

Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012

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Background: Studies from the United Kingdom, the United States, and Australia have reported increased childhood food allergy and anaphylaxis prevalence in the 15 years after 1990. **Objective:** We sought to examine whether childhood food allergy/anaphylaxis prevalence has increased further since 2004-2005.

Methods: We examined hospital anaphylaxis admission rates between 2005-2006 and 2011-2012 and compared findings with those from 1998-1999 to 2004-2005.

Results: Overall population food-related anaphylaxis admission rates (per 10⁵ population per year) increased from 4.5 in 2005-2006 to 8.2 in 2011-2012 (a 1.5-fold increase over 7 years). The highest rates occurred in children aged 0 to 4 years (21.7 in 2005-2006 and 30.3 in 2011-2012, a 1.4-fold increase), but the greatest proportionate increase occurred in those aged 5 to 14 years (5.8-12.1/10⁵ population/y, respectively, a 2.1-fold increase) compared with those aged 15 to 29 years and 30 years or older (a 1.5- and 1.3-fold increase, respectively). Not only did absolute food-related anaphylaxis admissions increase, but the modeled year-on-year rate of increase in overall food-related anaphylaxis admissions also increased over time from an additional 0.35 per 10⁵ population/y in 1998-1999 (all ages) to 0.49 in 2004-2005 and 0.63 in 2011-2012 ($P < .001$).

Conclusions: Food-related anaphylaxis has increased further in all age groups since 2004-2005. Although the major burden falls on those aged 0 to 4 years, there is preliminary evidence for a recent acceleration in incidence rates in those aged 5 to 14 years. This contrasts with the previous decade in which the greatest proportionate increase was in those aged 0 to 4 years. These findings suggest a possible increasing burden of disease

among adolescents and adults who carry the highest risk for fatal anaphylaxis. (*J Allergy Clin Immunol* 2015;■■■:■■■-■■■.)

Key words: Food allergy, anaphylaxis, epidemiology

In the absence of large-scale historical epidemiologic studies to provide baseline data, evidence of changing food allergy (FA) prevalence has been based on surrogate markers, such as hospital anaphylaxis admission rates,¹⁻⁴ changes in outpatient case mix load,^{1,5-8} and rates of prescriptions for allergy-related medication.⁹ In the United Kingdom (UK) anaphylaxis admission rates increased from 0.5 to 3.6 per 10⁵/population/y between financial years 1991 and 2001.² In the United States total population anaphylaxis admission rates increased almost 5-fold in New York from 1 to 4.7/10⁵ population/y between 1990 and 2006; 66% were attributed to FA, with peanut the most common trigger.³ A more recent American study described a doubling in total pediatric (defined as age <18 years) FA-related anaphylaxis admissions from 1085 per year in 2000 to 2253 per year in 2009 or when expressed as a proportion of total hospital admissions from 5.99 to 12.57 per 10⁵ hospital admissions over the same period.⁴

In Australia (using a mixture of International Classification of Diseases, 9th revision [ICD-9], and International Classification of Diseases, 10th revision [ICD-10] codes) we demonstrated that not only did Australia have the highest documented total population anaphylaxis admission rates compared with the UK and United States but that these admissions more than doubled in the overall population from 3.6 to 8.0/10⁵ population/y between the financial years ending June 1994 and 2005 almost entirely because of the 5.5-fold increase in FA-related anaphylaxis admissions observed in children aged 0 to 4 years, which increased from 4.1 to 19.7/10⁵ population/y over that period.^{10,11}

By using the same methodology examining Australian national hospital morbidity data, the aims of the current study were to determine whether anaphylaxis admissions have continued to increase in Australia since 2004-2005. Our specific interest was to examine whether rates of early childhood food-related anaphylaxis might also have continued to increase, whether they are increasing at the same rate, and whether a greater burden of anaphylaxis might be observed in older children as those born in 2000-2004 (infants aged 0-4 years in the previous cohort) have grown older.

METHODS

Hospital anaphylaxis admissions data

Australian National Hospital Morbidity Database principle diagnosis data cubes were obtained from the Australian Institute of Health and Welfare (AIHW).¹² These record primary (and important secondary) discharge hospital diagnoses based on ICD-10 codes¹³ for each financial year (July to June; eg, 1998-1999 denotes the period July 1998 to June 1999). Previous Australian studies of hospital anaphylaxis admission rates combined data derived from

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Abbreviations used

AIHW: Australian Institute of Health and Welfare
 FA: Food allergy
 ICD-9: International Classification of Diseases, 9th revision
 ICD-10: International Classification of Diseases, 10th revision
 UK: United Kingdom

ICD-9 codes (between 1993-1994 and 1997-1998) and ICD-10 codes (between 1998-1999 and 2004-2005).^{1,10,11} For consistency of analysis in this study, our data source was the period when ICD-10 codes were in use (1998-1999 to 2011-2012). This allowed direct comparison of admission rates over the 7 years between 1998-1999 and 2004-2005 with the 7 years spanning 2005-2006 to 2011-2012. We examined hospital admissions associated with FA (T78), serum-related anaphylaxis (T80.5), anaphylaxis otherwise unclassified (T78.2), and anaphylactic shock caused by adverse effects of drugs properly administered (T88.6). Sting-related anaphylaxis was excluded because ICD codes do not clearly distinguish between anaphylaxis and other adverse reactions (eg, toxicity). Hospital admissions attributed to conditions that might mimic or be mistaken for anaphylaxis, such as combined urticaria (L50) and angioedema (T78.3) and combined asthma (J45) and status asthmaticus (J46), were also examined separately. Discharge diagnoses were expressed as age-specific rates/10⁵ population by using a combination of AIHW and Australian Bureau of Statistics data, as previously described,¹ to facilitate comparison between different age groups (and evaluate time trends). Data were collapsed into age bands of 0 to 4, 5 to 14, 15 to 29, and greater than 30 years for data to be comparable with those of previous Australian studies.^{1,10} Age-specific admission rates were calculated by using the Australian Bureau of Statistics national population estimates for each calendar year¹⁴ and the AIHW discharge rates ending in the same calendar year.

