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ORIGINAL ARTICLE **Epidemiology of Allergic Disease**

# Socio-economic status, geographic remoteness and childhood food allergy and anaphylaxis in Australia

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**Summary**

*Background* The risk factors for food allergy (FA) and anaphylaxis remain uncertain.
*Objective* We examined the association between socio-economic status (SES), geographic remoteness and childhood FA and anaphylaxis in Australia.
*Methods* Sales of infant hypoallergenic formulae (IHF; 2008–2009) and EpiPens (2006–2007) in children aged 0–4 years and hospital anaphylaxis admission rates (2002–2006) in age groups 0–4, 5–14, 15–24, 25–64 and 65+ years were used as proxy markers of FA and anaphylaxis in Australia. Government and commercially derived data were analysed by SES and geographic remoteness (very remote, remote, outer regional, inner regional and major cities).
*Results* Annual IHF sales rates were higher in those with the greatest compared with the least socio-economic advantage (47 830 vs. 21 384 tins/100 000 population; $P<0.001$). EpiPen sales trends were also higher in those with the greatest socio-economic advantage in all age groups, most marked in those aged 0–4 (1713 vs. 669/100 000; $P=0.002$) and 5–14 years (1628 vs. 600/100 000; $P=0.001$). Formula sales rates were higher in major cities than remote/very remote regions (37 421 vs. 6704/100 000; $P<0.001$) with similar EpiPen sales trends, particularly in ages 0–4 (1166 vs. 601/100 000; $P=0.045$) and 5–14 years (1099 vs. 588/100 000; $P<0.001$). Socio-economic advantage and geographic remoteness remained statistically significant in multivariable analysis of prescription rates ($P<0.01$) and were unchanged by adjustment for health services access. While anaphylaxis admission rates were higher in those with the greatest compared with the least socio-economic advantage in children aged 0–4 years (129 vs. 92/100 000 population/year; $P=0.03$), the opposite was observed in older age groups (e.g. aged 25–64 years: 43 vs. 76, $P=0.01$). There was no association between geographic remoteness and anaphylaxis admissions.
*Conclusion* Socio-economic advantage and residence in major cities may be risk factors for developing childhood FA and anaphylaxis. Further study will determine the extent to which economic factors and location of residence also influence access to health services.

**Keywords** anaphylaxis, Australia, epidemiology, EpiPen, food allergy, geographic remoteness, infant hypoallergenic formula, rural, socio-economic status
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## Introduction

Despite recent increases in anaphylaxis hospital admissions in the United Kingdom, Australia and USA [1–3] and more frequent anaphylaxis diagnoses in community-based studies [4, 5], risk factors for food allergy (FA) and anaphylaxis remain poorly defined. Limited evidence suggests that a higher socio-economic status (SES) and location of residence [6, 7] may be associated with a higher risk of anaphylaxis. The objective of the present study was to examine the association between SES, geographic remoteness and FA/anaphylaxis in Australia by examining sales of infant hypoallergenic formula (IHF) and EpiPens (the only adrenaline autoinjector available in

Australia during the study period), supported by an analysis of hospital anaphylaxis admission rates, focusing on young children. Australia was considered an ideal location in which to explore regional variation in detail, given its relatively homogeneous ethnicity and socio-economic distribution, universal public health system [8], relatively high anaphylaxis hospital admission rates [2] and access to national IHF and EpiPen sales and hospital admissions data. Based on the limited evidence that socio-economic advantage and metropolitan living convey a higher risk of allergic respiratory disease and atopic eczema [9–13], we hypothesized that higher FA/anaphylaxis rates might also be observed in those with greater compared with lesser SES advantage, and in cities compared to more remote regions.

## Methods

### *Australian classification of socio-economic advantage*

The socio-economic indexes for areas (SEIFA) are a measure of SES, used by the Australian Bureau of Statistics (ABS) to assist in quantifying statistical differences in socio-economic advantage and disadvantage in geographic areas in deciles [14]. SEIFA categories range from 1 (least advantage) through to 10 (greatest advantage). SEIFA are constructed from a weighted average of selected variables including income, education, employment, occupation, housing, ethnicity, language spoken, mobility, marital status and presence or absence of disability, as recently reviewed in detail [14]. Because SEIFA are assigned to geographic areas (not individuals), they reflect the overall SES of the population living in an area, but not necessarily the circumstances of each individual in that location. SEIFA categories are ordinal and thus can be used to rank geographic areas but not to measure the magnitude of the difference in SES circumstances between different geographical areas.

