

Original article

Regional differences in EpiPen prescriptions in the United States: The potential role of vitamin D

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Background: The epidemiology of anaphylaxis is uncertain, especially its geographic distribution.

Objective: To address this deficit, we examined regional rates of EpiPen prescriptions in the United States.

Methods: EpiPen prescriptions in 2004 were obtained for all 50 states and Washington, DC, from NDCHealth, Pharmaceutical Audit Suite (Alpharetta, Ga). Data included the number of total filled prescriptions, including refills, and the actual number of EpiPens prescribed. Several data sets were used to obtain state-specific populations, as well as multiple demographic, health, and weather characteristics. State population was used to calculate the average number of prescriptions written per person.

Results: Overall, there were 1,511,534 EpiPen prescriptions filled during 2004. These prescriptions accounted for 2,495,188 EpiPens. On average, there were 5.71 EpiPens prescribed per 1000 persons. Massachusetts had the highest number of prescriptions per 1000 persons (11.8), whereas Hawaii had the lowest (2.7). In addition to state-to-state variation, there was an obvious regional difference: New England (Connecticut, Rhode Island, Massachusetts, Vermont, New Hampshire, Maine) had the highest values, with 8 to 12 EpiPen prescriptions per 1000 persons, whereas the southern states (between and including California and Mississippi) had only 3 prescriptions per 1000 persons. The New England finding persisted even when

controlling for all available factors (eg, population demographic characteristics, number of health care providers, prescriptions for other medications).

Conclusion: A strong north-south gradient was observed for the prescription of EpiPens in the United States, with the highest rates found in New England.

Clinical implications: The regional differences in EpiPen prescribing may provide important etiologic clues (vitamin D status) and merit further investigation. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Anaphylaxis, epidemiology, EpiPen, vitamin D

The epidemiology of anaphylaxis in the general population is uncertain. A review article by Neugut et al¹ estimated the US prevalence of anaphylaxis to be anywhere between 1% and 15%. By contrast, a population-based study in Olmsted County, Minn, concluded that the prevalence of anaphylaxis was less than 1%.² More recent studies from the United States, Canada, and the United Kingdom yield prevalence estimates ranging from 0.3% to 0.95%.³⁻⁶

The study yielding the highest prevalence estimate (0.95%) was by Simons et al⁴ and used a novel approach to estimating the burden of anaphylaxis: evaluating medication-dispensing data for epinephrine for out-of-hospital treatment during a 5-year period in Manitoba, Canada. A recent expert roundtable concluded that this approach may provide one of the best insights into the actual frequency of anaphylaxis.⁷ This approach also permits investigation of the geographic distribution of anaphylaxis, which is unknown. Our objective was to describe the geographic distribution of anaphylaxis in the United States and to explore potential mediators of any observed geographic differences. To do this, we examined state-specific EpiPen (Dey, Napa, Calif) prescriptions in 2004. Although our analysis was largely exploratory, we hypothesized—on the basis of the vitamin D–asthma hypothesis⁸—that northern states with less year-round sunlight (eg, New England) would have higher EpiPen prescriptions than southern states.

METHODS

US regions and divisions were defined based on the US Census Bureau classifications.⁹ The 9 divisions of the United States were

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The NDCHealth prescription data were purchased by Dey (Napa, Calif).