Ethics approval

The Human Research and Ethics committee of Calvary Bruce/Calvary John James Private Hospitals approved the study.

Statistical analysis

A modified form of Poisson regression was used to estimate the annual increase in admission rates as a percentage of a changing population. If there are Y_T cases in year T , then the desired model is as follows:

$$E[Y_T/N_T] = \alpha + \beta T,$$

where N_T is the population. This can be expressed as follows:

$$E[Y_T] = \alpha N_T + \beta (N_T T),$$

a regression model with no intercept. Then the parameter β is the annual increase in cases per unit population (we used rates per 10⁵ persons). Here $(N_T T)$ is a constructed variable obtained by multiplying the population size N_T by the year number T . For numeric stability, we defined T as the year minus 2000. Because Y values are observed count data, we fitted a Poisson model but with an identity link function in place of the usual log link. Because the population N_T appears explicitly in the model, an offset is not required. The quadratic term $\gamma(N_T T^2)$ was added to measure any acceleration in per capita admissions: then the annual rate of increase in year T is the derivative (ie, $\beta + 2\gamma T$). Analysis was undertaken using the glm command in Stata version 12 (StataCorp, College Station, Tex).

RESULTS**Hospital admissions data for allergic conditions from 1998-1999 to 2011-2012**

The number of admissions to Australian hospitals recorded for anaphylaxis, asthma, and urticaria/angioedema between July

1998 and June 2012 are summarized in [Table I](#). Over that period, total population hospital anaphylaxis admission rates per 10⁵ population increased from 6.3 in 1998-1999 to 10.6 in 2004-2005 (a 1.7-fold increase over 7 financial years), with a further 1.5-fold increase from 12.2 in 2005-2006 to 17.7 in 2011-2012 over the next 7 financial years ([Table II](#)). In the more recent reporting period of 2005-2006 to 2011-2012, anaphylaxis triggers were coded as attributed to food, "unclassified," medication, or serum, with age-related variations in cause ([Fig 1, A](#), and [Table II](#)). The number of FA-related anaphylaxis admissions as a proportion of total anaphylaxis admissions increased over time in all age groups, most prominently in those aged 5 to 14 and 15 to 29 years ([Fig 1, B](#)). By contrast, admission rates (absolute numbers and rates per 10⁵ population) were relatively flat for urticaria/angioedema and decreased for asthma ([Tables I and II](#)).

Anaphylaxis admissions by age group from 1998-1999 to 2011-2012

The highest total anaphylaxis admission rates were observed in children aged 0 to 4 years ([Fig 2](#) and [Table II](#)). By contrast, the greatest fold increases from 2005-2006 to 2011-2012 were observed in the next age cohort of 5 to 14 years, in which admissions increased 2.0-fold compared with a 1.5-fold increase for the overall population, with comparable 1.3- to 1.5-fold increases in the other age groups. The same pattern was observed for FA-related anaphylaxis in the 5- to 14-year age group: a 2.1-fold increase between 2005-2006 and 2011-2012 compared with a 1.5-fold increase in the overall population or 1.3- to 1.5-fold increases in the other age groups. When unclassified anaphylaxis and medication-related anaphylaxis were examined, the only substantial fold increases from 2005-2006 to 2011-2012 were observed in those aged 5 years or greater. By contrast, no significant changes were seen in serum-related anaphylaxis in any age group ([Table II](#)).

Total and food-related anaphylaxis admissions as a proportion of total admissions

The changes observed were not an artifact of changing total hospital admission rates. Total and food-associated anaphylaxis admissions actually increased as a proportion of all hospital admissions between 1998-1999 and 2011-2012 in the total population, as well as in all age groups examined, most prominently in the younger age groups ([Fig 3, A and B](#)). Urticaria/angioedema admission rates as a proportion of all hospital admissions increased modestly over the same time period in those aged 0 to 4 and 5 to 14 years but were relatively steady in other age groups ([Fig 3, C](#)). By contrast, asthma admissions decreased in absolute and relative terms in all age groups ([Fig 3, D](#)).

