

Age, sex, geographical and socio-economic variations in admissions for anaphylaxis: analysis of four years of English hospital data.

A. SHEIKH and B. ALVES

*Department of Primary Health Care and General Practice, Division of Primary Care and Population Health Sciences
Imperial College School of Medicine, London, UK*

Summary

Background Although the most severe of the allergic disorders, the epidemiology of anaphylaxis remains poorly described. Hospital admissions for anaphylaxis in England more than doubled during the 1990s.

Objective To provide baseline data for assessing future trends, and to assess whether there is sufficient regional variation in incidence to allow efficient testing of aetiological hypotheses, we sought to identify any age, sex, geographical and socio-economic variations in hospital inpatient admissions for anaphylaxis.

Methods We studied all emergency admissions for anaphylaxis to English NHS hospitals between 1991 and 1995. Poisson regression modelling was used to calculate rates of anaphylaxis admission per 100 000 emergency admissions by age, sex, deprivation and by residence in urban/rural, North/South and East/West England.

Results Of the 13.5 million emergency inpatient admissions, 2323 patients had a primary diagnosis of anaphylaxis. Poisson regression analyses showed significant age, gender, geographical and socio-economic variations in emergency admissions for anaphylaxis: adjusted Female rate ratio 1.19 (95% CI 1.09–1.29), South rate ratio 1.35 (95% CI 1.25–1.47), Rural rate ratio 1.35 (95% CI 1.17, 1.59), and Non-deprived rate ratio 1.32 (95% CI 1.19, 1.46).

Conclusion This study identifies striking national age, sex, geographical and socio-economic variations in the incidence of inpatient admissions for anaphylaxis in England, affording important opportunities to generate and test aetiological hypotheses. Risk of anaphylaxis admission is considerably increased in females of child-bearing age and those residing in southern, rural, and affluent areas are independent risk factors for anaphylaxis admission.

Keywords: anaphylaxis, epidemiology, hospital admissions, age, sex, geography, deprivation, England

Clinical and Experimental Allergy, Vol. 31, pp. 1571–1576. Submitted 13 October 2000; revised 10 January 2001; accepted 12 April 2001.

Introduction

The increasing disease burden posed by atopic disorders

Correspondence: Aziz Sheikh, Department of Primary Health Care & General Practice, Division of Primary Care and Population Health Sciences, Imperial College School of Medicine, St Dunston's Road, London, W6 8CP, UK. E-mail: aziz.sheikh@ic.ac.uk

has resulted in collaborative and systematic efforts aimed at characterizing the national and international epidemiology of these disorders [1,2]. Despite this, the epidemiology of the most severe of the allergic disorders, anaphylaxis, is poorly described. Recent time trend studies have shown English hospital admissions for anaphylaxis to have more than doubled during the 1990s, this almost certainly

reflecting a true increase in the incidence of anaphylaxis [3,4]. To provide baseline data for assessing future trends, and to assess whether there is sufficient regional variation in incidence to allow efficient testing of aetiological hypotheses, we sought to identify any age, sex, geographical and socio-economic variations in inpatient hospital admissions for anaphylaxis.

Materials and methods

The hospital episode statistics database captures information on every inpatient admission to National Health Service (NHS) hospitals in England. In addition to demographic data including age, sex and postcode of residence, each admission contains one mandatory primary diagnosis code [5]. We studied inpatient hospital admissions over four years who were discharged between 1 April 1991 and 31 March 1995 with a primary diagnosis of anaphylaxis (either 'anaphylactic shock' [ICD-9995.0] or 'anaphylactic shock due to serum' [ICD-9999.4]) admitted as emergencies.

