (Hobart and Tasmania) and far northern Queensland (2,318 vs 383 per 100,000 population per year) (Table 2). Similar gradients were observed for those aged 5 to 14 years (2,278 vs 395) and those 15 years and older (714 vs 112). There was no association between EpiPen prescription rates and statistical division population density (data not shown). In univariate analyses of the total population, statistical division-level factors were not associated with the rate of EpiPen prescriptions (data not shown). In children from birth to the age of 4 years,

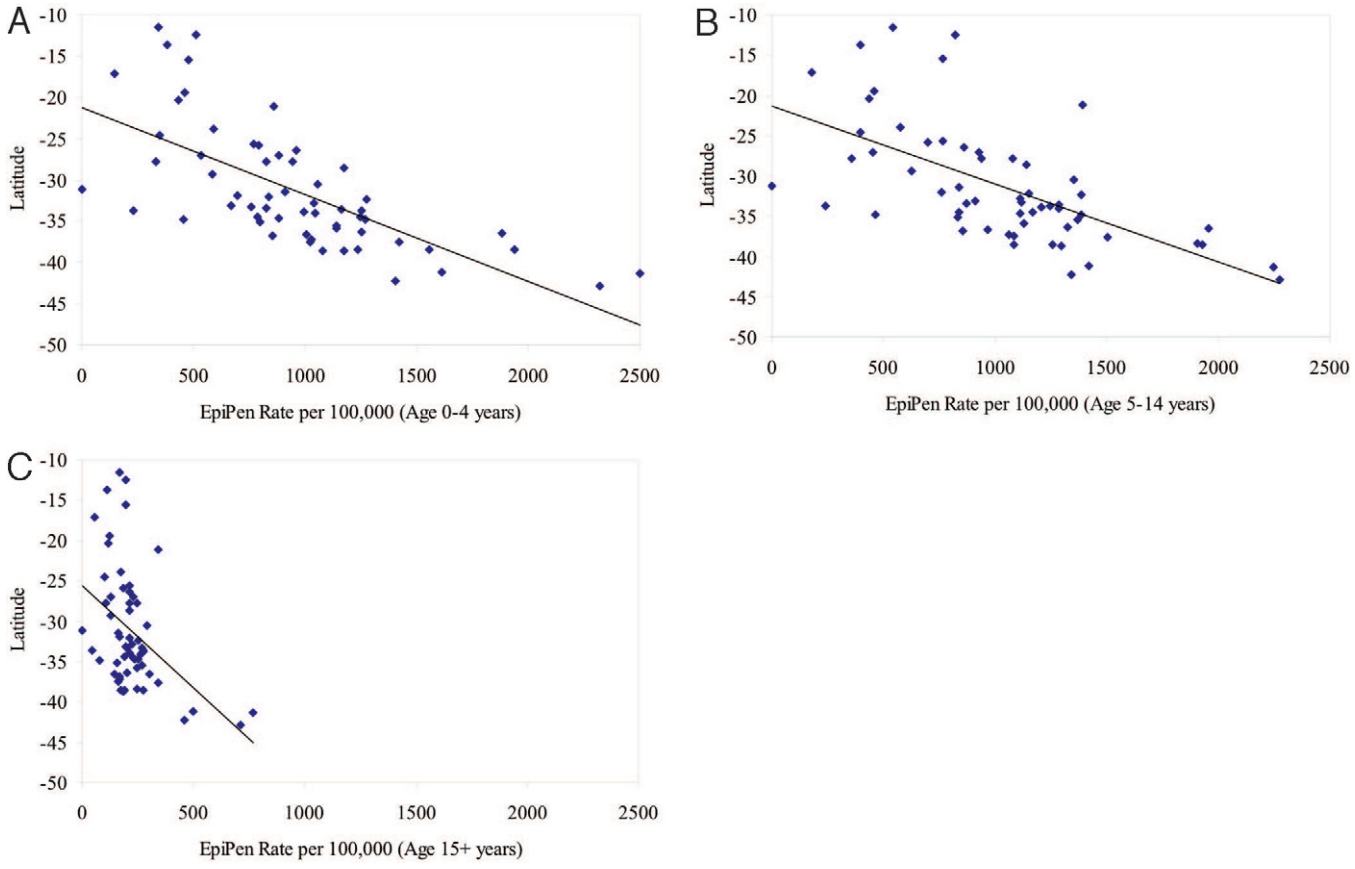

Figure 1. Geographic variation in epinephrine autoinjector (EpiPen) prescription rates. EpiPen prescription rates varied as a function of age and absolute latitude, being prescribed more commonly in southern regions of Australia and in patients from birth to the age of 4 years (A) and in patients aged 5 to 14 years (B) compared with those 15 years or older (C).

