
Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990–2006

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Background: Although an increase in the occurrence of anaphylaxis has been reported in several parts of the world, this phenomenon has not been described in the United States.

Objective: To characterize anaphylaxis hospitalizations in New York State in patients younger than 20 years.

Methods: Using a statewide administrative database, hospital admissions of patients with an allergic disease (anaphylaxis, angioedema, urticaria, and allergy unspecified) as the primary diagnosis were analyzed from 1990 through 2006 in New York State. Admission rates were calculated for the allergic disease groups, as were hospitalization characteristics. Statistical modeling and group comparisons were performed with the use of negative binomial distribution analysis.

Results: For patients younger than 20 years, the anaphylaxis hospitalization rate increased by more than 4-fold during the study period and by 2002 exceeded the combined hospitalization rates for urticaria, angioedema, and unspecified allergy. After the widespread adoption of food anaphylaxis codes in 1994, food anaphylaxis predominated hospitalizations for anaphylaxis. Peanut was the most common food allergen in food anaphylaxis admissions. The anaphylaxis hospitalization rate for males was significantly greater than that of females (risk ratio, 1.45; 95% confidence interval, 1.26–1.66). Blacks were not disproportionately hospitalized for anaphylaxis. An overall bimodal age distribution showed peaks in the very young and in teens.

Conclusion: These data demonstrate that in a populous Northeastern state in the United States, anaphylaxis requiring hospitalization is increasing in the age group younger than 20 years.

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INTRODUCTION

Anaphylaxis is a potentially life-threatening allergic condition that often results in hospital and/or emergency department admissions. Although an epidemic of asthma manifested with significant increases in hospitalization rates in several countries^{1,2} toward the end of the 20th century, less is known about trends in other allergic conditions such as anaphylaxis. Allergic disorders are thought to have increased in civilized countries in part because of conditions that favor the generation of T_H2 lymphocytes over T_H1 lymphocytes.³ T_H2 helper lymphocytes are associated with a proallergic cytokine profile.^{4,5} Anaphylaxis-related hospitalizations have been reported to be increasing outside the United States^{6,7}; however, some cohorts in the United States have not shown increases in anaphylaxis in emergency department databases⁸ or health maintenance organization (HMO) rosters.⁹ Thus, it is not clear that the United States has been affected by the purported worldwide increase in allergies.¹⁰ Trends in measurable out-

comes for nonasthmatic allergic disease, such as hospitalizations, would, if present, provide evidence for this assertion.

Administrative hospital discharge databases have been used to characterize the prevalence of various hypersensitivity disorders in large populations.^{11,12} In this study, we used the New York State hospitalization database to examine the pattern of hospitalizations related to both food-associated and non-food-associated anaphylaxis in children and young adults because this population is at particular risk for anaphylaxis.¹³

Database Characteristics and Case Selection

The Statewide Planning and Research Cooperative System (SPARCS) database was accessed in the manner prescribed by the New York State Department of Health policies. This database has been described in previously published studies.^{14,15} There is mandatory reporting to this database for all New York State acute care hospitalizations. Each SPARCS patient record contains more than 100 data fields that consist of demographic, clinical, and financial information. These fields include principal and nonprincipal diagnostic fields; procedure codes; race, age, sex, and ethnicity information; hospital characteristics; expected reimbursement; total charges; length of stay; admission; and disposition status. Both *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnoses and *Common Procedural Terminology* codes for each admission are input-

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ted for each record. The SPARCS databases for the years 1990 through 2006 (discharge year) in patients younger than 20 years were queried for ICD-9-CM codes of 995.6 (anaphylaxis due to food), 999.4 (anaphylaxis due to serum), and 995.0 (anaphylaxis not otherwise specified or due to adverse effect of correct medicinal substance properly administered) in the principal diagnosis. This formed the cohort of all hospitalizations principally related to anaphylaxis in younger persons. Admissions in which a nonanaphylaxis allergic disease angioedema (995.1), urticaria (708._), or allergy unspecified (995.3) was the principal diagnosis were also tabulated to compare group characteristics and hospitalization rates. Adverse drug effect diagnoses (E930 through E949, drugs, medicinal and biological substances causing adverse effects in therapeutic use) were also tabulated.