Using postcode of residence, we linked each admission to the characteristics of the area in which the patient lived. Based on their 1991 electoral ward of residence, admissions were categorized by four explanatory variables: deprivation level; rural/urban residence; North/South residence; East/West residence. Deprivation levels were assigned using population quartiles, that is, four Underprivileged Area score ranges of equal population size [6,7]. Rural/urban values were taken from the Office for National Statistics (ONS) classification based on land use and population counts [8]. Patients were classified as being either from the North, South, East or West by dividing England along the lines of 1995 regional health authority boundaries. Three age categories were used: children (< 15 years), adults (15–54) and older people (> 55). Records were excluded from the analysis if age, sex or postcode were missing or invalid or if the patient resided outside of England.

Our key measure of interest was the rate of anaphylaxis admissions per 100 000 emergency admissions. The likelihood of emergency admission for all causes varies by patient factors with high emergency admission rates in deprived areas [9]. Using emergency admissions as the denominator adjusts for this variation in emergency admission threshold. Univariate associations between anaphylaxis rates and each of the possible explanatory factors were investigated and crude rates and rate ratios were calculated. The Chi-squared test was used to look for linear trends in variations within each grouping. Rates were plotted by age and sex and a map of geographical variations in rate was produced.

We included in the regression model those factors which were significantly associated with variations in anaphylaxis

rate at the univariate level. We defined Poisson regression models to examine the strength of any independent association between the anaphylaxis rates and the factors described above. Deprivation level was dichotomised with patients classified as affluent if they were resident in areas with scores of less than 18 (the lower three quartiles). The Rural/urban variable was also dichotomised by combining the ONS categories. Results from the Poisson regression models are presented as rate ratios (with 95% confidence intervals (CI)) to estimate the independent effect of each factor on the admission-adjusted anaphylaxis rate.

Results

Of the 13.5 million emergency admissions from NHS hospitals during the study period, 2323 patient admissions had a clinician-made primary diagnosis of anaphylaxis recorded, with only 12 deaths. Three percent (72) of admissions were excluded from the analysis (three with invalid age, three with invalid sex, 57 with invalid ward of residence and nine resident outside of England).

Descriptive statistics and univariate analysis

The overall average anaphylaxis rate was 17 emergency anaphylaxis admissions per 100 000 emergency admissions. Crude rates increased during childhood and peaked in adults between 15 and 55 years (Fig. 1). Rates declined steadily with increasing age in those aged over 55 years. Age-related rates in males and females were similar, although rates were higher in women with a rate ratio of 1.20 (95% CI 1.11–1.31). This increased risk appeared to be restricted to females aged between 35 and 55 years, however, removing the distorting effect of gynaecological emergencies from the denominator showed that the true excess risk was for females aged 15–55 years (Fig. 1) with a rate ratio of 1.38 (95% CI 1.27–1.50). The map in Fig. 2 illustrates the geographical variations in anaphylaxis rate. North-east Thames, one of the four administrative health regions in London, had an unexpectedly low rate of three emergency anaphylaxis admissions per 100 000 emergency admissions, despite having similar levels of deprivation to other London areas.

Rates were higher in the West and in the South (Table 1). A linear trend was noted for variations by rural/urban residence (Chi-squared for trend = 45, $P < 0.001$) and by deprivation (Chi-squared test for trend = 48, $P < 0.001$) with higher rates associated with residence in rural and affluent areas.

Poisson regression analysis

Results from the Poisson regression are detailed in Table 2.

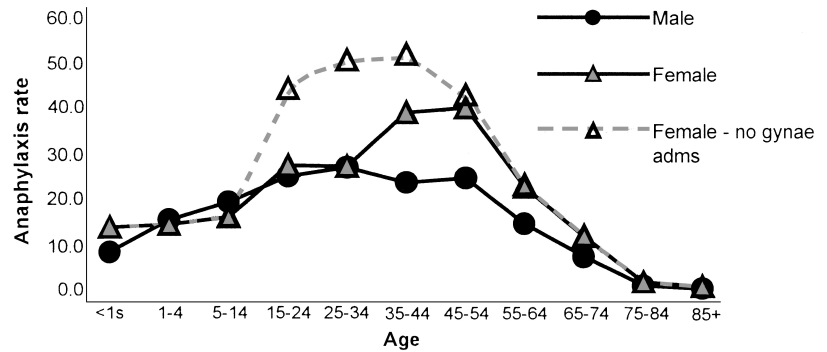


Fig. 1. Anaphylaxis admission rates by age and sex.