### *Australian remoteness classification*

The ABS uses the Australian remoteness classification to quantify statistical differences between rural and metropolitan areas, where the differences are defined as physical remoteness from goods and services, as recently reviewed [15, 16]. Six geographic remoteness categories are defined: migratory, very remote, remote, outer regional, inner regional and major cities, and contain approximately 0.003%, 0.8%, 1.5%, 9%, 20% and 69%, respectively, of the Australian population (Fig. 1; [17]). For the purpose of this study, the migratory category was omitted (due to small numbers and because geographic factors could not be determined) and the very remote/remote categories were combined (due to small numbers in the very remote category).

### *Australian population and demographic data*

We used ABS 2006 Census data [17] to derive Australian population statistics and demographic data (age, income, gender distribution, birth origin, ethnicity, education level, population density, employment, number of practicing medical practitioners and pharmacists) for each Australian Postal Area (the smallest geographic unit used in this study) and the number of paediatricians for each remoteness category. The Australasian Society of Clinical Immunology and Allergy provided regional practicing allergy/immunology specialist data (J. Smith, personal written communication, August 2009; [18]). The Pharmacy Guild of Australia provided data on the number and location of retail pharmacies, including non-members (S. Armstrong, Australian Pharmacy Guild, personal written communication, August 2009). Public hospital locations were obtained from government publications [19].

### *Infant formula and EpiPen sales data*

Hypoallergenic formulae were defined as extensively hydrolysed formulae (Alfare, Nestle Australia, Sydney; Pepti-Junior, Nutricia Australia, Sydney) or elemental formulae (Elecare, Abbott Australasia, Sydney; Neocate, Nutricia Australia, Sydney). IMS Health Australia (Sydney) provided national sales data for the 2 years from January 2008 to December 2009. Commonwealth Serum Laboratories (Melbourne, Australia) and IMS Health Australia provided national EpiPen sales data for the 2 years from November 2005 to October 2007. Specifically, IHF sales data described the number of tins sold (standard prescription is eight tins/sale) whereas EpiPen sales data describe the number of occasions that EpiPens were sold (standard prescription is two devices/sale for those aged less than 18 years and one for older patients), without differentiating between initial and repeat sales. The Federal Department of Health and Aging (DOHA; Canberra) supplied information on the proportion of EpiPens prescribed by age group (0–4, 5–14, 15–24, 25–65 and 65+ years). EpiPen was the only adrenaline autoinjector device available in Australia during the study period.

### *Australian criteria for infant formula and EpiPen subsidy*

The Australian Pharmaceutical Benefits Authority Scheme (PBAS) criteria for subsidized IHF limits subsidy to combined cow's milk/soy protein intolerance in a child up to the age of 2 years in consultation with a paediatrician or allergy specialist, but neither for treatment of colic nor for FA prevention. Patients must first fail to respond to a hydrolysed formula [20] but prescription criteria do not differentiate between IgE-dependent and -independent mechanisms. EpiPen is also subsidized under the PBAS for the anticipated emergency treatment of