Acceleration in the rate of increase in anaphylaxis admissions

When we examined whether the rate of increase in anaphylaxis admissions was constant or changing over time, we found a highly significant acceleration of incidence in total anaphylaxis and FA-related anaphylaxis admissions ([Fig 4](#) and [Table III](#)). The modeled year-on-year rate of increase in overall total anaphylaxis admissions also increased over time from an additional 0.59 per 10⁵ population/y in 1998-1999 (all ages) to 0.83 (2004-2005) and 1.11 (2011-2012, $P < .001$), with age-specific changes significant

TABLE I. Number of hospital admissions for allergic conditions: 1998-1999 to 2011-2012

Hospital admissions	July 1998-June 2005 (7 y)	July 2005-June 2012 (7 y)	Total (14 y)
Anaphylaxis			
Food	4,133	9,941	14,074
Unclassified	4,343	6,625	10,968
Medication	2,989	5,331	8,320
Serum	100	160	260
Total	11,565	22,057	33,622
Asthma	303,546	264,701	568,247
Urticaria/angioedema	20,847	24,869	45,716

Admissions to Australian hospitals between July 1998 and June 2012 for anaphylaxis, asthma, and urticaria/angioedema.

only in those aged 5 to 14 and 15 to 29 years. The modeled year-on-year rate of increase in overall FA-related anaphylaxis admissions also increased over time from an additional 0.36/10⁵ population/y in 1998-1999 (all ages) to 0.48 (2004-2005) and 0.62 (2011-2012, $P < .001$). Age-specific changes were again only significant in those aged 5 to 14 and 15 to 29 years.

DISCUSSION

Consistent with other studies in Australia,^{1,10,11} the UK,² and the United States,⁴ we confirmed a 1.7-fold increase in overall anaphylaxis admissions in Australia in the 7 years between 1998-1999 and 2004-2005 by reanalyzing data using ICD-10 codes alone for consistency. Importantly, we now report a further 1.5-fold increase in overall anaphylaxis admission rates and a 1.5-fold increase in FA-related anaphylaxis admissions in the subsequent 7 years between 2005-2006 and 2011-2012, which is consistent with more recent studies from the UK,¹⁵ Italy,¹⁶ and the United States.¹⁷ With the exception of increases in medication-related anaphylaxis in those aged 30 years or more, most of this change was driven by the increase in cases attributed to FA. Although our data provide indirect surrogate evidence that FA and anaphylaxis have continued to increase over the last decade, our conclusions are also supported by similar findings in community-based studies in Australia,^{1,18} the UK,^{7,8} and the United States.^{5,6} As with previous observations, asthma-related admissions decreased over the period of observation,¹⁹ but in contrast to older studies,² admissions related to urticaria/angioedema appear to have stabilized. The highest anaphylaxis admission rates are still seen in those aged 0 to 4 years, yet the highest fold increase has now shifted to older children aged 5 to 14 years, in whom the rate of increase is accelerating. Furthermore, this age group also has the highest proportion of all hospital admissions attributable to anaphylaxis. These observations contrast with the previous decade when both the highest anaphylaxis admission rates and the greatest rate of increase were observed in those aged 0 to 4 years.^{1,10,11} These data suggest a possible cohort effect with a continuing increase in the rate of FA-related anaphylaxis admissions for the cohort previously aged 0 to 4 years and now aged 5 to 14 years, as one might expect as those with FA to triggers like peanut/tree nut allergy grow older. Our observations are not merely an artifact of increases in overall hospital admission rates: pediatric food-related anaphylaxis admissions as a proportion of total admissions actually increased over time and were found to be substantially higher than comparable United States-derived data, particularly in the youngest 0- to 4-year age group.⁴

TABLE II. Hospital admission rates for allergic conditions from 1998-1999 to 2004-2005 and from 2005-2006 to 2011-2012

Age group (y)	Observed cases per 10 ⁵ population (fold increase from previous time point)			
	1998-1999	2004-2005	2005-2006	2011-2012
All anaphylaxis				
All ages	6.3	10.6 (1.7)	12.2	17.7 (1.5)
0-4	9.0	19.5 (2.2)	26.4	35.1 (1.3)
5-14	3.9	6.9 (1.7)	9.0	17.8 (2.0)
15-29	6.9	11.3 (1.6)	12.4	18.8 (1.5)
≥30	6.4	10.3 (1.6)	11.3	15.4 (1.4)
Food anaphylaxis				
All ages	2.0	4.5 (2.2)	5.6	8.2 (1.5)
0-4	7.3	16.7 (2.3)	21.7	30.3 (1.4)
5-14	1.7	3.7 (2.1)	5.8	12.1 (2.1)
15-29	2.6	6.1 (2.4)	6.7	10.3 (1.5)
≥30	1.3	2.8 (2.1)	3.4	4.3 (1.3)
Unclassified anaphylaxis				
All ages	2.8	3.5 (1.2)	3.5	5 (1.4)
0-4	1.5	2.4 (1.6)	3.9	0.4 (0.1)
5-14	1.5	2.7 (1.8)	2.5	8.3 (3.3)
15-29	2.9	3.7 (1.3)	3.7	9.2 (2.5)
≥30	3.5	3.7 (1.1)	3.6	14.8 (4.1)
Medication anaphylaxis				
All ages	1.4	2.6 (1.8)	3.1	4.3 (1.4)
0-4	0.2	0.2 (1.0)	0.6	0.1 (0.2)
5-14	0.5	0.3 (0.4)	0.6	2.4 (4.0)
15-29	1.4	1.4 (1.0)	2.1	4.9 (2.3)
≥30	1.8	3.8 (2.1)	4.2	16.4 (3.9)
Serum anaphylaxis*				
All ages	0.06	0.09	3.0	0.15
0-4	0	0.2	1.0	0.03
5-14	0	0.2	0	0.2
15-29	0.02	0.05	8.0	0.3
≥30	0.06	0.07	12	0.4
Asthma				
All ages	286.6	185.7 (0.6)	185.4	170.2 (0.9)
0-4	1345.5	1020.4 (0.8)	1084.2	892.2 (0.8)
5-14	454.5	279.8 (0.6)	270.6	295.5 (1.1)
15-29	193.9	99.2 (0.5)	92.2	81.1 (0.8)
≥30	155.1	105.8 (0.7)	103.6	96.8 (0.9)
Urticaria/angioedema				
All ages	14.1	16.7 (1.2)	17.9	16.0 (0.9)
0-4	28.4	32.2 (1.1)	36.1	38.5 (1.1)
5-14	10.2	10.3 (1)	11.4	13.6 (1.2)
15-29	11.1	13.4 (1.2)	13.7	11.0 (0.8)
≥30	14.3	17.3 (1.2)	18.5	15.8 (0.9)