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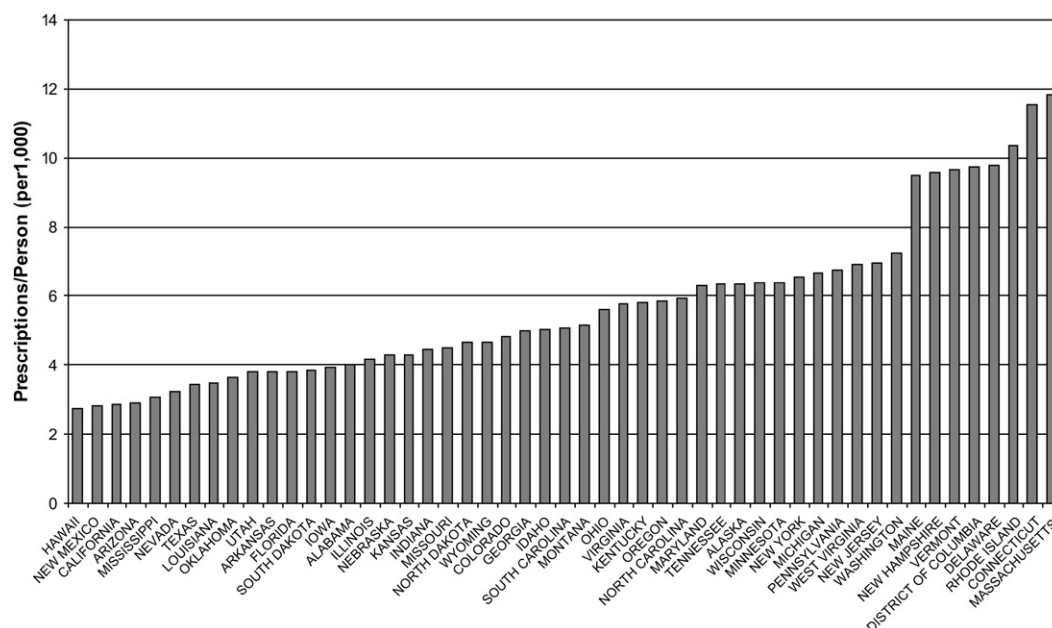


FIG 1. Number of EpiPen prescriptions per 1000 persons by state, ranging from 2.7 (Hawaii) to 11.8 (Massachusetts).

New England (Maine, New Hampshire, Vermont, Massachusetts, Connecticut, Rhode Island), Middle Atlantic (New York, Pennsylvania, New Jersey), South Atlantic (Delaware, Washington, DC, Maryland, West Virginia, Virginia, North Carolina, South Carolina, Georgia, Florida), East North Central (Michigan, Wisconsin, Illinois, Indiana, Ohio), East South Central (Kentucky, Tennessee, Alabama, Mississippi), West North Central (North Dakota, Minnesota, South Dakota, Nebraska, Iowa, Kansas, Missouri), West South Central (Oklahoma, Arkansas, Texas, Louisiana), Mountain (Montana, Idaho, Wyoming, Nevada, Utah, Colorado, Arizona, New Mexico), and Pacific (Washington, Oregon, California, Alaska, Hawaii). The 4 US regions were Northeast (New England and Middle Atlantic), Midwest (East North Central and West North Central), South (South Atlantic, East South Central, and West South Central), and West (Mountain and Pacific). Finally, region was divided into 2 groups—New England versus other US regions—to evaluate further the most clear-cut geographic difference in EpiPen prescribing.

EpiPen prescriptions and other medication prescriptions during 2004, for all 50 US states and District of Columbia, were obtained from NDCHealth, Pharmaceutical Audit Suite (Alpharetta, Ga). In 2004, there were no competitive self-injectable epinephrine products in the US marketplace. Data were obtained on the number of total filled prescriptions (including refills) and the actual number of EpiPens dispensed for EpiPen 0.3 mg, EpiPen Jr, and total EpiPens (0.3 mg and Jr combined). Additional data obtained from NDCHealth were the number of allergist, pediatrician, adult primary care (ie, adult generalist, family physician), and emergency physician prescription writers per state, and filled prescriptions for a few other medications (eg, inhaled corticosteroids, atorvastatin). Data on demographic factors (eg, age, race/ethnicity, income) and state population were downloaded from the US Census.⁹

Data on other health characteristics were obtained from state-specific estimates provided by the 2004 Behavioral Risk Factor Surveillance System website.¹⁰ Health characteristics data included health insurance status, history of asthma, history of diabetes, self-reported general health status, smoking history, alcohol consumption, and flu and pneumonia vaccinations for individuals age 65 years and

older. State-level data on average annual temperature, average annual precipitation, average January normal temperature, and average July normal temperature were obtained from the National Oceanic and Atmospheric Administration for 1971 to 2000.¹¹ Estimated 2004 melanoma incidence, an admittedly crude surrogate for sun exposure,^{12,13} was obtained from the American Cancer Society.¹⁴

Statistical analysis

All analyses were performed using STATA 9.0 (StataCorp, College Station, Tex). State population was used to calculate the number of prescriptions filled per person. All rates are presented per 1000 state population. Means are presented with SDs and medians with interquartile ranges. The association between factors of interest and region (ie, New England vs other US regions) was evaluated using the Student *t* test and Kruskal-Wallis test, as appropriate. Multivariate linear regression was used to evaluate the association between state factors and EpiPen prescriptions. All β coefficients are presented with 95% CIs.