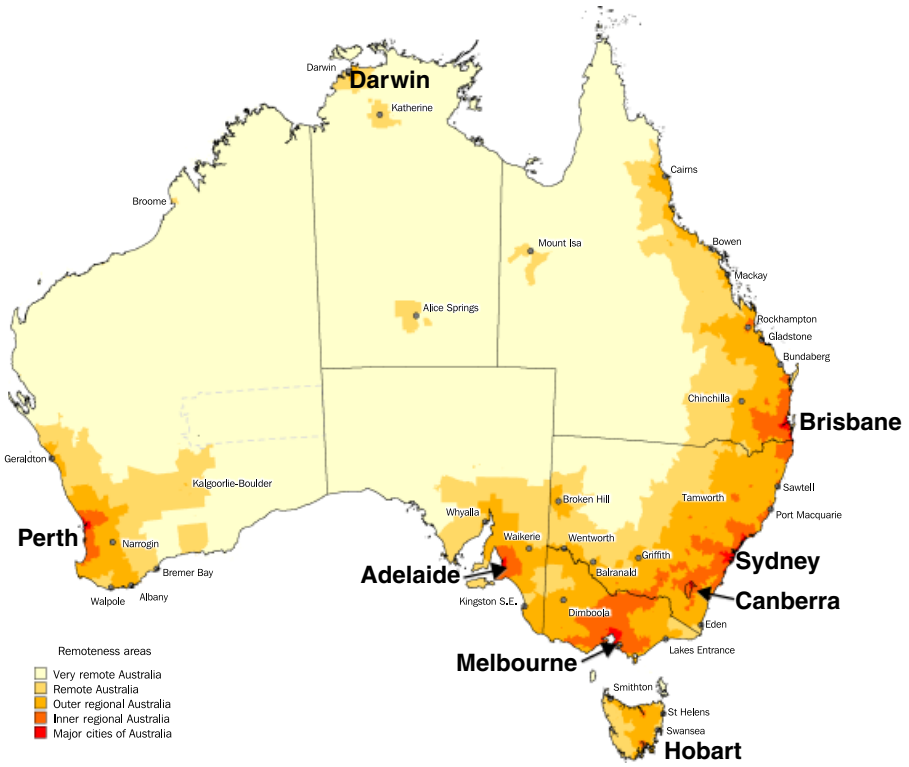


Fig. 1. Australian geographic remoteness classification. The Australian geographic remoteness classification recognizes six geographic remoteness categories: migratory, very remote, remote, outer regional, inner regional and major cities [15]. Map courtesy of the Australian Bureau of Statistics.

acute anaphylaxis using criteria as described previously [21]; two devices are subsidized for those aged $<18$ years and one for older patients (changing to two devices for all patients on 1 July 2010). Importantly, direct-to-consumer promotion of prescription drugs (including EpiPens and IHF) is banned in Australia, penalties exist for doctors providing Authority prescriptions outside government guidelines (V. Mabbott, DOHA, personal communication, February 2009) and medical practitioner advertising is restricted to government-approved criteria. IMS Australia provided data on the proportion of sales with PBAS subsidy.

### *Mapping of infant hypoallergenic formula and EpiPen sales data to socio-economic status and geographic location*

Sales data were mapped to the postal areas where prescriptions were filled and then to SEIFA deciles using ABS-derived data for each postal area and then to four remoteness categories: very remote/remote combined, outer regional, inner regional and major cities.

### *Hospital anaphylaxis admissions*

The Australian Institute of Health and Welfare (AIHW) provided Australian National Hospital Morbidity Database Principal Diagnosis data for the age groups 0–4, 5–14, 15–24, 25–65 and 65+ years for 5 years from July 2002 to June 2007. These record primary and important secondary hospital discharge diagnoses classified using the *International Classification of Diseases*, version 10 (ICD-10; [22]) for each financial year (July–June). Anaphylaxis admissions associated with food (T78), medication (T88.6) and unclassified anaphylaxis (T78.2; which includes not only idiopathic anaphylaxis but also cases not attributed to any one cause by the treating doctor) were examined. Sting anaphylaxis was excluded, as it was not possible to distinguish anaphylaxis from other adverse reactions (e.g. toxicity) using ICD-10 codes. Anaphylaxis related to serum (T80.5) was also excluded as (a) only 82 cases were observed over the study period and (b) AIHW data suppression for small numbers precluded analysis by SES or geographic location. Emergency room visit data without admission were not available. Population rates were calculated using the mean ABS national population estimates for the same period in these regions. Discharge diagnoses attributed to admissions were expressed as age-specific rates/100 000 population/year by collapsing the SEIFA category deciles into quintiles and by the location of usual residence by remoteness category. Importantly, hospital admissions data were from an independent unlinked database to IHF and EpiPen sales data.

*Ethics approval*

The Human Research and Ethics Committee (Calvary Bruce/Calvary John James Private Hospitals) approved the study.

*Statistical analysis*

Analyses were performed using STATA 10.0 (StataCorp, College Station, TX, USA). Simple and multivariable linear regression were used to evaluate the association between the major exposures (SEIFA deciles and geographic remoteness categories) and major outcomes (IHF and EpiPen sales and anaphylaxis admissions). To facilitate a comparison between different groups, age-specific rates for IHF and EpiPen sales and anaphylaxis admissions were expressed per 100 000 population/year. Means are presented with standard deviation and medians with an interquartile range (IQR). All β-coefficients are presented with 95% confidence intervals (CI). A two-sided *P*-value $<0.05$ was considered statistically significant.

## Results

*Infant hypoallergenic formula sales rates*

During the 2008–2009 calendar years, 894 287 tins of IHF were sold (20% hydrolysed formulae; 80% elemental formulae), 99.5% of which were dispensed with PBAS subsidy.

*EpiPen sales rates*

Between November 2005 and October 2007, 69 227 EpiPens were sold (38 861 of 0.3 mg; 30 366 of 0.15 mg; [21]). Sales rates (per 100 000 population/year) were higher for children aged 0–4 (951) and 5–14 years (1024), compared with those aged 15+ years (223) or the overall population mean of 324 (median 297; IQR 247–393; [21]). PBAS-subsidized and private sales accounted for 87% and 13% of sales, respectively.