Anaphylaxis admission rates (per 10⁵ population) were calculated for total anaphylaxis admissions, as well as those related to food, "unclassified," medication, or serum and compared with those related to asthma or urticaria/angioedema.

*Fold changes were not calculated for serum anaphylaxis because of low numbers.

As with similar studies reliant on hospital-derived admissions data, potential shortcomings of our study are the possible influence of coding errors, variations in patient health-seeking behavior, or access to hospital services or hospital admission policies, as previously discussed.^{1,4,15} Importantly, financial barriers are unlikely to have influenced admissions data; Australian public hospital emergency department and inpatient treatment is free. Furthermore, the fact that only a small proportion of infants with FA/food-related anaphylaxis presentations are admitted to the hospital in Australia²⁰ suggests that patients with relatively minor symptoms are more likely to be classified as having urticaria (and discharged) rather than anaphylaxis

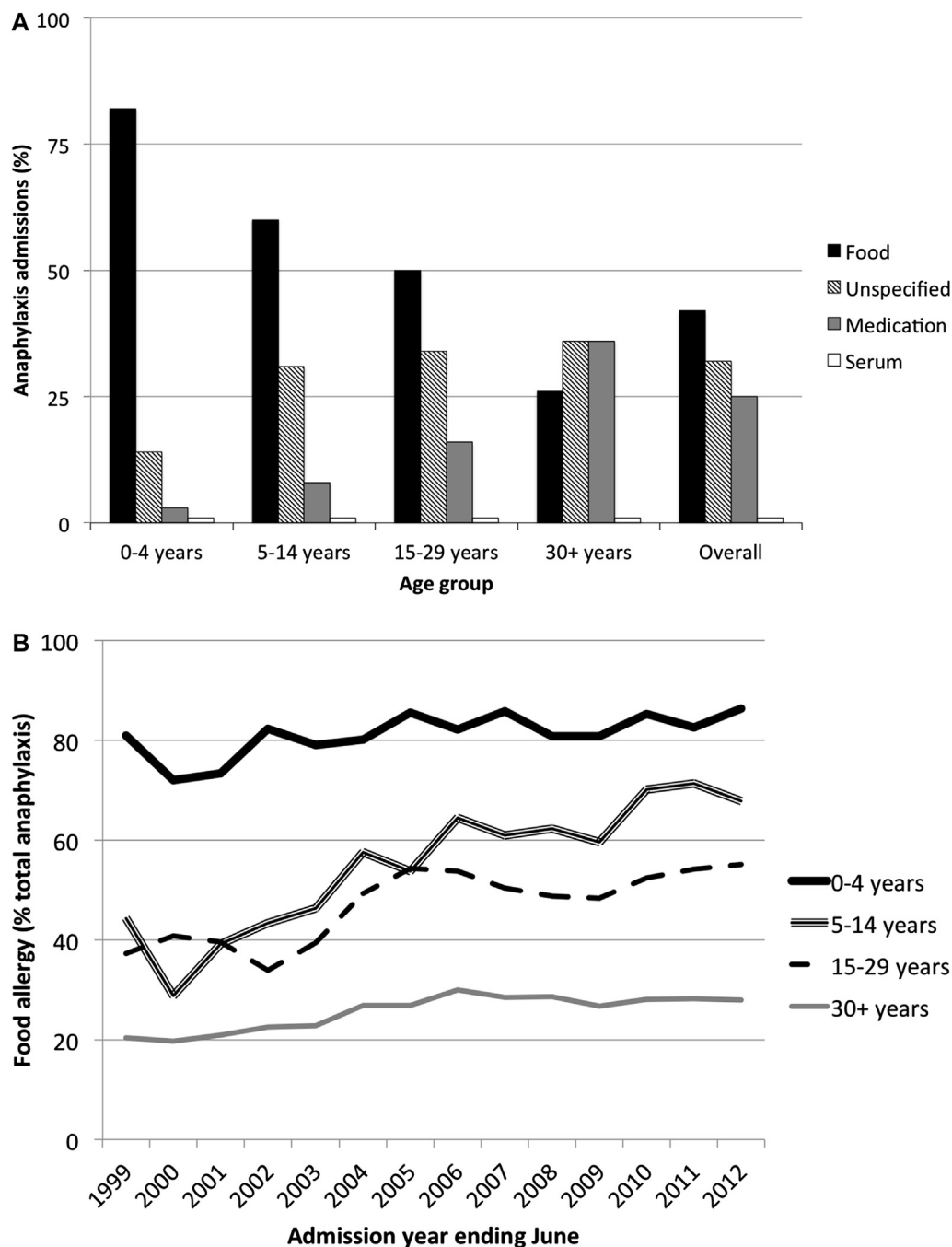


FIG 1. Cause of anaphylaxis admission by age group: 1998-1999 to 2011-2012. **A**, Anaphylaxis admissions by attributed cause and age group. **B**, Time trends for food-associated anaphylaxis as a proportion of total admissions by age group.