RESULTS

In 2004, including refills, there were a total of 1,511,534 EpiPen 0.3 mg and EpiPen Jr prescriptions filled, with EpiPen 0.3 mg accounting for 78% (1,178,229) of prescriptions and EpiPen Jr 22% (333,305). These 1.5 million EpiPen prescriptions led to dispensing of 2,495,188 EpiPens or an average of 1.6 EpiPens per prescription. There were an average of 1.6 EpiPen 0.3 mg devices per prescription and an average of 1.9 EpiPen Jr devices per prescription.

We found considerable state-to-state variation when looking at the absolute number of EpiPens prescribed, from a high of 125,540 in New York to a low of 2369 in Wyoming. When adjusting for population differences, by looking at the prescription rates per 1000 state population,

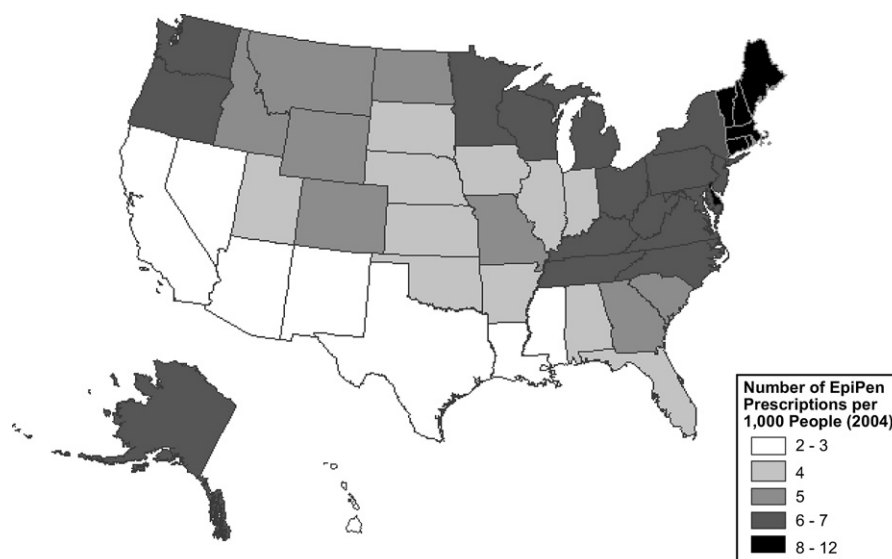


FIG 2. Regional differences in EpiPen prescriptions per 1000 persons.

there were an average of 5.71 EpiPens prescribed per 1000 persons. As shown in Fig 1, state-to-state variation persisted, with the highest rates seen in Massachusetts (11.8) and the lowest rates seen in Hawaii (2.7).

In addition to state-to-state variation, we observed a striking regional difference (Fig 2). The Northeast had the most EpiPen prescriptions, with 8 to 12 prescriptions per 1000 persons, and the Southern states had $\frac{1}{4}$ the prescriptions at 2 to 3 prescriptions per 1000 persons. When separating EpiPen 0.3 mg and EpiPen Jr, we found that these regional trends were similar with both sizes of EpiPen (data not shown). In an unadjusted linear regression model, all other US regions had significantly fewer EpiPen prescriptions than New England (reference group): Mid Atlantic (β , -3.64; 95% CI, -5.46 to -1.84), East North Central (β , -4.96; 95% CI, -6.50 to -3.41), West North Central (β , -5.84; 95% CI, -7.27 to -4.42), South Atlantic (β , -4.29; 95% CI, -5.64 to -2.94), East South Central (β , -5.60; 95% CI, -7.25 to -3.95), West South Central (β , -6.82; 95% CI, -8.47 to -5.17), Mountain (β , -6.35; 95% CI, -7.73 to -4.97), and Pacific (β , -5.40; 95% CI, -6.95 to -3.85).