*Anaphylaxis admissions rates*

Ten thousand nine hundred ninety-five admissions were coded as anaphylaxis between July 2002 and June 2007, attributed to food (42% cases), unclassified (32%), medication (25%) or serum (0.1%) in the overall population (Table 1). FA was the dominant trigger in children aged 0–4 years (83% admissions). Age-specific rates of anaphylaxis admission were the highest in children aged 0–4 years compared with older age groups, and in males more than females in those aged 0–14 years (Fig. 2).

*Relationship between socio-economic status and infant hypoallergenic formula and EpiPen sales*

In children aged 0–4 years, IHF sales rates were significantly higher in those with greatest compared with the least socio-economic advantage (47 830 vs. 21 384 tins/100 000 population; $P<0.001$; Fig. 3a). A similar pattern was observed for EpiPen sales rates in all age groups, such that there was a significant increase in the rate of EpiPen prescriptions for every one unit increase in SEIFA index (Fig. 3b): age 0–4 (β 85.3; $P=0.002$), 5–14 (β 88.9; $P=0.001$), 15–24 (β 12.2; $P=0.006$), 25–64 (β 9.5; $P=0.002$) and 65 years (β 11.7; $P<0.001$). Sales rates of IHF and EpiPen by postal area were highly correlated (data not shown; $r=0.927$; $P<0.001$).

*Relationship between socio-economic status and anaphylaxis admission rates*

Whereas anaphylaxis admission rates were higher in those of the greatest compared with the least socio-economic advantage in children aged 0–4 years (β 7.8; $P=0.03$), the relationship in older age groups was either flat (ages 5–14s; 15–24s; 65+ years; all $P>0.05$) or weakly negative (β −8.5; age 25–64 years; $P=0.01$; Fig. 4). The same relationship was observed in male and females (data not shown).

*Relationship between geographic remoteness, infant hypoallergenic formula and EpiPen sales and anaphylaxis admission rates*

In children aged 0–4 years, IHF sales rates were higher in major cities compared with very remote/remote regions (37 421 vs. 6704/100 000; $P=0.08$; Fig. 5a). A similar pattern was observed with EpiPen sales rates in age groups 0–4 ($P=0.045$), 5–14 ($P<0.001$) and 25–64 years ($P=0.048$; Fig. 5b). By contrast, there was no significant association between geographic remoteness and anaphylaxis admission rates, whether the analysis was undertaken on the entire population, by age group (as defined above) or when repeated with the remote and very remote categories split or combined.

*Multivariable analysis of infant hypoallergenic formula and EpiPen sales rates*

In a multivariable model of IHF and EpiPen sales rates, both SEIFA and geographic remoteness remained statistically significant ($P<0.001$; Tables 2 and 3). The association between geographic remoteness and IHF and EpiPen sales rates remained after adjusting for rate of medical practitioners and population density (Table 3). Healthcare access (as estimated by the number of medical practitioners, allergists and pharmacists) did not affect the

**Table 1.** Anaphylaxis admissions by age group and attributed cause

| Anaphylaxis | 0–4 years | 5–14 years | 15–24 years | 25–64 years | 65+ years | Total |
|---|---|---|---|---|---|---|
| Drug | 33 | 80 | 243 | 1746 | 634 | 2736 |
| Food | 1173 | 595 | 779 | 1837 | 232 | 4616 |
| Serum | 10 | 11 | 7 | 45 | 9 | 82 |
| Unclassified | 200 | 346 | 497 | 2097 | 421 | 3561 |

The number of patients admitted to hospital with a diagnosis of anaphylaxis is shown by age group and recorded cause of anaphylaxis.

association between the major exposures (SEIFA deciles and geographic remoteness) and IHF or EpiPen prescription rates (Table 3). Similarly, neither population density nor latitude materially affected the findings (Table 3).

## Discussion

In line with our hypothesis, we found evidence that childhood FA and anaphylaxis is more common in residents of more affluent areas of Australia, underpinned by an analysis of all IHF and EpiPens sold in Australia (whether subsidized or purchased privately), supported by an analysis of all anaphylaxis admissions over a 5-year period. While data on this topic are sparse, our findings are consistent with higher anaphylaxis admission rates in the more affluent regions in the United Kingdom [4] and positive correlation between EpiPen prescriptions rates and SES in Canadians, independent of access to specialist medical care [6]. A relationship between SES and incidence of atopic disease is not unprecedented and consistent with African-, Australian-, European-, UK- and USA-based studies demonstrating higher rates of allergic rhinitis and eczema in those of higher SES [13, 23–28]. By contrast, less consistent findings are described for wheezing and asthma, perhaps related to the confounding influences of infection, occupation or exposure to pollutants such as tobacco smoke [29].