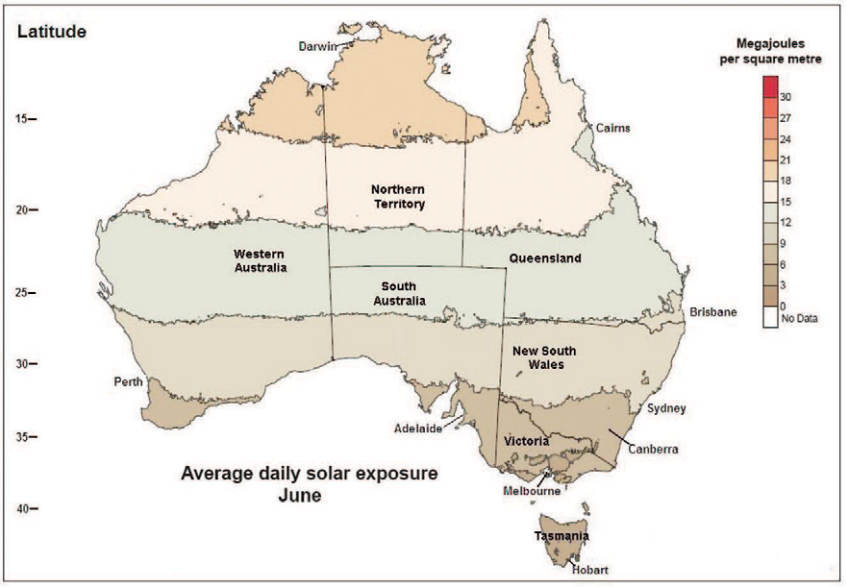

Figure 2. Average solar radiation exposure in June (Winter). There is a latitudinal gradient in solar radiation exposure (measured in megajoules per square meter) such that exposure is greater in northern than southern regions of Australia (modified from the map provided by the Australian Bureau of Meteorology).

however, EpiPen prescriptions were more common in statistical divisions with higher unemployment (in the overall statistical division population) and less common in statistical divisions with more people per household or a higher proportion of the indigenous population (in the overall statistical division population) (Table 1). Rerunning final models after excluding statistical divisions with large Studentized residual values (ie, $r > 121$) did not materially change the results (data not shown).

Anaphylaxis Admissions

Between July 1, 2002, and June 30, 2007, 10,994 admissions were coded as anaphylaxis. In the overall population, anaphylaxis was attributed to food (42% of cases), unclassified (32% of cases), medication (25% of cases), or serum (1% of cases). Food was the dominant trigger in children from birth to the age of 4 years, accounting for 81% of admissions. The mean age-specific rates of anaphylaxis admission were highest in children from birth to the age of 4 years (22.3) compared with those aged 5 to 14 years (7.8), 15 to 24 years (10.9), 25 to 64 years (10.2), or 65 years or older (8.8) (numbers in parentheses are per 100,000 population per year). Although the association was not statistically significant, anaphylaxis admission rates were higher in southern than northern regions in all age groups. In children from birth to the age of 4 years, for example, rates were 3-fold higher in southernly Tasmania (far south Australia; 24.2 admissions per 100,000 population per year) compared with northern Queensland (6.8 per 100,000 population per year) (Fig 3). (Separate analysis of admissions by region and individual cause was precluded by Australian Institute of Health and Welfare data suppression policies for small numbers in some regions.)

Region-level factors, such as longitude, sex, median household size, median weekly income, physician numbers, and population density, were not associated with admission rates (data not shown). Adjusting for 1 region-level factor/time did not materially change the association between absolute latitude and anaphylaxis admissions. Of interest, ACT and Adelaide (with similar latitudes) had anaphylaxis admission rates outside the general regional trend, having very low and high rates, respectively. If sensitivity analysis was repeated excluding these regions, the negative association between absolute latitude and anaphylaxis admission rates was statistically significant (β, -0.89; 95% CI, -1.54 to -0.24; $P = .02$).

