

Season of birth and childhood food allergy in Australia: A role for ultraviolet radiation/vitamin D?

Raymond J Mullins (1); Sunday Clark (2); Constance Katelaris (3); Victoria Smith (4); Graham Solley (5); Carlos A Camargo Jr (6)

1 Suite 1, John James Medical Centre, 175 Strickland Crescent, Deakin ACT 2600, Australia; 2 Division of General Internal Medicine, University of Pittsburgh, Pittsburgh, PA, USA; 3 Department of Medicine, University of Western Sydney, Sydney, Australia; 4 Rose Cottage Medical Center, Launceston, Tasmania, Australia; 5 Watkins Medical Center, Brisbane, Queensland, Australia; 6 Department of Emergency Medicine, and Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

INTRODUCTION

Of several environmental factors postulated to contribute to the pathogenesis of food allergy (FA), low vitamin D status has been proposed as a potential contributor. This hypothesis is based (in part) on:

- Latitudinal variations in EpiPen prescription rates in the USA and Australia (1, 2);
- Similar differences in hypoallergenic infant formula (IHF) prescriptions in Australia (3);
- Latitudinal variations in childhood anaphylaxis admissions rates in the USA (4), and;
- Low vitamin D intake during pregnancy and subsequent food sensitization in infants (5).

HYPOTHESIS

Given seasonal fluctuations in sun exposure and vitamin D status, we hypothesized that:

- Children born in autumn or winter months (with less sunlight exposure) might have higher rates of medically confirmed FA than those born in spring or summer, and;
- To address issues regarding generalisability, these seasonal differences would also be reflected in two proxy measures of FA: national adrenaline autoinjector (EpiPen) and IHF prescription data for children the same age.

METHODS

The birth month and season status of all medically confirmed IgE-mediated FA for children aged 0-4 years in an ACT-based specialty referral practice were examined.

The relative rate of FA by birth month was calculated using the number of ACT-resident with FA adjusted for the number of live births per year between 1997 and 2007.

National EpiPen (aged 0-4 years) and IHF prescriptions (age 0-2 years) were obtained from government sources.

RESULTS

Patient characteristics

835 ACT patients aged 0-4 years (58% male) had FA; 341 (41%) with peanut allergy; 365 allergic to hen's egg; (365), 223 to cow's milk, 145 to tree nuts or 129 to other foods.

Association between season of birth and food allergy

Although live births in the general ACT population during 1997 to 2007 were evenly distributed across the year (29,362 [50%] autumn/winter vs. 29,167 [50%] spring/summer; $P=0.42$), seasonal differences were found for FA patients: of 835 ACT patients 0-4 years, 475 (57%) were born autumn/winter compared to 360 (43%) spring/summer ($P<0.001$; **Figure 1**). Seasonal trends were observed for the relative rate of FA by birth month, most prominent for peanut (**Figure 2**).

Association between UVR and relative food allergy rate

There was a strong inverse correlation between ultraviolet light radiation exposure per month in the ACT and the relative rate of FA per birth month for FA ($P=0.05$) and peanut allergy ($P=0.01$; **Figure 3**). Similar (but non-significant trends) were observed for egg and cows milk but not tree nuts (data not shown).

Association between season of birth and EpiPen and IHF prescriptions

EpiPens were prescribed more commonly in children born in autumn/winter compared to those born in spring/summer (4964 [54%] vs. 4194 [46%]; $P<0.001$). A similar pattern was observed for IHF prescriptions, with higher rates in children born in autumn/winter compared to those born in spring/summer (5276 [54%] vs. 4585 [46%]; $P<0.0001$). These findings were not explained by monthly fluctuations in national birth rates between 1997 and 2007 (**Figure 4**).

CONCLUSIONS

FA rates were higher among children with autumn/winter births compared to spring/summer births.