There are, however, theoretical caveats to interpreting the relationship between SES and IHF/EpiPen sales, specifically whether the data reflect real differences in disease incidence or are an artefact of differences in health-seeking behaviour. SES is strongly related to education and health literacy [30], and hence it is conceivable that some of the sales trends observed might (in part) be explained by differences in one or more of: (a) recognition and reporting of health-related symptoms by those of higher SES; (b) health-seeking behaviour in wealthier (and more educated) individuals and their families [31]; (c) ability to afford private specialty care (rather than reliance on public health services with longer waiting lists; [18]) or (d) compliance with filling prescriptions (as described for asthma in Australia despite subsidized medication; [32]). Variations in prescribing and referral practice between doctors working in the private (compared with the public) sector or in affluent (compared with economically disadvantaged) regions might also have

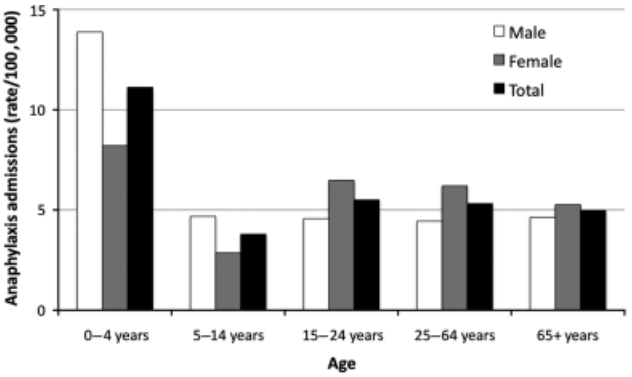


**Fig. 2.** Anaphylaxis admission rates as a function of age and gender. Age-specific hospital anaphylaxis admission rates were highest in children aged 0–4 years compared with older age groups, and in males more than females in those aged 0–14 years.

influenced the data [33]. Furthermore, because SEIFA indexes are assigned to geographic areas (but not individuals), they indicate the overall SES of the population living in an area, but not necessarily the circumstances of each individual in that location. While it was not possible to quantify each of these theoretical concerns in this ecological study, it is difficult to explain financial barriers as the major influencing factor when almost all IHF (99%) and most EpiPens (87%) are sold with government subsidy. Furthermore, if SES-related differences in health-seeking behaviour were the only explanation, one might reasonably expect EpiPen sales trends to be uniform across all age groups, and not isolated to younger age groups as observed.

Of interest was the age-rated disparity in the relationship between SES and proxy markers of anaphylaxis – EpiPen sales (most prominent in those aged 0–14 years) and anaphylaxis admission rates (only significant for children aged 0–4 years). The reasons for these age-related differences (and the more modest gradient across SEIFA of admissions compared with EpiPen) could be related to the greater reliability of EpiPen prescription rates [6] compared with admission rates (23-fold higher overall; 34-fold higher in children aged 0–4 years. i.e. a type II error), or perhaps the possibility that EpiPen prescriptions more accurately reflect risk assessment for current FA (the major identifiable cause of anaphylaxis in young Australian children; [34, 35]) and future anaphylaxis than past episodes *per se*. Of particular interest is the intriguing