Table I shows population demographic and health characteristics in the New England region compared with those in all other US regions combined. The state populations in the New England region had a higher median age, median household income, and percentage of people reporting health insurance. The number of allergists and emergency physicians was similar, but New England also had more pediatricians and adult primary care providers (per 1000 population). New England also prescribed more inhaled corticosteroids and atorvastatin per 1000 population; other studied medications did not significantly differ.

In univariate analyses, several state-level factors were associated with the number of EpiPen prescriptions per state (Table II). Number of EpiPen prescriptions was positively associated with percentage of the state population

that was female but did not differ by other sociodemographic factors. Strong associations were seen for number of healthcare providers (especially allergists), and with medication prescriptions of all types. Average temperature and average precipitation were not significantly associated with number of EpiPen prescriptions. Melanoma incidence had a significant inverse association with EpiPen prescriptions.

Other factors describing the general health of the state population also were evaluated, including history of asthma, history of diabetes, self-reported general health status, cigarette smoking, alcohol consumption, and flu and pneumonia vaccinations for individuals age 65 years and older. We also examined confidential data on Dey marketing efforts in the different states. However, none of these factors were significantly associated with the number of EpiPen prescriptions filled (data not shown).

To identify population characteristics that might mediate the marked regional differences, we evaluated the rate of EpiPen prescriptions in the New England (highest prescription rates) compared with all other regions while controlling for all available factors (Table III). Controlling for these factors attenuated the higher rate of EpiPen prescriptions in the New England region, but the finding remained statistically significant ($P < .001$).

DISCUSSION

To address uncertainty about the geographic distribution of anaphylaxis and overcome sparse and often problematic data on healthcare utilization for this condition,⁷ we examined EpiPen prescription rates across the United States. We found a strong north-south gradient, with the highest rates of EpiPen prescriptions in New England. Population-adjusted rates (ie, number of EpiPen prescriptions filled per 1000 people) were positively

TABLE I. State characteristics in New England region versus other US regions*

	New England region	Other US regions	P value
Median age in state (y)	39 ± 1	36 ± 2	.002
Percent female in state	51 ± 0.4	51 ± 0.8	.07
Percent white in state	92 ± 5	80 ± 14	.05
Median household income (US \$)	62,696 ± 8576	52,500 ± 7688	.004
Percent high school graduates	84 ± 3	82 ± 4	.14
Percent any type of health insurance coverage	89 ± 2	84 ± 4	.01
No. of healthcare providers (per 1000 population)			
Allergists	0.01 (0.01-0.02)	0.01 (0.01-0.02)	.95
Pediatricians	0.32 (0.26-0.36)	0.22 (0.17-0.26)	.006
Adult primary care providers	1.31 (1.14-1.47)	1.02 (0.90-1.12)	.002
Emergency physicians	0.17 (0.14-0.22)	0.14 (0.13-0.17)	.08
No. of allergy/asthma medications (per 1000 population)			
Albuterol	31.2 (23.9-34.6)	36.2 (28.3-40.8)	.13
Inhaled corticosteroids	62.3 (56.5-62.4)	37.1 (30.7-41.5)	<.001
Montelukast	70.3 (62.1-83.2)	79.3 (62.3-86.5)	.77
Pimecrolimus cream	11.2 (8.2-15.7)	12.4 (10.0-16.4)	.38
No. of other medications (per 1000 population)			
Atorvastatin	349.4 (303.9-453.8)	226.5 (185.0-262.6)	.001
Oral hypoglycemic agents†	319.7 (307.2-358.3)	337.3 (280.0-391.1)	.60
Hypertension medications‡	1957.4 (1905.7-2072.9)	1978.5 (1577.0-2346.6)	.88
Average temperature (°F)	46 (43-49)	53 (48-59)	.06
Average precipitation (in)	46 (43-48)	39 (23-46)	.10
Melanoma incidence	280 (280-700)	910 (420-1390)	.14

*Data presented as means ± SDs, or medians with interquartile ranges.

†Includes sulfonylureas, meglitinides, amino acid derivatives, biguanides, insulin sensitizers, α-glucosidase inhibitors, noninsulin combinations, and noninsulin others.

‡Includes Universal System of Classification codes 41000 (Diuretics, Ethical) and 31000 (Vascular Agents).