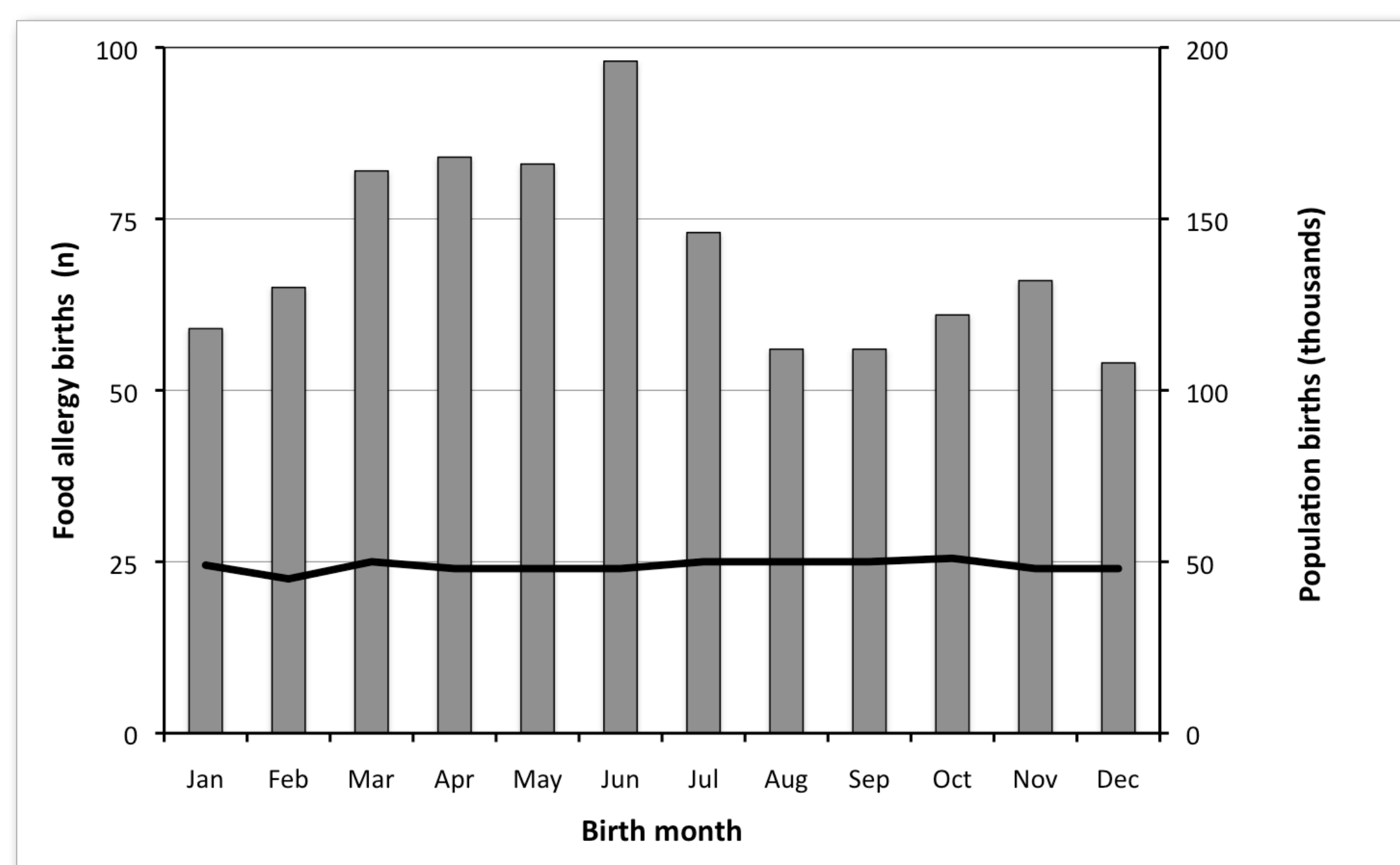
When analysed by birth month, food and peanut allergy rates were up to 2-3 fold higher in children born in mid-winter compared to mid-summer. These findings were not an artefact of month-to-month variation in birth rates.

The generalisability of our findings is supported by an analysis of national EpiPen and IHF prescription data.

The association between season of birth and relative FA rates in early childhood likely reflects one of many potential allergen-independent factors operating in early life to increase the risk of FA, and provides the rationale for further work in this area.

High rates of vitamin D deficiency in Australia (specifically in pregnant women without specific risk factors) provides a rationale to screen high-risk patients and to supplement individuals found to have very low vitamin D status.

Figure 1. Distribution of food allergy births by month. The birth month distribution of 835 children aged 0-4 years, in the Australian Capital Territory, diagnosed with food allergy between 1995 and 2009 (grey bars) is compared with the distribution of live births between 1997 and 2007, by birth month (black line).