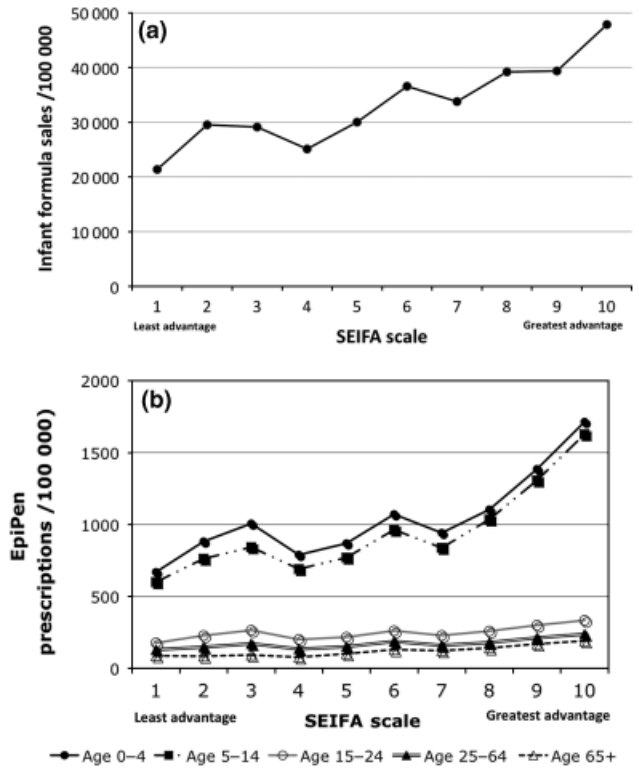


Fig. 3. The relationship between socio-economic status and infant hypoallergenic formula (age 0–4 years) and EpiPen sales rates (all age groups). (a) In children aged 0–4 years, infant hypoallergenic formula sales rates were higher in those living in areas with a greater as compared with a lesser socio-economic status, as assessed by SEIFA deciles. (b) In all age groups, EpiPen sales rates were higher in those living in areas with greater as compared with lesser socio-economic status, such that there was a significant increase in the rate of EpiPen prescriptions for every one unit increase in SEIFA index.

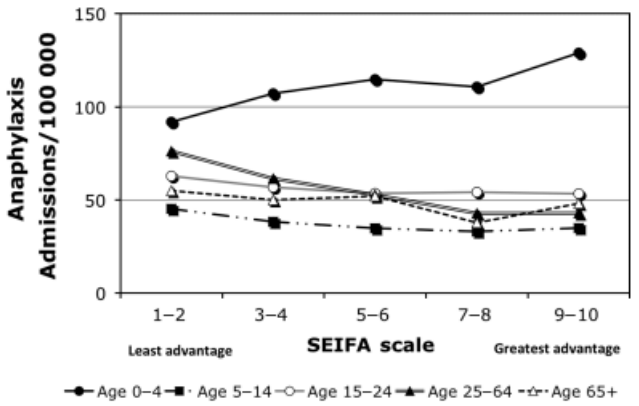


Fig. 4. The relationship between socio-economic status and anaphylaxis admission rates. In children aged 0–4 years, anaphylaxis admission rates were higher in those living in areas with greater as compared with lesser socio-economic status, as assessed by higher compared with lower SEIFA deciles, respectively. In older age groups, the relationship was either flat or weakly negative.

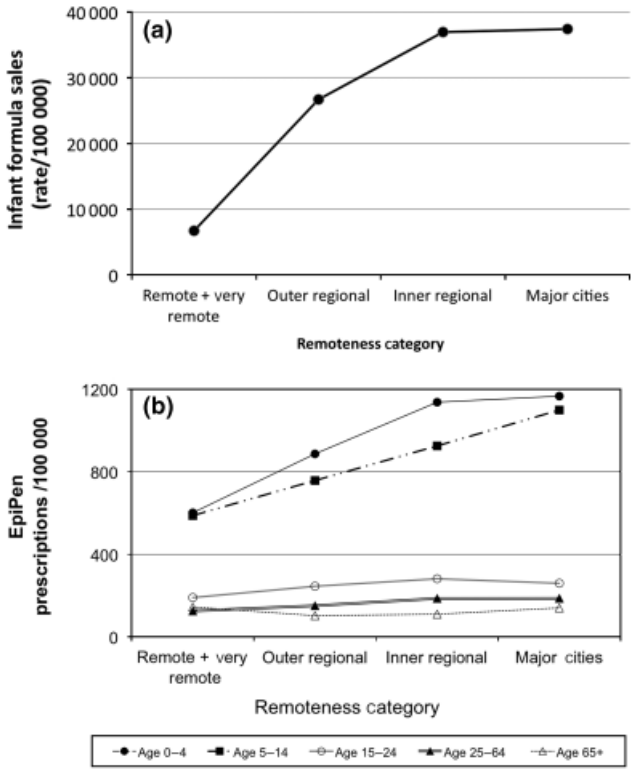


Fig. 5. The relationship between geographic remoteness and infant hypoallergenic formula sales rates (age 0–4 years) and EpiPen sales rates (all ages). (a) In children aged 0–4 years, infant hypoallergenic formula sales rates were higher in those living in major cities than in very remote/remote regions. (b) In patients aged 0–4, 5–14 and 25–64 years, EpiPen sales rates were higher in major cities compared with very remote/remote regions, whereas in other age groups, the relationship was flat.

possibility that these findings may point to an age or allergen-related mechanism (e.g. for FA) that is more common or important in early life but become less so as patients age. While it could be argued that IHF sales data fail to distinguish between prescriptions for IgE-mediated and independent FA, the scant data available suggest that IgE-mediated reactions are predominant, with a ratio of 50 : 1 in one Australian study of patients referred to a hospital-based paediatric allergy/immunology clinic [36].