DISCUSSION

In the first examination of geographical variation of anaphylaxis in Australia, we found a significant south-north gradient in the EpiPen prescription rate. The higher rates in southern Australia could not be accounted for by regional differences in demographics, socioeconomic status, housing or population density, or access to medical care. The robustness of these findings is underpinned by an analysis of all EpiPens dispensed in Australia (subsidized or purchased privately), supported by a south-north gradient in anaphylaxis-related hospital admissions. Financial barriers to accessing EpiPen are unlikely to have distorted the data, with 87% of patients purchasing a subsidized EpiPen. These Australian data mirror the north-south gradient in EpiPen prescriptions observed in the United States,[10] despite stringent requirements in Australia for subsidized EpiPen prescriptions (and penalties for those prescribing outside government guidelines) (Vanna Mabbott, DOHA, written communication, February 2009) in the context of a different health care system.[21]

The overall EpiPen prescription rate (per 100,000 population per year) in Australia was 349, midway between population estimates of 190 in Canada[9] and 520 in the United States.[10] As in other studies,[9] prescription rates were highest in children, likely reflecting the higher incidence of food allergy/anaphylaxis and hospital admissions in that group.[6,15,16] Because EpiPen prescription rates might more accurately reflect risk evaluation for future anaphylaxis than past episodes per se, one might expect prescriptions to exceed actual anaphylaxis rates, a prediction consistent with the 23-fold difference between EpiPen prescription and admission rates observed overall (34-fold in those 0–4 years) and

Table 1. Univariate Predictors of Epinephrine Autoinjector (EpiPen) Prescriptions in Children From Birth to the Age of 4 Years

Predictor	β (95% confidence interval)	*P* value
Latitude (per ↓ 1°)	−44.4 (−57.0 to −31.8)	<.001
Longitude (per ↑ 1°)	6.9 (-4.5 to 18.3)	.23
Age for statistical division (per ↑ 1 y), median, y	55.3 (21.2 to 89.5)	.002
Females from birth to the age of 4 y in the statistical division (per ↑ 1%), %	33.2 (−108.4 to 174.8)	.64
Australian citizen in the statistical division (per ↑ 1%), %	31.8 (−2.15 to 65.70)	.07
Born in Australia in the statistical division (per ↑ 1%), %	1.6 (-17.6 to 20.7)	.87
Born overseas in the statistical division (per ↑ 1%), %	8.4 (−12.8 to 29.7)	.43
Indigenous in the statistical division (per ↑ 1%), %	−22.4 (−35.7 to −9.1)	.001
English only spoke at home (per ↑ 1%), %	15.1 (−0.7 to 30.8)	.61
Professionals (per ↑ 1%), %	32.7 (−1.6 to 67.0)	.06
Unemployed (per ↑ 1%), %	84.0 (2.0 to 166.1)	.045
Household income per week (per ↑ $1), median	−0.4 (−1.0 to 0.1)	.12
House population (per ↑ 1), median	−1008.9 (−1710.8 to −307.0)	.006
Persons per bedroom (per ↑ 1), mean	−2006.6 (−4073.0 to 59.8)	.06
High school graduate (per ↑ 1%), %	13.9 (−5.5 to 33.3)	.16
Health care providers (per ↑ 1 providers)		
Allergists	5.1 (−9.1 to 19.3)	.47
Pediatricians	1.2 (−1.5 to 3.9)	.38
Medical practitioners	0.0 (−0.0 to 0.1)	.30

Table 2. Multivariable Model of Regional Epinephrine Autoinjector (EpiPen) Prescriptions by Age Group[a]

Factor	Age group, y				
	0–4	5–14	15–24	25–64	≥65
Unadjusted	−44.4 (−57.0 to −31.8)[b]	−39.6 (−53.0 to −26.3)[b]	−13.1 (−17.9 to −8.2)[b]	−7.5 (−11.4 to −3.5)[b]	−1.6 (−8.0 to 4.8)
Model 1[c]	−49.6 (−68.1 to −31.1)[b]	−53.3 (−71.3 to −35.3)[b]	−18.0 (−25.0 to −11.1)[b]	−11.6 (−17.4 to −5.8)[b]	−15.0 (−23.3 to −6.7)[b]
Model 2[d]	−51.9 (−71.0 to −32.9)[b]	−54.8 (−73.6 to −36.0)[b]	−18.8 (−26.0 to −11.5)[b]	−12.4 (−18.3 to −6.4)[b]	−16.6 (−25.1 to −8.2)[b]