TABLE II. Univariate predictors of number of EpiPen prescriptions per state

	β	95% CI	P value
Median age (per ↑1 y)	−95	−3826, 3637	.96
Percent female in state (per ↑1%)	1.26	0.48, 2.05	.002
Percent white in state (per ↑1%)	−106	−699, 486	.72
Median household income (per ↑\$10,000)	9005	−407, 18418	.06
Percent high school graduates (per ↑1%)	−1314	−3152, 523	.16
Percent any type of health insurance coverage	191	−1865, 2249	.85
Healthcare providers (per ↑1 provider)			
Allergists	233	202, 265	<.001
Pediatricians	15	13, 17	<.001
Adult primary care providers	4.0	3.7, 4.6	<.001
Emergency physicians	30	25, 35	<.001
Allergy/asthma medications (per ↑1 prescription)			
Albuterol	0.10	0.09, 0.12	<.001
Inhaled corticosteroids	0.12	0.10, 0.13	<.001
Montelukast	0.06	0.05, 0.07	<.001
Pimecrolimus cream	0.29	0.24, 0.33	<.001
Other medications (per ↑1 prescription)			
Atorvastatin	0.019	0.017, 0.021	<.001
Oral hypoglycemic agents*	0.012	0.011, 0.014	<.001
Hypertension medications†	0.002	0.002, 0.003	<.001
Average temperature (per ↑1°F)	472	−468, 1412	.32
Average precipitation (per ↑1 inch)	371	−186, 928	.19
Melanoma incidence	24	20, 27	<.001

*Includes sulfonylureas, meglitinides, amino acid derivatives, biguanides, insulin sensitizers, α-glucosidase inhibitors, noninsulin combinations, and noninsulin others.

†Includes USC codes 41000 (Diuretics, Ethical) and 31000 (Vascular Agents).

TABLE III. Multivariate model of regional EpiPen prescriptions (per 1000 state population), comparing New England region vs other US regions

	β	95% CI	P value
Unadjusted	5.39	4.11-6.67	<.001
Model 1*	4.07	2.77-5.36	<.001
Model 2†	3.79	2.20-5.39	<.001
Model 3‡	3.59	1.94-5.23	<.001
Model 4§	3.55	1.86-5.24	<.001

*Model 1 controls for 6 factors: median age, percent female, percent white, median household income, percent high school graduates, and percent with health insurance.

†Model 2 controls for above, plus 4 factors: number of allergists, pediatricians, adult primary care providers, and emergency physicians.

‡Model 3 controls for above, plus 7 factors: number of prescriptions for albuterol, inhaled corticosteroids, montelukast, pimecrolimus cream, atorvastatin, oral hypoglycemic agents, and hypertension medications.

§Model 4 controls for above, plus melanoma incidence.

associated with several different factors, including percentage of the population that was female, the number of healthcare providers (especially allergists) per 1000 people, and the frequency of medication prescribing in general. Nevertheless, a multivariate analysis controlling for all of these factors suggested that these factors did not mediate the observed north-south gradient.

Ecologic studies are, by their very nature, exploratory, but they can yield important etiologic clues about disease. For example, it has been known for decades that the incidence of multiple sclerosis varies by latitude.¹⁵ This geographic pattern may be explained by differences in vitamin D status, with higher incidence of multiple sclerosis at higher latitudes where vitamin D insufficiency is more common.¹⁶ Vitamin D₃ (cholecalciferol) is a vital nutrient available from dietary sources (eg, fortified milk, nutritional supplements), but most is made in the skin after direct exposure to sunlight.¹⁷ It has become clear, especially in the northeastern United States,^{18,19} that a large proportion of Americans have inadequate vitamin D intake, as reflected by serum 25(OH)D levels.²⁰

On the basis of these data, and emerging evidence of an inverse association between vitamin D status and risk of childhood wheezing,⁸ we hypothesized *a priori* that we would find a north-south gradient in anaphylaxis, as reflected by regional differences in filled EpiPen prescriptions. Indeed, residence in the northeastern United States was the strongest independent predictor of EpiPen prescriptions per 1000 persons.