(and admitted) and coded accordingly. Although it could be argued that the admissions data available to us do not distinguish between single and multiple admissions for the same patient, the relative infrequency of recurrent anaphylaxis in one Australian follow-up study²¹ and limited data from one Italian study¹⁶ suggest that the majority of admissions recorded are for single patient admissions. Finally, it is also conceivable that our findings might reflect the fact that allergic subjects experience reactions of greater severity during later childhood and adolescence (compared with milder reactions in young children <5 years

old) rather than an increase in FA prevalence over time. Taken as a whole, however, the consistent increases in anaphylaxis admission rates in all age groups (and from all causes) suggest that our data reflect a true increase in FA and anaphylaxis over the last 7 years and that differential age-related admission rates reasonably reflect age-related differences in incidence.

During the 7 years since 2005-2006, the fold increases in total anaphylaxis admission rates in those aged 0 to 4 years, 15 to 29 years, and 30 or more years were similar to the overall population increase (1.5-fold), but we noted a greater 2.0-fold

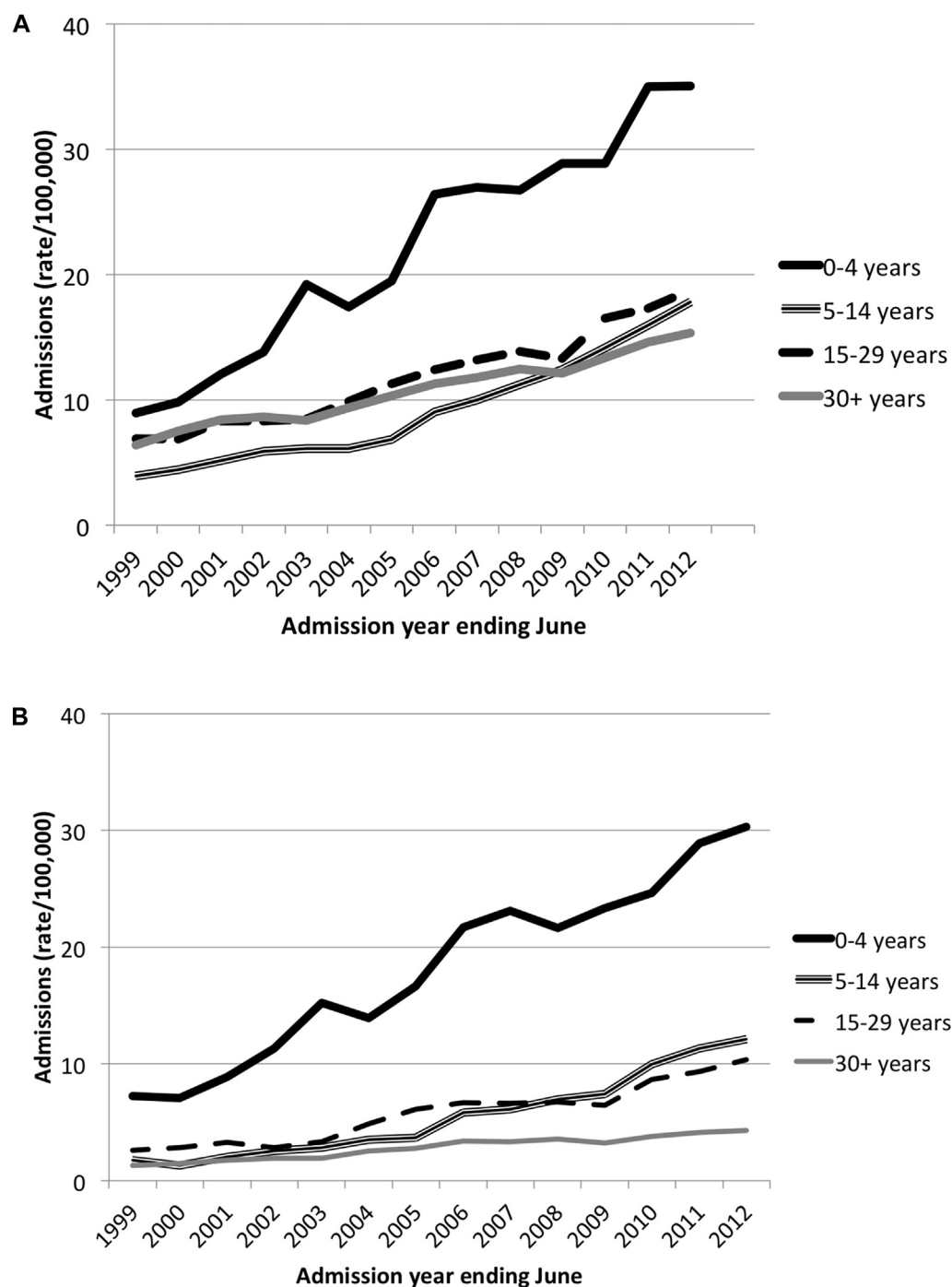


FIG 2. Australian hospital morbidity data: 1998-1999 to 2011-2012. Age-specific admission rates to Australian hospitals (per 10^5 population per year) for total anaphylaxis (**A**) and food-related anaphylaxis (**B**) are shown.