We carried out two regressions, including and excluding North-east Thames because of the unusually low number of anaphylaxis admissions in this area. With North-east Thames data included, each of the six factors (age, sex, residence in South, West, rural and affluent areas) was independently associated with increased risk of anaphylaxis admission. Exclusion of North-east Thames data changed these results slightly with residence in the West becoming non-significant. Neither Poisson model required adjustment for over-dispersion. Highest admission-adjusted anaphylaxis rates are associated with living in rural, affluent areas in the South-west of England. Rates in affluent rural areas

in the South-west were 32 per 100 000 emergency admissions, 2.6 times (95% CI 2.0–3.4) the rates in deprived urban areas in the North-east (12 per 100 000 emergency admissions).

Discussion

This national study of all anaphylaxis inpatient admissions over a four-year period is over 20 times larger than any study describing the epidemiology of anaphylaxis conducted hitherto and provides strong evidence to suggest that risk of anaphylaxis varies considerably with age, gender,

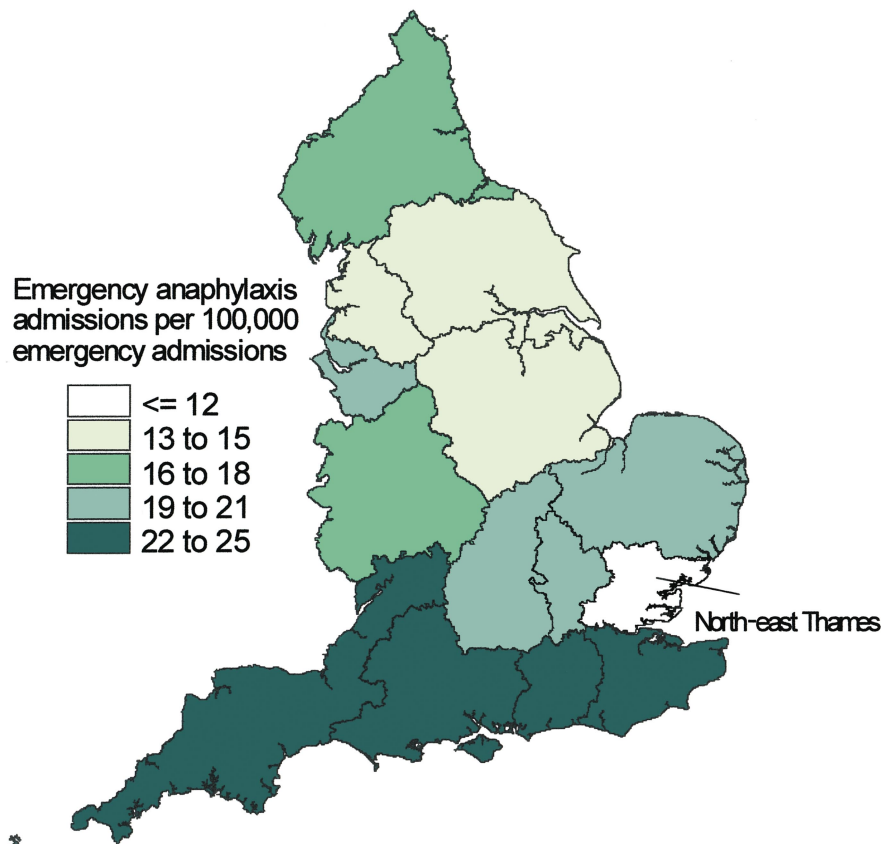


Fig. 2. Anaphylaxis admission rates by 1995 regional health authorities in England.