[a] Data are given as β coefficient (95% confidence interval).
[b] Significant results.
[c] Model 1 controls for 5 factors: median age, percentage female (in the specified age group), percentage indigenous, median weekly household income, and percentage high school graduates.
[d] Model 2 controls for the previously listed factors plus 3 additional factors: number of allergists, number of pediatricians, and number of medical practitioners.

a 10-fold difference between outpatient treatment for anaphylaxis and hospital admission after an episode.[5]

We were unable to differentiate between initial and renewed prescriptions (potentially leading to an overestimate of EpiPen use), and our data source indicated where EpiPens were dispensed rather than where patients resided. We were also unable to evaluate the rate at which the devices were being used, potentially a more accurate indicator of anaphylaxis incidence. Although differing prescribing practices might have influenced EpiPen prescription rates, we were unable to quantify this variable. Cofactors (such as asthma), prescribing guidelines,[22] accuracy of diagnosis, or nonmedical factors (such as medicolegal pressures or parental anxiety)[24] may also have been a source of variation, but it is unlikely that all factors operated on a systematic level to explain the clear south-north gradient. Although some demographic factors (eg, housing density, employment rates, and ethnicity) were linked with EpiPen prescriptions in young children in univariate analysis, these associations disappeared

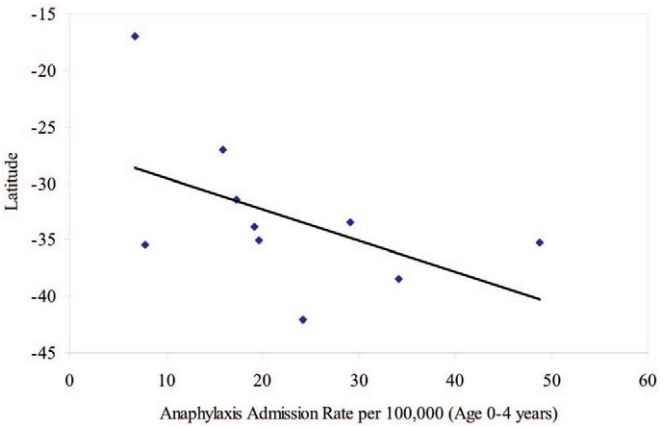

Figure 3. Geographic variation in anaphylaxis admission rates in patients from birth to the age of 4 years. Anaphylaxis admission rates varied as a function of age and latitude, being more common in patients from birth to the age of 4 years than in other age groups and more common in southern than northern regions.

on multivariable analysis. Study design precluded any analysis of these secondary results.

UK anaphylaxis admissions are more common in rural, affluent, and southern (greater sun exposure) areas.[25] Interpretation of that study, however, is limited by the small number of regions examined and the narrow range of latitude of that country (approximately 8° vs Australia or the United States [approximately 33° and 25°, respectively]). By contrast, our analysis showed that anaphylaxis admissions were more common in less sunny southern Australian regions (Fig 3). The following factors are important: (1) these data reflect the rate of anaphylaxis-related admissions in those regions, because only patients who resided in the region (not visitors) were included in the data set; and (2) the admissions were unbiased by the inability to access hospital facilities, because only admissions in major population-dense regions were considered. Although our analysis was limited (for privacy reasons) to a relatively small number of major regions (n = 10), we nonetheless encompassed regions in which 73% of all Australians (and 64% of children from birth to the age of 4 years) live.

Potential (but unlikely) variables to hospital admissions data include errors in hospital coding and inability to distinguish between single and multiple presentations for the same patient. The fact that only a small proportion of infantile food allergy/anaphylaxis presentations are admitted, however,[5] suggests that patients with relatively minor symptoms are more likely to be coded as urticaria (and discharged), rather than as anaphylaxis (and admitted). Selective immigration of children at risk of food allergy/anaphylaxis to the south is unlikely to have influenced the data, given that the major population drifts in Australia are in the opposite direction.[26] Of interest, regional differences in hospital admission criteria might explain 2 "outliers" to the geographical trend: the ACT (south-east Australia; latitude, −34.5° [very low rates]) and Adelaide (southern Australia; latitude, −35.3° [very high rates]). Because only 8 children from birth to the age of 4 years were hospitalized in the ACT, even minor changes would have significantly influenced calculated rates. By contrast, admission polices in one Adelaide hospital mandating admission of pediatric anaphylaxis cases (Mark Webb, MD, written communication, November 2008) may have increased rates. Our inability to demonstrate a statistically significant association between absolute latitude and anaphylaxis admission rates is perhaps not surprising when considering our ability to analyze only the relatively small proportion of patients with anaphylaxis who are hospitalized (10 data points), compared with 100% of EpiPens dispensed (60 data points).