Anaphylaxis Categorization

If any code for anaphylaxis caused by food allergy was present in a given admission, the anaphylaxis associated with that hospitalization was considered to be food related. Otherwise, the anaphylaxis hospitalization was considered as not being food related. Food anaphylaxis admissions due to various food categories were characterized.

Calculation of Hospitalization Rates

The US Census Bureau data were accessed to obtain New York State resident population estimates for the years 1990 to 2006¹⁶ for the age groups of interest. For calculations related to race after 1999, the population estimates based on 5 race categories (white alone or in combination, black alone or in combination, American Indian or Alaskan Native alone or in combination, Asian alone or in combination, and Native Hawaiian/other Pacific Islander or in combination) were used. For the years after 1999, the black alone or in combination population estimates were increased by 3.5% to adjust for the anticipated underreporting of these groups due to differences in the 2000 US Census.¹⁷ These population estimates were used as denominators to calculate hospitalization rates for specific allergic diseases.

Other Clinical Features

Death during the admission was tabulated, as was respiratory or cardiorespiratory arrest, identified by the codes respiratory arrest (799.1) or cardiorespiratory arrest (427.5), hypotension (458), and respiratory failure, which used the code for acute respiratory failure (518.81). Respiratory and resuscitative interventions were also identified and tabulated. The latter were defined by the coding for endotracheal intubation (960.4), mechanical ventilation (967.1), laryngoscopy/tracheoscopy (314.2), continuous positive airway pressure/bilevel positive airway pressure (993.0), cardiopulmonary resuscitation (996.0), or vasopressor administration (00.17). Repeat admission within the same calendar year was also calculated as previously described.¹⁴ The ICD-9-CM code for toxic effect of venom (989.5) was also tabulated in nonprincipal diagnoses. Medicaid and Medicaid HMO as expected reimbursement categories were considered as a single group, and Medi-

care/Medicare HMO hospital charges and length of stay were also characterized.

Analysis of Data

Estimates and modeling¹⁸ of predicted hospitalizations were generated using the GENMOD procedure in SAS statistical software for Windows, version 9 (SAS Institute Inc, Cary, North Carolina) with the negative binomial distribution option.^{19,20} Population at risk, year, and group effects were included in analyzing the SPARCS data. Hospitalization rates were plotted using Excel software (Microsoft Corp, Bellevue, Washington).

RESULTS

General Aspects

There were 1,972 hospitalizations with a principal diagnosis of anaphylaxis for patients younger than 20 years during the study period (Table 1). The next most common allergic disease admission category was urticaria, followed by angioedema. The median age for anaphylaxis was 11 years, which was older than the mean age for the other allergic disease groups. The overall distribution of admission age in the anaphylaxis groups showed peaks in the very young and in teens (Fig 1). A diagnosis of asthma was present in 26.98% of anaphylaxis patients. A lower proportion of the other allergic disease groups had asthma. Forty-one percent of patients with anaphylaxis were female. The proportion of female patients was higher in the other allergic disease groups; 21.96% of anaphylaxis admissions were African American patients. Less than 1% of anaphylaxis admissions had Medicare. Food anaphylaxis coding was not used in the database until 1994. For the years 1994 through 2006, 66.04% of anaphylaxis admissions had food anaphylaxis codes; 1,166 allergy admissions had food anaphylaxis diagnoses, of which 1,155 were in admissions in which anaphylaxis was the principal diagnosis. Only 4 deaths occurred in all patients admitted with anaphylaxis allergic diseases. These were all food anaphylaxis admissions (0.2%), with 1 death each associated with milk, peanut, unspecified food, and tree nut/seed. Two of these 4 deaths had a diagnosis of asthma. After 1993, 6.3% of anaphylaxis admissions without food allergy were associated with cardiorespiratory interventions/resuscitative procedures or with diagnoses of respiratory/cardiopulmonary arrest or respiratory failure. A similar percentage (5.9%) of food allergy-related anaphylaxis admissions for this period was associated with these interventions, procedure, or diagnoses. Adverse drug effect codes were used from 1993 onward, and these codes were present in 25.14% of anaphylaxis admissions for this period. Toxic effect of venom coding was observed in 0.1% of anaphylaxis admissions, 0.76% of urticaria admissions, and 0.64% of angioedema admissions. The median age for anaphylaxis admissions ranged from 8 years in 1995 to 14 years in 1993.