increase in older children aged 5 to 14 years. FA-related anaphylaxis admissions showed similar trends: a 2.1-fold increase in those aged 5 to 14 years compared with the overall population (1.5-fold). This suggests a possible cohort effect with a spreading of the burden of anaphylaxis (and FA-related anaphylaxis in particular) to include older children and teenagers (possibly representing those born 2000-2004 who have grown older) in addition to those currently aged less than 5 years. Other potential contributors to these changes in rates of anaphylaxis

admissions include *de novo* allergy development in subjects aged 5 to 14 years, although allergy to important persistent triggers, such as peanut, is usually established very early in life.^{16,22} It is also conceivable that some of the acceleration in rates of increase in this age group might be secondary to increased severity of reactions in those with established disease. Because it is known that adolescents experience higher rates of more serious reactions than younger patients with FA,¹⁸ a potential contributor to the data might be development of more serious reactions in

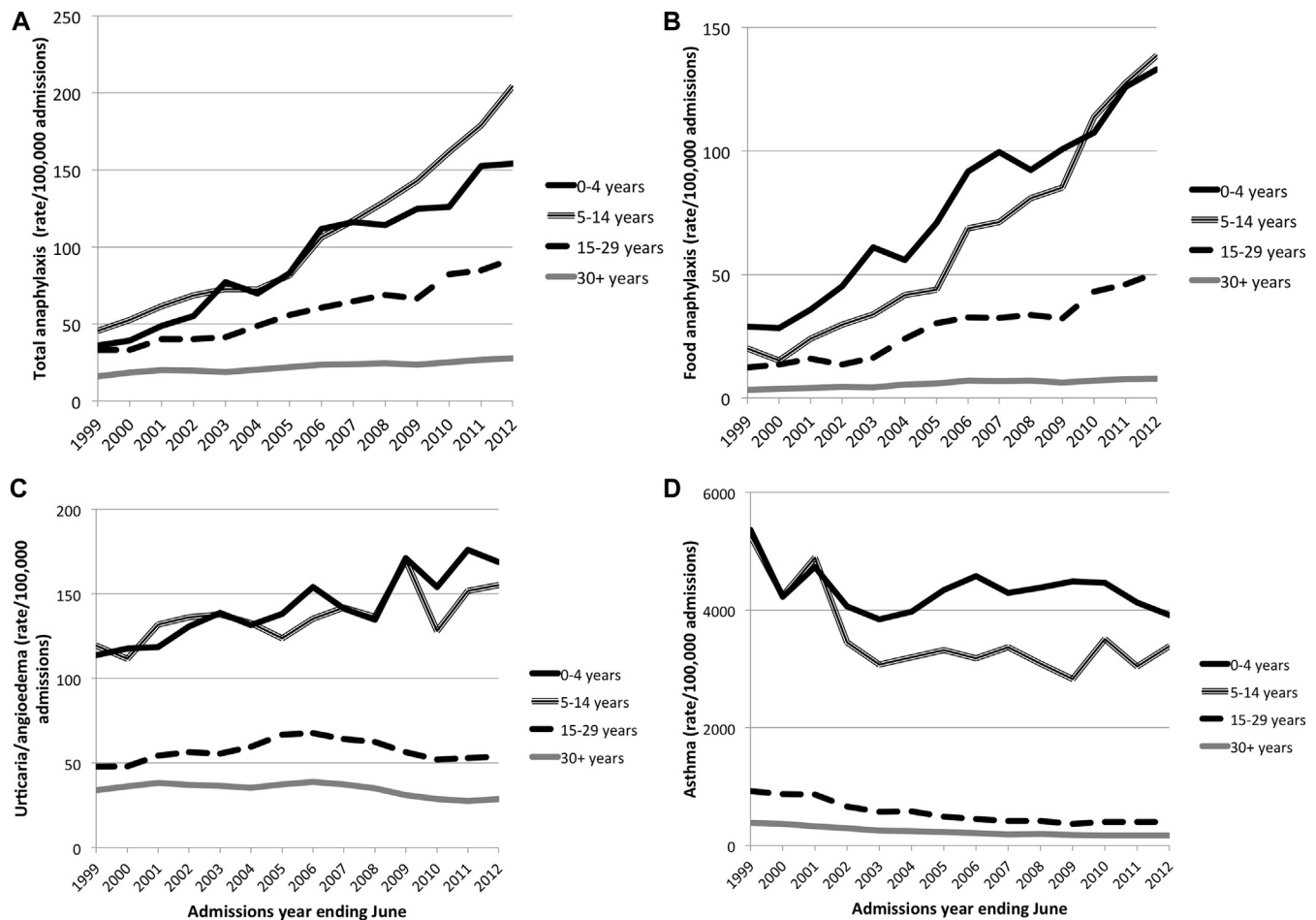


FIG 3. Australian hospital morbidity data: 1998-1999 to 2011-2012. Relative rates of admission (per 10^5 total admissions) for total anaphylaxis (A) and food-related anaphylaxis (B), urticaria/angioedema (C), and asthma (D) are shown.

patients as they age and move from the less than 5-year age group to the 5- to 14-year age group. Accepting that there are various potential reasons for a greater acceleration in rates of anaphylaxis among patients aged 5 to 14 years, our findings raise concern that in the future, these changes will flow on to higher rates in older cohorts, with potential implications for health care resource planning and perhaps FA-related mortality rates. If the anaphylaxis admission trends truly reflect FA prevalence in Australia, then our data contrast with apparent plateauing in the incidence of peanut allergy by birth year on the Isle of Wight, where the incidence in those born in 1994-1996, 1989, and 2001-2002 was estimated at 0.5%, 1.4% and 1.2%, respectively.⁸ It is conceivable that there might eventually be a point of saturation in which the majority of those who are predisposed to FA have the condition, but our data suggest that this point has not yet been reached in Australia.