The south-north gradient in young Australian children most likely reflects real differences in the prevalence of food allergy, the most common trigger for anaphylaxis in this age group.[15,16] A positive relationship between latitude and allergy-related disorders is not unprecedented, having been described for atopic eczema in European children,[27] allergic rhinitis in young adults,[28] and food allergy in Italian adults and US children.[29,30] Although several factors have been postulated to play a role in the pathogenesis of food allergy,[31–34] limited exposure to sunlight (low vitamin D status) is a newly proposed risk factor.[10]

There is growing evidence that sunlight exposure/vitamin D status has important effects on the immune system, as recently reviewed.[35–38] The vitamin D receptor is present in most cells of the immune system, including T lymphocytes, neutrophils, and antigen-presenting cells (dendritic cells and macrophages).[35,37,38] Vitamin D has known immunomodulatory effects on both T_H1 and T_H2 responses, with deficiency postulated to play a role in the pathogenesis of autoimmune diseases (eg, multiple sclerosis and type 1 diabetes), malignant neoplasms, and infectious disease, perhaps induced by vitamin D–mediated changes in the disease-related major histocompatibility complex class 2 gene.[39–41] Recent studies have also shown associations between vitamin D receptor polymorphism and atopic disease; between genetic variants in the vitamin D activation enzyme, vitamin D levels, and total IgE[42,43]; between low vitamin D intake during pregnancy and the presence and severity of allergic rhinitis in offspring[44]; and between low vitamin D levels and childhood asthma severity.[45]

Despite Australia's reputation for having high rates of sun exposure–related skin cancer,[46,47] vitamin D deficiency is common, affecting up to 8% of 8-year-olds, 68% of 16-year-olds, 15% of pregnant women (and 11% of neonates), and 67% of adult women in southern regions.[48–50] Approximately 90% of vitamin D is synthesized in the skin after UV light exposure.[36] Dietary exposure to vitamin D is relatively sparse, restricted to small amounts in oily fish, fortified soy, or cow's milk and compulsory fortification of nondairy spreads and margarines (Hikmat Hayder, PhD, Food Standards Australia New Zealand, e-mail communication, June 2009). Otherwise, there is no regular fortification of foods in Australia with vitamin D.[51] Lack of sun exposure is the major risk factor for deficiency in older children and adults.[52] In young childhood, however, the major risk factor is maternal vitamin D status, dark skin, and prolonged breastfeeding (vitamin D–insufficient mothers have low levels in breast milk).[52]

Our data underline that regional differences in food allergy/anaphylaxis may exist and that one cannot automatically extrapolate data obtained from one location to an entire population. Although we can be confident of the regional differences in EpiPen prescription rates, other confounding demographic or environmental factors (eg, unidentified exposure to infectious or parasitic organisms)[53] may also play a role in food allergy/anaphylaxis pathogenesis and might also contribute to the patterns observed. Although association is not equivalent to causation (and our evaluation of vitamin D status and its possible influence is indirect and based on population rather than individual exposures), our data provide a rational basis for a closer examination of the possible role of vitamin D (among other factors) in the pathogenesis of food allergy/anaphylaxis in early childhood. Until results are available from cohort studies with blood levels of 25-hy-

droxyvitamin D (with follow-up for the development of food allergy) or from randomized controlled trials to formally test our hypothesis, it is premature to disregard current policies regarding safe sun exposure or to increase vitamin D intake for the specific prevention of anaphylaxis.[54]

ACKNOWLEDGMENTS

We thank staff from the ABS (Jennie Dunn) and the Australian Institute of Health and Welfare (George Bodilsen, Cid Riley, Phil Tennant, and Katie Williams) for their assistance with data coordination; Bev Huttman (CSL Australia) and Jenny Hrehoresen (IMS Health Australia) for provision of EpiPen sales data; and Vanna Mabbott (DOHA) for provision of additional EpiPen-related data.

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Answers to CME examination—*Annals of Allergy, Asthma & Immunology*, December 2009 Cox LS: Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol*. 2009;103:451–460.

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