Table 1. Characteristics of Different Allergic Disease Admissions in Patients Younger Than 20 Years

Variable	Anaphylaxis	Angioedema	Urticaria	Allergy unspecified
No.	1,972	626	1,451	292
Female, %	41.38	50.32	45.90	45.55
Black, %	21.96	35.78	21.64	31.85
Median age, y	11	9	6	6
Median LOS, d	1	1	2	1
Asthma, %	26.98	12.62	13.37	8.90
Food anaphylaxis in any diagnosis since 1994, %	66.04	0.41	0.83	0
Urticaria or AE in nonprincipal diagnosis, %	10.75	60.70	54.03	9.59
Cardiorespiratory intervention, %	3.90	2.24	0.07	0.68
Cardiorespiratory arrest, respiratory failure, or hypotension, %	4.06	1.12	0.34	0.34
Death, %	0.20	0	0	0
Additional admission in same calendar year, %	0.96	1.60	0.55	0.68
Median charge, \$	2,617	2,373	2,479	2,132
Medicaid, %	25.65	30.60	37.58	35.54
Adverse drug effect ≥ 1993 , %	25.14	22.56	16.54	21.78

Abbreviations: AE, angioedema; LOS, length of stay.

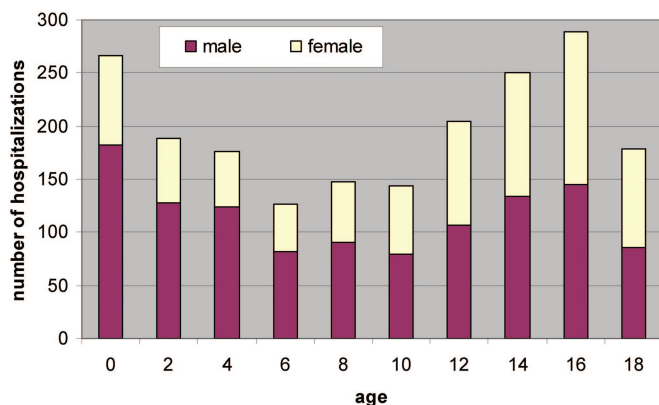


Figure 1. Age and sex distribution of anaphylaxis admissions. Ages are tabulated in 2-year intervals. The first group (0) comprises children younger than 2 years, the second group (2) comprises children 2 years or older but younger than 4 years, and so forth.

Hospitalization Trends

There was a significant group (allergic disease groups) by year effect for allergic disease admissions ($P < .001$). The difference in hospitalization rates for allergic disease groups is illustrated in Figure 2. The change in anaphylaxis admissions over time was different (greater) from that observed for angioedema alone ($P < .001$) and from that observed for angioedema, urticaria, and allergy unspecified, taken together as a comparator ($P < .001$). No covariate effect was observed for age (median age in years), and including age did not abrogate the group by year effects. The hospitalization rate for anaphylaxis was 1.0 per 100,000 in 1990 and increased to 4.7 per 100,000 by 2006. By 2002, the hospitalization rate for anaphylaxis exceeded the combined hospitalization rates for angioedema, urticaria, and allergy unspecified. The hospitalization rate for anaphylaxis was consistently higher for male patients compared with female patients. Statistical analysis

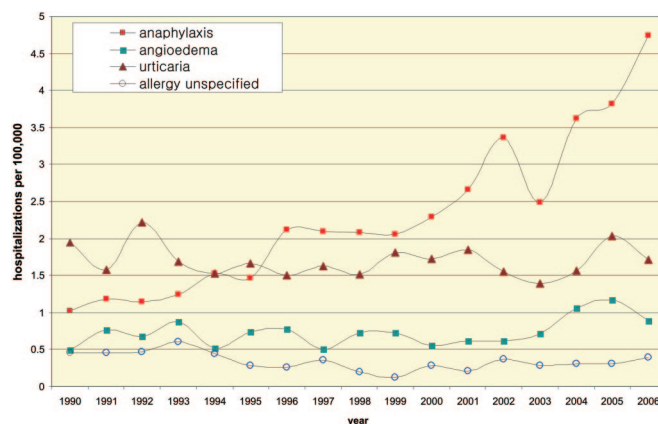


Figure 2. Incidence of hospitalization for various allergic disease categories by year.