FUNDING & ACKNOWLEDGMENTS

Dr Mullins received unrestricted investigator-initiated grants from Commonwealth Serum Laboratories Australia and Alphapharm Australia (the past and current Australian distributors of EpiPen), Abbott Nutrition Australia and the Ilhan Food Allergy Foundation. Dr Camargo has received investigator-initiated research grants from, and consulted for, Dey (Basking Ridge, NJ, USA) and sanofi-aventis (Bridgewater, NJ, USA). Study sponsors had no input into study design, data interpretation or the contents of this manuscript. The other authors report no conflict of interest.

Figure 2. Relative rates of food allergy by birth month. The relative rates of food allergy in children aged 0-4 years in the ACT adjusted by live birth rates/month in the same region.

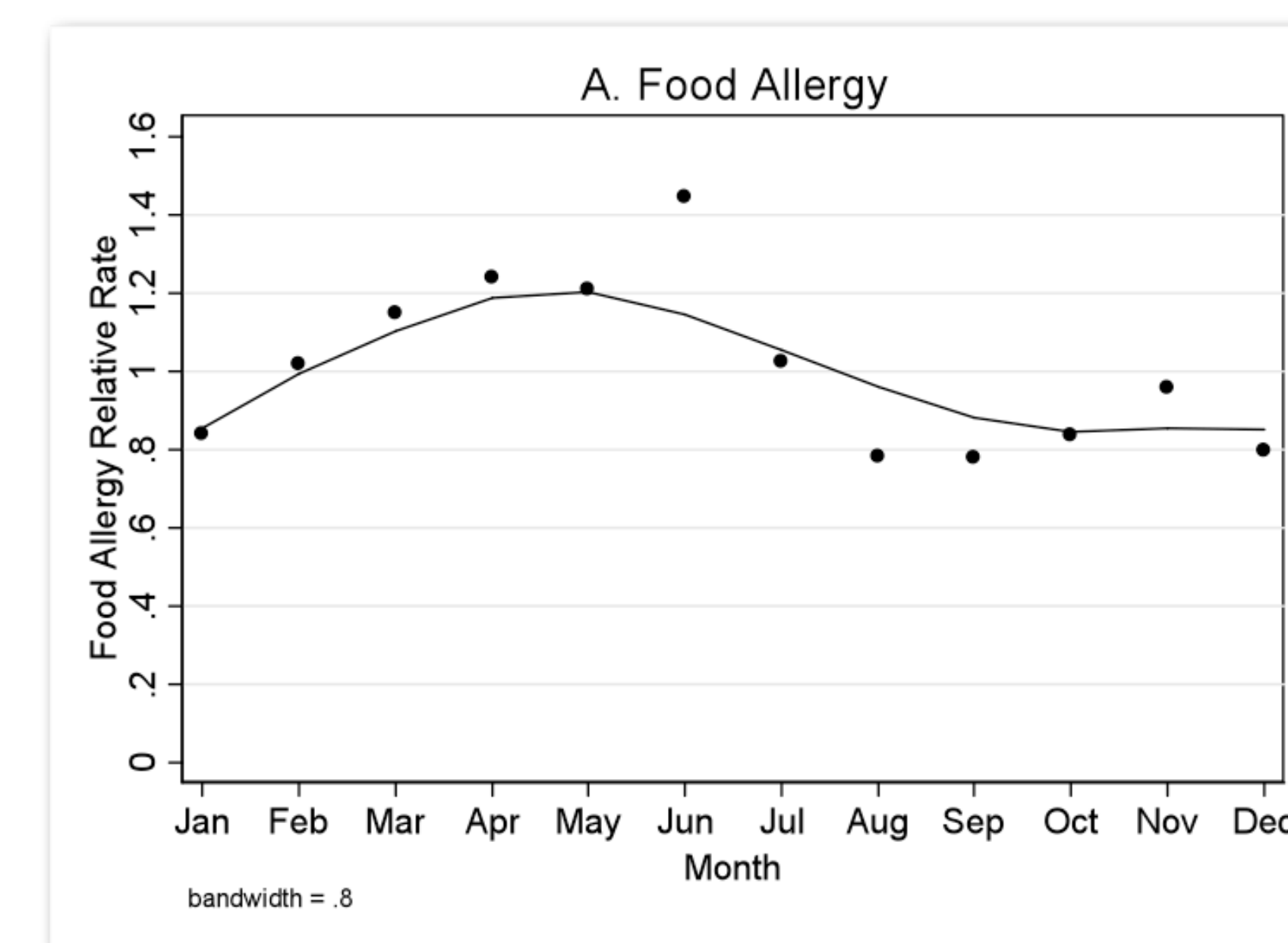


Figure 3. The relationship between average monthly UVR and food and peanut allergy rates per month. The intensity of UVR was inversely associated with relative rates of food allergy (closed circles) and peanut allergy (open circles) in children, aged 0-4 years, in the ACT. Trend lines for food allergy (unbroken line; solid circles) and peanut allergy (dotted line; open circles) are shown.