We also acknowledge that while hospital anaphylaxis admissions data have been used as surrogate markers of anaphylaxis incidence and recent increases [1–3], there are a number of inherent limitations to interpretation including episodes occurring in the community where medical attention is not sought (estimated ~50% of patients; [37]), absent information on the number of patients treated but discharged from hospital without admission, the likelihood that such data under-represent the true community incidence of anaphylaxis [35], the inability to differentiate between single and repeat admissions for the same patients (estimated at only one episode/10 patient years; [37]), a reliance on the accuracy of the recorded clinical diagnoses (and the limited ability of assessing doctors to attribute risk in an emergency

**Table 2.** The relationship between SEIFA and geographic remoteness (using postal area data) and IHF formula prescription rates

| | β | 95% CI | *P*-value |
|---|---|---|---|
| SEIFA | | | |
| Unadjusted | 31.74 | 16.51, 46.97 | <0.001 |
| Model 1A | 21.57 | 4.22, 38.92 | 0.02 |
| Model 2 | – | – | – |
| Model 3 | 49.46 | 31.17, 67.76 | <0.001 |
| Model 4 | 37.68 | 20.63, 54.74 | <0.001 |
| Model 5 | 31.78 | 16.53, 47.03 | <0.001 |
| Remoteness | | | |
| Unadjusted | 111.28 | 57.40, 165.17 | <0.001 |
| Model 1B | 74.42 | 13.07, 135.78 | 0.02 |
| Model 2 | 148.51 | 70.61, 226.42 | <0.001 |
| Model 3 | 123.29 | 67.61, 178.98 | <0.001 |
| Model 4 | 138.23 | 76.36, 200.10 | <0.001 |
| Model 5 | 121.89 | 65.53, 178.25 | <0.001 |

CI, confidence interval; SEIFA, socio-economic indexes for areas.

Model 1A adjusts for geographic remoteness category, whereas Model 1B adjusts for SEIFA deciles.

Model 2 adjusts for percentage of individuals born in Australia, indigenous, speaking only English, unemployed, high school education, and mean income.

Model 3 adjusts only for population rate of medical practitioners, allergists, and retail pharmacies.

Model 4 adjusts only for population density.

Model 5 adjusts only for latitude.

**Table 3.** The relationship between SEIFA and geographic remoteness (using postal area data) and EpiPen prescription rates

| | β | 95% CI | *P*-value |
|---|---|---|---|
| SEIFA | | | |
| Unadjusted | 30.76 | 18.49, 43.03 | <0.001 |
| Model 1A | 18.41 | 3.81, 33.01 | 0.01 |
| Model 2 | – | – | – |
| Model 3 | 17.00 | 2.54, 31.46 | 0.002 |
| Model 4 | 22.52 | 8.78, 36.26 | 0.001 |
| Model 5 | 29.09 | 16.80, 41.38 | <0.001 |
| Remoteness | | | |
| Unadjusted | 89.29 | 55.49, 123.10 | <0.001 |
| Model 1B | 63.09 | 22.50, 103.68 | 0.002 |
| Model 2 | 33.35 | −12.47, 79.16 | 0.15 |
| Model 3 | 60.34 | 23.97, 96.71 | 0.001 |
| Model 4 | 65.98 | 26.20, 105.76 | 0.001 |
| Model 5 | 78.59 | 43.36, 113.83 | <0.001 |

CI, confidence interval; SEIFA, socio-economic indexes for areas.

Model 1A adjusts for geographic remoteness category, while Model 1B adjusts for SEIFA deciles.

Model 2 adjusts for percentage of individuals born in Australia, indigenous, speaking only English, unemployed, high school education, and mean income.

Model 3 adjusts only for population rate of medical practitioners, allergists, and retail pharmacies.

Model 4 adjusts only for population density.

Model 5 adjusts only for latitude.