confirmed a significant group effect for sex ($P < .001$). The relative risk for male over female anaphylaxis admissions was 1.45 (95% confidence interval, 1.26–1.66). No African American ethnicity effect was observed ($P > .50$). Food anaphylaxis constituted the reason for most anaphylaxis admissions after 1993. In 1994, 53.9% of anaphylaxis admissions were associated with food anaphylaxis codes. Thereafter, the food anaphylaxis proportion ranged from 63.6% (2004) to 74% (1997) of anaphylaxis with a mean of 67.4% (95% confidence interval, 65.3%–67.4%). Graphic representation of food anaphylaxis hospitalizations stratified by sex suggested that anaphylaxis due to food was more prominent in male subjects, whereas nonfood anaphylaxis hospitalization rates did not appear to differ by sex (Fig 3). Admission rates for anaphylaxis associated with adverse drug effect coding were less than 0.1 per 100,000 in 1993 and 1994 and peaked at 0.19 per 100,000 in 2006. Adverse drug coding was not used before 1993. No significant sex difference was

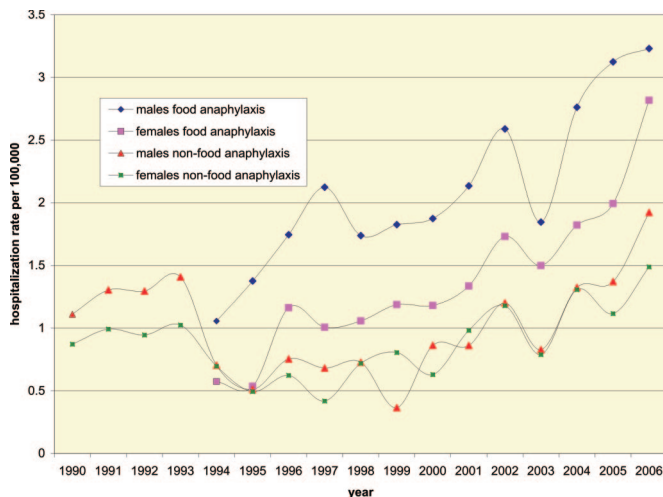


Figure 3. Age-specific hospitalization rate by sex for food and nonfood anaphylaxis.

found in the admission rates for adverse drug effect associated anaphylaxis (data not shown).

Food Anaphylaxis Categories

The food category associated with the greatest number of admissions was peanut ($n = 285$), followed by other specified foods ($n = 274$), tree nuts/seeds ($n = 153$), fish ($n = 124$), and milk ($n = 118$). Crustaceans, unspecified foods, fruits/vegetables, and eggs were associated with 72, 65, 59, and 33 admissions, respectively. Sixty-eight admissions had coding for anaphylaxis due to more than 1 category of food. The least number of admissions was noted for the category of anaphylaxis to food additives ($n = 11$). In 2006, food anaphylaxis admissions percentages were 28.9% for peanut, 24.5% for other specified foods, 12.6% for unspecified foods, 12.0% for tree nuts/seeds, 10.1% for fish, 5.7% for egg, 4.4% for milk, and 4.4% for crustaceans. Age distributions (Fig 4) showed early age peaks for milk and egg and predominantly later age peaks for fish and crustaceans. The other food categories showed more typical bimodal age peaks. The number of cases of peanut and other specified food admissions appeared to be increasing more than the other food groups (Fig 5).

DISCUSSION

This study demonstrates that severe anaphylaxis in younger people is increasing in a populous state in the United States. This pattern of increasing rates of anaphylaxis is similar to that reported in Australia from 1994 through 2005⁸ and in the United Kingdom from 1990 through 2004.⁹ In the Australian report, anaphylaxis admission rates were highest for the youngest age category, and food anaphylaxis admissions in younger people increased at a greater rate than anaphylaxis not related to food. In the United Kingdom, increasing rates of anaphylaxis in both children and adults were observed with similar hospitalization rates for all age groups by 2004. In our