When reviewing data related to time trends in unclassified anaphylaxis, it is important to be aware that this does not represent idiopathic anaphylaxis but rather cases in which a cause has not been attributed in hospital coding data. This is of particular relevance in children aged 0 to 4 years in whom a decrease in unclassified anaphylaxis from 2005-2006 to 2011-2012 was accompanied by a parallel increase in cases attributed to FA. In interpreting time trends for medication-related

anaphylaxis (overall population increase with transient decreases only in those aged 0-4 and 5-14 years), the data cannot be interpreted with confidence in the younger age groups given the small numbers between 1998-1999 and 2011-2012 (102 cases at 0-4 years and 201 cases at 5-14 years compared with 1174 cases at 15-29 years and 6763 cases at ≥ 30 years). By contrast, there was a clear increase in medication-related anaphylaxis in older subjects (ie, age ≥ 30 years). Although the reasons for these observations remain uncertain, previous sensitization and greater exposure to medications, such as antibiotics, nonsteroidal anti-inflammatory medications, or anesthetic agents, are all potential contributing factors. Importantly, our observations are consistent with case series in which most fatalities occur in older patients.^{11,15,17,23}

Although the explanation underlying increases in FA and FA-related anaphylaxis remain uncertain, risk factors are starting to emerge. These might include differential exposure to environmental risk factors, perhaps causing inheritable epigenetic changes by activating or silencing genes important to immune regulation.^{24,25} Evidence in favor of the hygiene hypothesis, for example, includes lower risk of egg allergy in those exposed to older siblings or an indoor dog at home in the first year of life but not cesarean section delivery, antibiotic use in infancy, child-care attendance, or maternal age.²⁶