Table 1. Univariate analysis: crude anaphylaxis rates and rate ratios by age, sex, socio-economic status and geography

	Anaphylaxis admissions	% Pop.*	Anaphylaxis rate (95%CI)**	Rate ratios (95% CI)	Chi-squared test for trend
Age					
< 15 years	350	19	16.3 (14.7–18.1)	1	
15–54 years	1392	56	30.5 (28.9–32.1)	1.87 (1.66–2.10)	
> 55	509	26	8.2 (7.5–9.0)	0.50 (0.44–0.58)	
Sex					
Male	988	49	15.8 (14.8–16.8)	1	
Female	1263	50	19.0 (18.0–20.1)	1.20 (1.11–1.31)	
East/West					
East	1156	57	15.9 (15.0–16.8)	1	
West	1095	43	19.5 (18.4–20.7)	1.23 (1.13–1.34)	
North/South					
North	1200	53	16.2 (15.3–17.2)	1	
South	1051	47	19.1 (17.9–20.2)	1.17 (1.08–1.28)	
Rural/Urban residence					
Urban (wholly)	1615	75	16.2 (15.4–17.0)		
Urban (predominantly)	313	13	19.5 (17.4–21.7)	1.20 (1.06–1.36)	
Mixed Urban (more urban)	105	4	22.0 (18.2–26.7)	1.36 (1.12–1.66)	Chi ² = 45 P < 0.001
Mixed Rural (more rural)	40	1	26.3 (19.3–35.8)	1.62 (1.18–2.22)	
Rural (predominantly)	18	1	31.4 (19.8–49.8)	1.93 (1.22–3.08)	
Rural (wholly)	160	6	24.5 (20.9–28.6)	1.51 (1.28–1.77)	
Deprivation					
UPA < –7	556	26	20.6 (19.0–22.4)	1	
UPA –7 to 4	549	24	19.3 (17.8–21.0)	0.94 (0.83–1.06)	Chi ² = 48 P < 0.001
UPA 4 to 18	605	25	17.6 (16.3–19.1)	0.86 (0.76–0.96)	
UPA > 18	541	25	13.8 (12.7–15.0)	0.67 (0.59–0.75)	

*Based on 1993 Office for National Statistics population estimates.

**Emergency anaphylaxis admissions per 100 000 emergency admissions.

Table 2. Poisson regression model for risk of anaphylaxis admission

Variable	Rate Ratio (95% CI)
England including North-east Thames	
Rural residence	1.39 (1.21–1.60)
Affluent residence	1.40 (1.27–1.54)
Living in the South	1.18 (1.08–1.28)
Living in the West	1.20 (1.10–1.30)
Female	1.18 (1.08–1.28)
Age 15–54	1.82 (1.62–2.04)
Age > = 55	0.48 (0.42–0.55)
England excluding North-east Thames	
Rural residence	1.36 (1.18–1.55)
Affluent residence	1.32 (1.19–1.46)
Living in the South	1.35 (1.24–1.47)
Living in the West	1.07 (0.98–1.16)
Female	1.19 (1.09–1.29)
Age 15–54	1.83 (1.63–2.06)
Age > = 55	0.49 (0.43–0.56)

socio-economic and geographical factors. Anaphylaxis is a life-threatening disorder that often necessitates hospital admission [10]; studying national hospital admissions is therefore likely to provide useful insights into the overall epidemiological picture of this condition. Our data almost certainly provides a more reliable profile of the true epidemiology of anaphylaxis than previous studies conducted which have focused on incident cases in the context of anaesthesia, hospitalized patients, case series analyses of patients presenting to hospital allergy clinics or cases leading to death [10–13]. Nonetheless, caution needs to be exerted in extrapolating the associations described to the very many anaphylaxis patients who will be treated in accident and emergency departments without recourse to inpatient admission [10].