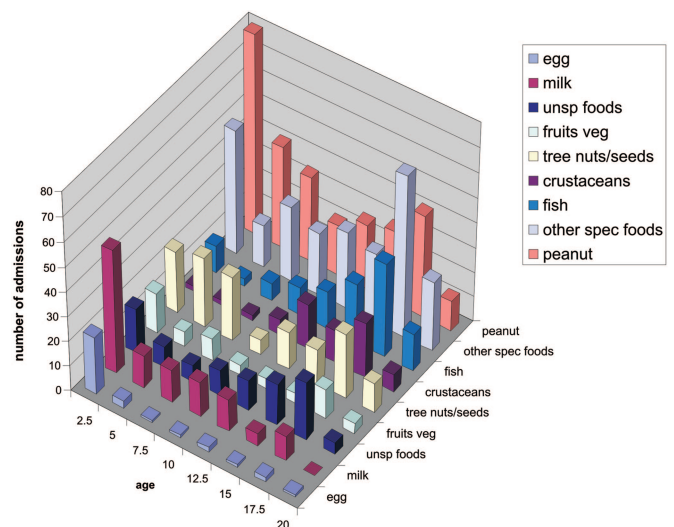


Figure 4. Age distribution for anaphylaxis admission for various food groups. Ages are tabulated in 2.5-year intervals. The first group (0) comprises children younger than 2.5 years, the second group (2.5) comprises children 2.5 years or older but younger than 5 years, and so forth. Spec indicates specific; unsp, unspecified; veg, vegetables.

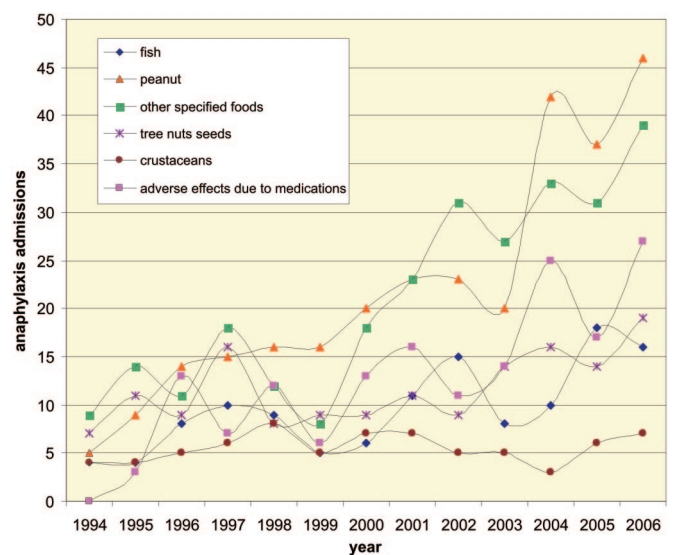


Figure 5. Admission counts for different food groups and for adverse drug effects by year.

present study on the pediatric age group, the increasing food anaphylaxis rates also appeared to drive the observed overall increasing rate of anaphylaxis. It could be argued that the increases in anaphylaxis hospitalizations were due to an increased tendency to admit food allergy cases. However, in the climate of greater managed care scrutiny²¹ in the United States, it seems unlikely that there would be a greater likelihood for admitting anaphylaxis cases of any cause unless the manifestations were severe or prolonged.^{22,23} Another factor

that could affect the rate of hospitalization is the recent expert statement, which called for increased observation time for cases of anaphylaxis.²² However, this is unlikely to account for the changes found in this study because this statement was issued during the last year of the study. Male patients had a greater anaphylaxis hospitalization rate than did female patients, and this difference was most apparent with food-related anaphylaxis. This is in contrast with the observations in England¹¹ during the 1990s, in which female patients had higher anaphylaxis hospitalization rates than did male patients. In a previous study on childhood asthma hospitalizations in New York State, we also observed a higher hospitalization for male patients.¹³ This would appear to be consistent with the observations in other countries^{6,24,25} that allergy in younger people may be more prevalent in male patients. Unlike our findings in asthma,¹³ however, we did not observe an ethnic difference in anaphylaxis hospitalization rates.