Although measurement of serum 25(OH)D levels is the best available approach to determine vitamin D status,²⁰ average state-specific or region-specific values are not available. Indeed, the measurement of sun exposure itself has proven quite challenging. Epidemiologists who study the relation of sun exposure with skin cancer continue to debate the advantages and disadvantages of self-reported information on regular versus intermittent sun exposure, frequency of sun burns, regularity of sunscreen use, and more.^{12,13} For lack of any better available alternative,

we used melanoma incidence rates as an admittedly crude surrogate measure of sun exposure and the resulting vitamin D levels. Sun exposure generally has a positive association with melanoma risk, but there is some evidence that chronic (regular) sun exposure may actually reduce risk of melanoma.^{12,13} Thus, we recognize the probable limitations of our exploratory analysis. Regardless, we found that melanoma incidence rates had a significant inverse association with EpiPen prescriptions, but that adjustment for melanoma incidence did not eliminate the observed north-south gradient. Other meteorology variables, such as average temperature and precipitation, were not associated with the number of EpiPen prescriptions, but these variables are even more indirect measures of sunlight exposure, let alone vitamin D status.

Laboratory research suggests several potential mechanisms for how vitamin D could affect risk of allergic reactions and anaphylaxis. For example, vitamin D modulates antigen-presenting cells such as macrophages,^{21,22} as well as the generation of regulatory T cells^{23,24} that express potentially inhibitory cytokines (IL-10 and TGF- β), and the ability to inhibit antigen-specific T-cell activation potentially.²⁵ Although many laboratory studies suggest that vitamin D induces a shift in the balance between T_H1 and T_H2-type cytokines toward T_H2 dominance,²⁶ Pichler et al²⁷ found that in CD4⁺ as well as CD8⁺ human cord blood cells, vitamin D not only inhibits IL-12-generated IFN- γ production but also suppresses IL-4 and IL-4-induced expression of IL-13. Thus, the differences between the studies on the T_H1-T_H2 dominance may lie in the timing of exposure of the cells to vitamin D (ie, prenatal versus postnatal); the response of naive T cells to vitamin D exposure may differ from that of mature cells when exposed to vitamin D.²⁸ Another possibility is that the association differs by dose. In other words, nonpharmacologic doses of vitamin D (eg, as obtained from sunlight exposure) may have different consequences than high-dose oral supplementation, where an excess of vitamin D may indeed have opposite effects. These hypotheses merit further investigation.

Our exploratory study has several potential limitations. First, we assume that EpiPen prescriptions accurately reflect the underlying prevalence of anaphylaxis (ie, that geographic locations with higher EpiPen prescriptions have more anaphylaxis). Although the exact nature of the association between EpiPen prescriptions and actual anaphylaxis prevalence is not clear, this approach may be preferable to other more problematic sources of anaphylaxis data.⁴ Accordingly, research on EpiPen prescriptions has been promoted by leading authorities in anaphylaxis epidemiology.⁷ Second, we recognize that there are apparent inconsistencies in the north-south gradient (eg, Why doesn't Alaska have the highest rate?) and there is a suggestion of an east-west gradient across the United States. These inconsistencies are not surprising in an ecologic analysis of US states and, in this case, may reflect differences in dispensing of epinephrine ampules and/or epinephrine-containing inhalers, practice variation without medical explanation, or myriad other factors.

Future studies will need to explore these possibilities in more detail. Third, our study may suffer from the ecologic fallacy, in which individual exposures are not linked with individual outcomes and, therefore, one cannot be certain of the actual associations in individual patients. In our study, we can be confident about the observed regional differences in EpiPen prescriptions but are less confident that the multivariate analysis adequately controlled for the potential confounding factors (eg, socioeconomic factors). For this reason, we encourage additional research to confirm the observed north-south gradient and to uncover the factors that best explain it.

Summary

We observed a surprisingly strong north-south gradient for the prescription of EpiPens in the United States. The southwestern United States (and Hawaii), with its warmer climate and more year-round sunlight, had the least EpiPen prescriptions per 1000 persons, whereas those in the northern United States (especially New England) had the highest rates. The regional differences may result from several different associations, but we were not able to eliminate the finding by adjusting for regional differences in many sociodemographic and healthcare delivery factors. We suggest that these data provide additional support for the hypothesized link between low vitamin D levels and respiratory/allergic disorders.⁸ Given the paucity of data on anaphylaxis risk factors⁷ and ongoing concerns about magnitude of this allergic problem,²⁹ we believe this novel hypothesis merits further study.

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