We considered alternative explanations for our findings including issues to do with data quality and accuracy, and regional differences in threshold for admission. Although hospital episode statistics have been in use since 1987, data quality in the years before 1990 is generally acknowledged

to be poor. In the Oxford Region for example, only 79% of records had diagnostic data for the years 1987–90 [14]. Furthermore, a study of hospital episode statistics in East Anglia found 20% of records without a primary diagnosis in 1990/1, this figure improving to only 3% by 1991/2 [15]. We decided therefore to use data from 1991/92 onwards confining our study to the period in which ICD-9 was operational. In 1995/6, the hospital episode statistics database switched from using ICD-9 to ICD-10 codes; current advice from the NHS Executive is that the degree of equivalence between these revisions is minimal [16].

A study of the reproducibility of clinical codes found coding to be better for acute conditions than for chronic disorders, suggesting that issues to do with data accuracy are an unlikely explanation [17]. Common misdiagnoses for anaphylaxis include panic attacks and angioedema. Panic attack will, in most cases, be managed in accident and emergency departments without need for admission and are thus unlikely to represent an important source of bias in our study. More relevant in the context of this study however, is the possibility that a proportion of angioedema cases may have been misclassified as anaphylaxis or vice versa. Short of conducting a formal study designed to validate HES anaphylaxis codes, we were unable to reliably estimate the magnitude of this potential source of bias. We were however, able to compare data on length of stay for the two conditions which, as would be expected, showed average admission length to be significantly shorter for anaphylaxis when compared to angioedema (1.6 days (sd 3.0) vs. 2.1 days (sd 2.9), $P < 0.001$) suggesting that any misclassification bias is minimal. Whilst both poor data quality and poor accuracy could cause variations in anaphylaxis rates, it is likely that the resulting misclassification of cases (either failing to record true cases or recording an admission of anaphylaxis in error) would not be related systematically to the factors in the regression model. These effects would therefore tend to blur associations rather than create false ones.

The lower than expected admission rates in North-east Thames did however, cause us concern. Possible explanations include a higher threshold for admission in this region, regional differences in coding or the possibility of a genuinely low incidence of anaphylaxis in North-east Thames. We decided to treat North-east Thames as an outlier because it had an exceptionally low anaphylaxis rate (Fig. 2), less than 15% the rate of the other Thames regions. We believe that the second model which excludes North-east Thames data (Table 2) is likely to provide better estimates of the true rate ratios although both models are presented.

Admissions for anaphylaxis show a clear peak in the 15–55 age group, the subsequent waning incidence of anaphylaxis with age is a finding consistent with other

allergic disorders such as asthma, eczema and rhinitis. We found anaphylaxis admissions to be significantly more common for females, an observation that is in keeping with the results of the International Collaborative Study of Severe Anaphylaxis which looked at 123 incident cases of anaphylaxis in hospitalized patients and showed females to be at greatest risk in each of the three countries studied [18]. Similar gender differences have also been reported in a study of 43 consecutive cases of anaphylaxis attended to by the London Ambulance Service [19]. Studying the age-sex characteristics has showed however, that this gender difference is mainly seen in women of child-bearing age (rate ratio of 1.38 95% CI 1.27–1.50 after excluding gynaecological admissions) suggesting that endocrine factors may be important in its pathogenesis, as is postulated with many of the auto-immune disorders, and has recently been shown for vernal keratoconjunctivitis [20,21].

Most surprising of all however, are the geographical and demographic variations noted. It is well recognized that emergency admissions vary by geographical and socio-economic factors with highest admission rates in deprived areas [9]. To take account of possible regional variations in admission threshold we used emergency-adjusted admission rates. Despite these adjustments, rates of anaphylaxis admission were clearly higher in southern, rural and affluent regions of England, this strongly suggesting that our findings reflect genuine variations in the incidence of anaphylaxis.

Environmental exposures that may account for these variations are many and could include differences in diet, hygiene, childhood infection, and the number and type of vaccinations [3,22–24]. Whilst much work remains to be done to accurately describe the epidemiology of anaphylaxis, such as understanding the importance of ethnicity and smoking for example, this study adds valuable new lines of inquiry into possible reasons underlying the increasing incidence of anaphylaxis.