Peanut as the major food associated with food anaphylaxis admissions underscores the importance of this single allergen.²⁶ The second most common category was, however, other specified food, for which the name of the food was not recorded. The development of more precise coding for food anaphylaxis in the future may allow for identification of the types of allergens that related to these admissions, which accounted for nearly a quarter of all food anaphylaxis admissions. The present *ICD-9-CM* coding used in the SPARCS database includes minor food allergens such as food additives,²⁷ which, in this study, only accounted for less than 1% of food anaphylaxis admissions. Coding for more common allergens such as soybean/other legumes and wheat²⁸ might be more helpful.

Also of interest is the teenage peak pattern observed with many food allergen admissions. Although the development of the gastrointestinal immune system and oral tolerance^{26,29} may explain why an early age peak occurs for certain foods, the causes for a later age peak in the teen years are not known. Differential distributions of age in younger people could not account for this because the difference between the most populous and least populous single-year age groups is relatively small within the younger than 20 years population.¹⁶ Social^{30,31} or hormonal factors could hypothetically play a role. The fact that teens appear to have an increased prevalence of food allergies points toward a possible need for education of teens regarding food allergy,^{30,31} as well as possible targeting for preventive and/or developing treatments such as antiallergic medication and/or tolerizing vaccines^{32,33} in this age group.

There are difficulties in describing the epidemiology of anaphylaxis, some of which relate to the lack of sensitive biomarkers and differences in defining the condition.²² In a United Kingdom study reported by Peng and Jick,³⁴ the incidence of anaphylaxis was estimated to be 8.4 per 100,000 person-years during the period of 1994 through 1999. In this report, cases with only urticaria were considered mild anaphylaxis. A recent anaphylaxis symposium suggested work-

ing criteria,²² wherein dermal manifestations alone are inadequate to diagnose anaphylaxis with high likelihood. Thus, the anaphylaxis incidence may have been overestimated in this United Kingdom study. However, in Switzerland³⁵ from 1996 to 1998, the rate of anaphylaxis was estimated at 7.9 to 9.6 per 100,000, which is similar to that observed in the United Kingdom study. Estimates of the rates of anaphylaxis in the United States are imprecise, with national prevalence rates varying by more than 10-fold between low and high estimates (1.21%–15.04%).³⁶ Furthermore, some anaphylaxis epidemiology studies are based on samples with very limited numbers of patients,³⁷ whereas others have limited geographic^{38,39} or temporal⁴⁰ scope. Considering that the present study did not include emergency department anaphylaxis patients (in which most anaphylaxis cases probably would be encountered) who were not hospitalized and that studies^{36,38,48} have shown that only a few (3% to 33%) anaphylaxis patients presenting to North American emergency departments are admitted, we conservatively estimate an emergency department anaphylaxis rate for New York State (assuming the highest 33% admission rate from the emergency department) in 2006 to be 14 per 100,000 population for younger patients.

A recent study⁴¹ showing high rates of epinephrine prescriptions in northern states of the United States may have relevance to the increasing anaphylaxis hospitalizations in New York State observed in the present study. It has been hypothesized that relative vitamin D deficiency relates to increased anaphylaxis rates in northern latitudes.⁴² Mulla and Simon³⁸ calculated anaphylaxis rates in Florida during the year 2001. Using a more liberal definition of anaphylaxis, they calculated an anaphylaxis admission rate for persons younger than 20 years to be less than 2 per 100,000. In New York, the admission rate for this age group was 2.66 per 100,000 for the same year. Studies of anaphylaxis hospitalization rates on a US national level are needed to confirm whether higher rates of anaphylaxis hospitalizations mirror higher rates of epinephrine prescriptions in the northern latitude states (such as New York State) because epinephrine prescriptions are believed to overestimate anaphylaxis incidences.⁴³

There are limitations of this study that relate to the database structure and the retrospective nature of the investigation. For example, only the clinical manifestations of anaphylaxis that have codes (eg, hypotension or angioedema) can be evaluated, and this would only be possible if the codes were actually inputted.⁴⁴ Thus, it is difficult to accurately evaluate the severity of anaphylaxis or to ascertain the diagnostic accuracy for each admission. Coding accuracy is also a limitation of the study. For example, the attribution of anaphylaxis to specific causes (such as food) is dependent on history without confirmatory data. Nevertheless, the marked overall increase in anaphylaxis hospitalization rates for younger people in New York State appears to be consistent with the concept of anaphylaxis being the latest allergy epidemic.²⁸

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