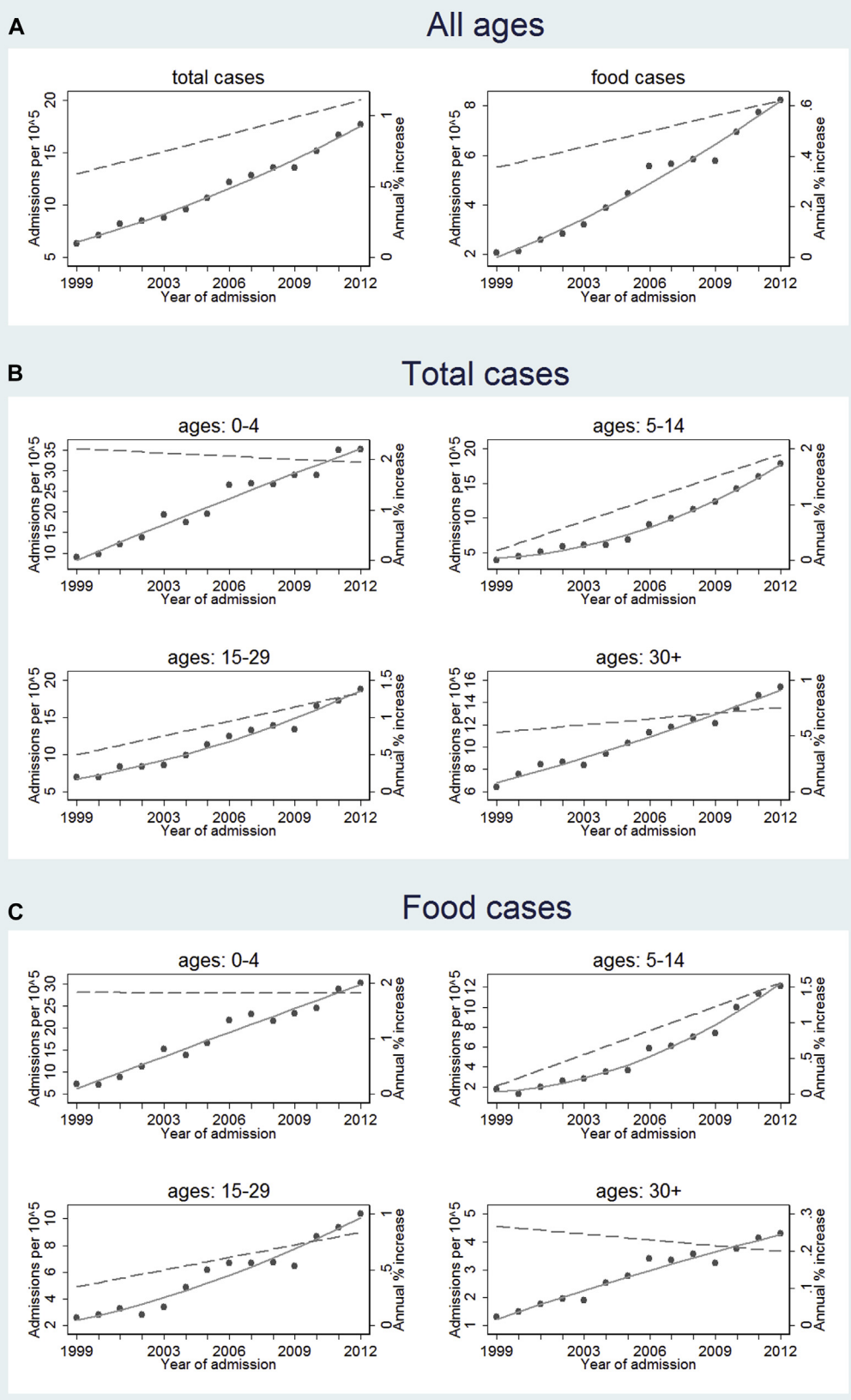


FIG 4. Australian hospital morbidity data: 1994-1995 to 2011-2012. Dots and fitted curve (left axis) show annual admission rates per 100,000 persons. Dashed lines (right axis) fitted annual increase in admission rate (because the model is quadratic, the rate of increase changes linearly over time). **A**, All ages: total and food-related anaphylaxis. **B**, Age-specific changes in total anaphylaxis. **C**, Age-specific changes in food-related anaphylaxis.

TABLE III. Changes in age-specific anaphylaxis admission rates

Age group (y)	Average annual increase in cases per 10 ⁵ persons*	Smoothed instantaneous annual rate of increase per 10 ⁵ population in July 1998, 2005, and 2012, respectively (quadratic model)
All anaphylaxis admissions	$P < .001$ between ages†	
All ages	0.83 (0.01 [0.80-0.86])	0.57, 0.85, 1.13; $P < .001$
0-4	2.09 (0.08 [1.94-2.24])	2.22, 2.08, 1.93; $P = .63$
5-14	0.94 (0.03 [0.88-1.01])	0.11, 1.04, 1.97; $P < .001$
15-29	0.89 (0.03 [0.82-0.95])	0.46, 0.91, 1.36; $P = .001$
≥30	0.64 (0.02 [0.60-0.68])	0.52, 0.66, 0.77; $P = .10$
Food-related anaphylaxis admissions	$P < .001$ between ages†	
All ages	0.47 (0.01 [0.46-0.49])	0.35, 0.49, 0.63; $P < .001$
0-4	1.82 (0.07 [1.68-1.96])	1.83, 1.82, 1.81 [sic]; $P = .98$
5-14	0.71 (0.02 [0.67-0.76])	0.06, 0.84, 1.62; $P < .001$
15-29	0.57 (0.02 [0.52-0.61])	0.33, 0.59, 0.86; $P < .003$
≥30	0.24 (0.01 [0.22-0.26])	0.27, 0.23, 0.20; $P = .32$

Linear (constant rate) and quadratic (changing rate) models were fitted to each age group and used to estimate rates of increase in annual admissions for total anaphylaxis admissions and food-related anaphylaxis admissions.

*Estimated from a linear model (ie, assuming no trend in rate): estimate (SE [95% CI]).

†Likelihood ratio tests comparing models with common and with distinct slopes across ages.

Timing of introduction of allergenic food might also play a role. Delayed introduction of egg beyond 12 months in one Australian study was associated with a nonsignificant increased risk of egg allergy compared with introduction at age 4 to 8 months.²⁷ These findings have been reinforced by data from the Learning Early About Peanut Allergy study, demonstrating a significant decreased risk of peanut allergy development by introduction of peanut in the first year of life compared with delayed introduction.²⁸

Vitamin D status has also been raised as a potential influence based on its immunomodulatory properties and high rates of insufficiency and ecological studies linking indirect evidence of FA incidence with latitude and sun exposure.²⁹ However, observational and interventional trials have thus far provided conflicting results.³⁰⁻³²

Other potential risk factors proposed include city living, higher maternal education, infant feeding practices, higher socioeconomic status and income (perhaps surrogate markers of a westernized lifestyle),^{6,33,34} use of acid-suppressive medication, altered exposure to gut microbiota in early life (eg, childcare and exposure to pets or farm animals),³⁵ family history,²⁹ and filaggrin loss-of-function gene mutations and early-onset atopic eczema,³⁶ perhaps increasing food sensitization risk through non-intact skin.

FA and anaphylaxis have become an increasing public and personal health burden in developed countries over the last 2 decades, contributing to increased demand for specialty services, significant economic cost of care, and reduced quality of life for children with FA and their families.^{37,38} Effective strategies for primary prevention are currently lacking, and secondary prevention is limited to strategies to reduce the risk of unintentional exposure. Although specific immunotherapy appears promising,³⁹ it remains at the investigational stage at this time and requires intensive medical and nursing resources that are not currently available. We have found evidence that childhood FA is continuing to increase but also found provisional evidence that the burden is now shifting to older children and teenagers. The challenges for health care systems will be how best to develop evidence-based policies to reduce the risk of FA development, to care for younger children presenting with new cases of FA/FA-

related anaphylaxis, and to manage the shifting burden to older teenagers and young adults, in whom persistent FA has more likely become a chronic morbidity and in whom the relative risk for fatal anaphylaxis is at its highest compared with other age groups.^{11,15,17}

Clinical implications: Acceleration in the rate of increase in food-related anaphylaxis in older children and teenagers has implications for management of FA in these age groups, who are at greatest risk of fatal anaphylaxis.

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