While the correlation is modest (0.57), it is statistically significant ($P<0.001$).

situation without the ability to undertake confirmatory allergy testing) and the need to exclude serum anaphylaxis (due to small numbers) and insect sting anaphylaxis (due to limitations in ICD-10 coding). While it would have been desirable to analyse subgroups of anaphylaxis by attributed cause by SEIFA and geographic location, the variable degree of 'unclassified' anaphylaxis (which may have not only included idiopathic anaphylaxis but also admissions related to other causes) would have introduced an unacceptable degree of diagnostic error that would have rendered such an analysis difficult to interpret, particularly when attempting to analyse by age group, SEIFA and geographic location. Despite these limitations, if differences in SES-related health seeking behaviour influenced a decision to seek hospital treatment, they are less likely have biased a decision to treat and discharge (a factor more likely to correlate inversely with severity) rather than admit (and thus be recorded in hospital statistics). Furthermore, if SES-related behavioural differences were the only explanation, one might reasonably expect the SES–anaphylaxis admission rate trend to be uniform across all age groups, and not isolated to younger age groups as observed. Finally, public hospital treatment in Australia is free, making financial barriers alone an inadequate explanation for the trends observed.

A secondary finding of our study was conflicting evidence that FA/anaphylaxis might also be more common in major cities compared with more remote areas. IHF sales rates were over fivefold higher in major cities compared with more remote areas, and EpiPen sales rates in major cities were approximately twice that found in remote/very remote areas in patients aged 0–4 and 5–14 years, consistent with studies of anaphylaxis and atopic disorders [7–9]. By contrast, there was no significant relationship between geographic location and anaphylaxis admission rates. This is not surprising if one considers that location-specific factors might, for example, play a role in the food sensitization in young children (as reflected in IHF/EpiPen sales rates), without influencing the frequency and severity of episodes which (other than for the excluded sting anaphylaxis) are less likely to be location dependent. Alternatively, issues regarding the reliability of admission rates compared with EpiPen sales rates (as discussed above) may have resulted from a type II error.

Rural and remote areas are characterized by barriers to access to primary and specialist medical care, longer waiting lists compared with urban areas and higher out of pocket medical costs and non-medical costs incurred by time off work and travelling to access specialty care [38]. While we were unable to find any relationship between access to medical practitioners, allergists or number of retail pharmacies and EpiPen prescription rates, it is

conceivable that factors we were unable to measure (e.g. access to paediatric care, differences in prescribing practices or patient/parent health-seeking behaviour) might have influenced the data. When we considered the potential for data distortion introduced by examining data where IHF and EpiPens were sold rather than where patients lived, we found no substantial difference in regional distribution of retail pharmacies or pharmacists. Although it could be argued that geographic remoteness is a co-dependent marker of lower SES, both factors remained significant on multivariable analysis after adjusting individually for several SES-related factors (Tables 2 and 3). Finally, the age-dependent regional pattern of EpiPen prescriptions (observed in younger but not older age groups) argues against these factors being a major source of bias.

The similar pattern in all three proxies of FA/anaphylaxis examined combined with the age differential in EpiPen sales and admissions argues in favour of a real (not artefactual) relationship between SES, geographic remoteness and FA/anaphylaxis, most prominent in young patients. This most likely also reflects real differences in the prevalence of childhood FA, the most common cause of anaphylaxis in this age group [2, 34, 35]. While various environmental factors (reviewed in Lack [39]) have been postulated to contribute to the pathogenesis of FA, it is difficult to relate all of these exposures to either SES or geographical remoteness. For example, information on exposure to the 'protective effect' of rural living is restricted to that conferred by farm-related exposures, specifically exposure to farm animals and unpasteurized milk [13, 40], of little relevance to the majority of the population given that only 1.7% of Australian families live on farms and only 3.1% of the working population is involved directly or indirectly in agriculture [41]. Caesarean section as a risk factor [42] is more common in urban than rural environments, and in mothers of higher SES [43, 44]. Dietary factors [45] can be influenced by geographic location, with higher costs and restricted availability of fresh foods in rural compared with urban areas of Australia [46]. Finally, lower rate of FA/anaphylaxis in rural and remote areas might (in part) conceivably be explained by higher rates of UVR exposure [47], postulated in recent studies being partially protective against the development of allergic disease [21, 48–51].

Taken as a whole, our data suggest that higher SES and city living could be regarded as surrogate markers of a 'westernized lifestyle' and risk factors for FA/anaphylaxis development. While this does not preclude the possible protective effect of the converse – the protective effect of rural living – the relatively small proportion of the Australian population living in rural areas makes this less likely to be a major factor operating at a population level. Even though the operative risk factors linked to SES and geographic location remain to be unidentified, they appear to be more important in younger than older patients. Although association is not equivalent to causation (and our assessment of the potential influence of SES and geographic remoteness is indirect and based on population rather than individual exposures), our data provide a rational basis for a closer examination of the possible role of these factors in the pathogenesis of FA/anaphylaxis in early childhood and the extent to which economic factors and location of residence influence access to health services and patient care.

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