Acknowledgements

We thank Professor Stephen Durham, Professor Bonnie Sibbald, Professor Brian Hurwitz, Dr Azeem Majeed and Dr Paul Aylin for their helpful comments on an earlier draft of this paper. Aziz Sheikh is supported by funding from a NHS R & D National Primary Care Award.

References

- 1 European Community Respiratory Health Service. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community health Survey (ECRHS). *Eur Respir J* 1996; 9:687–95.

- 2 The International Study of Asthma and Allergies in Childhood Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; 351:1225–32.
- 3 Sheikh A, Alves B. Hospital admissions for acute anaphylaxis: time trend study. *BMJ* 2000; 320:1441.
- 4 Wilson R. The upward trend in acute anaphylaxis continues in 1998–9. *BMJ* 2000; 321:1021.
- 5 Majeed A. Hospital admissions data: why are they collected? *Clinician Manage* 1998; 7:160–6.
- 6 Jarman B. Identification of Underprivileged Areas. *BMJ* 1983; 312:1705–9.
- 7 Jarman B. Underprivileged Areas. validation and distribution of scores. *BMJ* 1984; 289:1587–92.
- 8 1991 Census Key Statistics for Urban and Rural Areas. London: ONS, 1997.
- 9 Reid FD, Cook DG, Majeed A. Explaining variation in hospital admission rates between general practices: cross sectional study. *BMJ* 1999; 319:98–103.
- 10 Stewart AG, Ewan PW. The incidence, aetiology and management of anaphylaxis presenting to an Accident and Emergency department. *Q J Med* 1996; 89:859–64.
- 11 Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anaesthesia in Australia. *Ann Fr Anesth Reanim* 1993; 12:97–104.
- 12 Dibs SD, Baker MD. Anaphylaxis in children: a 5-year experience. *Pediatrics* 1997; 99:E7.
- 13 Pumphrey RSH. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; 30:1144–50.
- 14 Goldacre M, Gill L. Interpreting hospital death rates. *BMJ* 1995; 310:599.
- 15 Hyndman SJ, Williams DR, Merill SL, Jipscombe JM, Palmer CR. Rates of admission to hospital for asthma. *BMJ* 1994; 308:1596–600.
- 16 NHS Centre for Coding and Classification. A Guide to the Use of Tables of Equivalence Between ICD-9 and ICD-10. Loughborough: NHS Executive, 1995.
- 17 Dixon J, Sanderson C, Elliott P, Walls P, Jones J, Petticrew M. Assessment of the reproducibility of clinical coding in routinely collected hospital activity data: a study of two hospitals. *J Public Health Med* 1998; 20:63–8.
- 18 The International Collaborative Study of Severe Anaphylaxis. An epidemiological study of severe anaphylactic and anaphylactoid reactions among hospital admissions: methods and overall risks. *Epidemiology* 1998; 9:141–6.
- 19 Snooks H. Care of anaphylactic patients by crews of the London Ambulance Service. *Network* 1999; 30:1–4.
- 20 Bonini S, Lambiase A, Schiavone M, Centofanti M, Palma LA, Bonini S. Estrogen and progesterone receptors in vernal keratoconjunctivitis. *Ophthalmology* 1995; 102:1374–9.
- 21 Bonini S, Bonini S, Lambiase A et al. Vernal keratoconjunctivitis revisited. a case series of 195 patients with long-term follow-up. *Ophthalmology* 2000; 107:1157–63.
- 22 Matricardi PM, Rosmini F, Riondino S, Fortinin F, Ferrigno L, Rapicetta M. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000; 320:412–7.
- 23 Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science* 1997; 275:77–9.
- 24 Kramer U, Heinrich J, Wjst M, Wichmann H-E. Age of entry to day nursery and allergy in later childhood. *Lancet* 1999; 353:450–4.