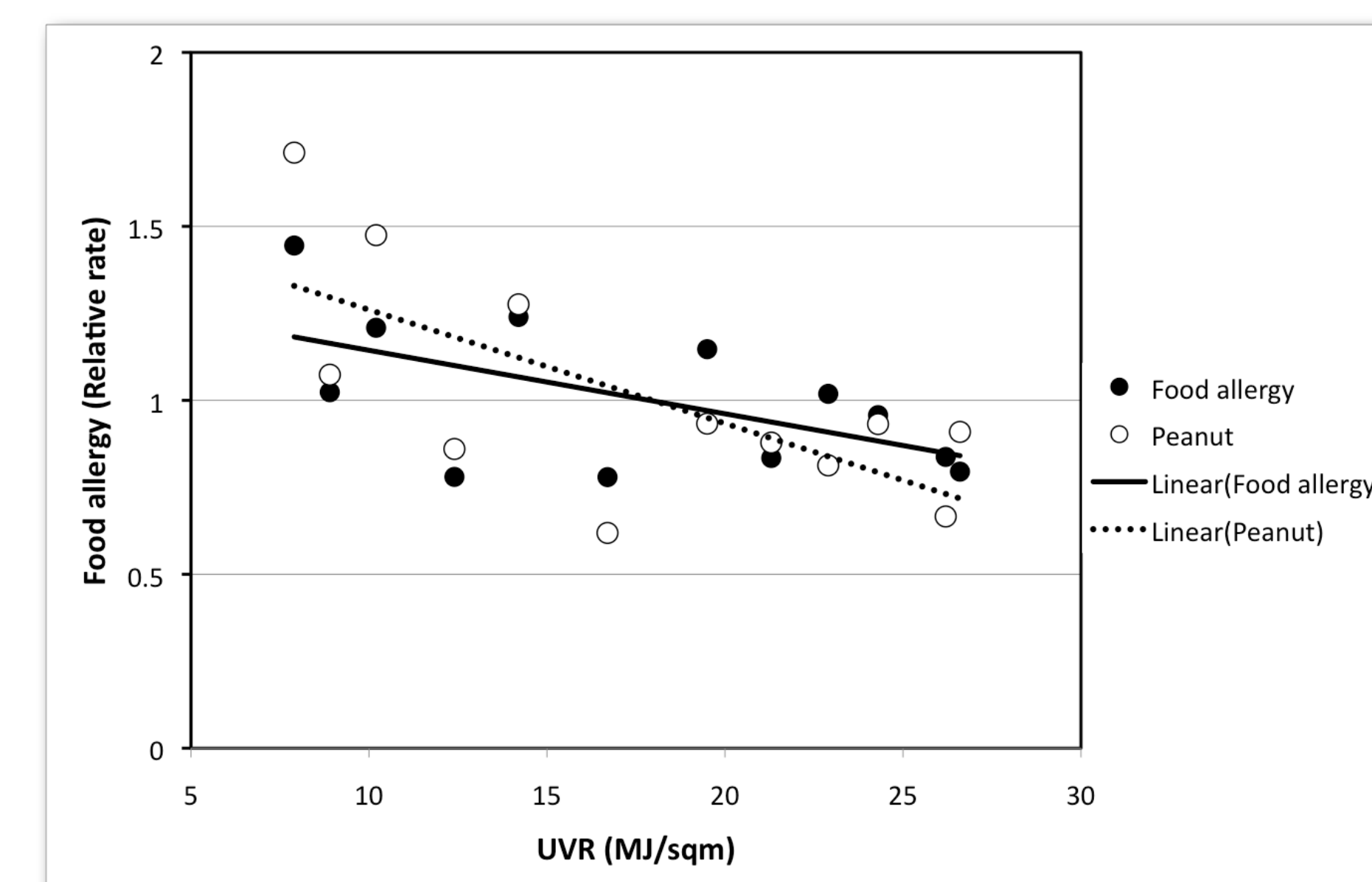
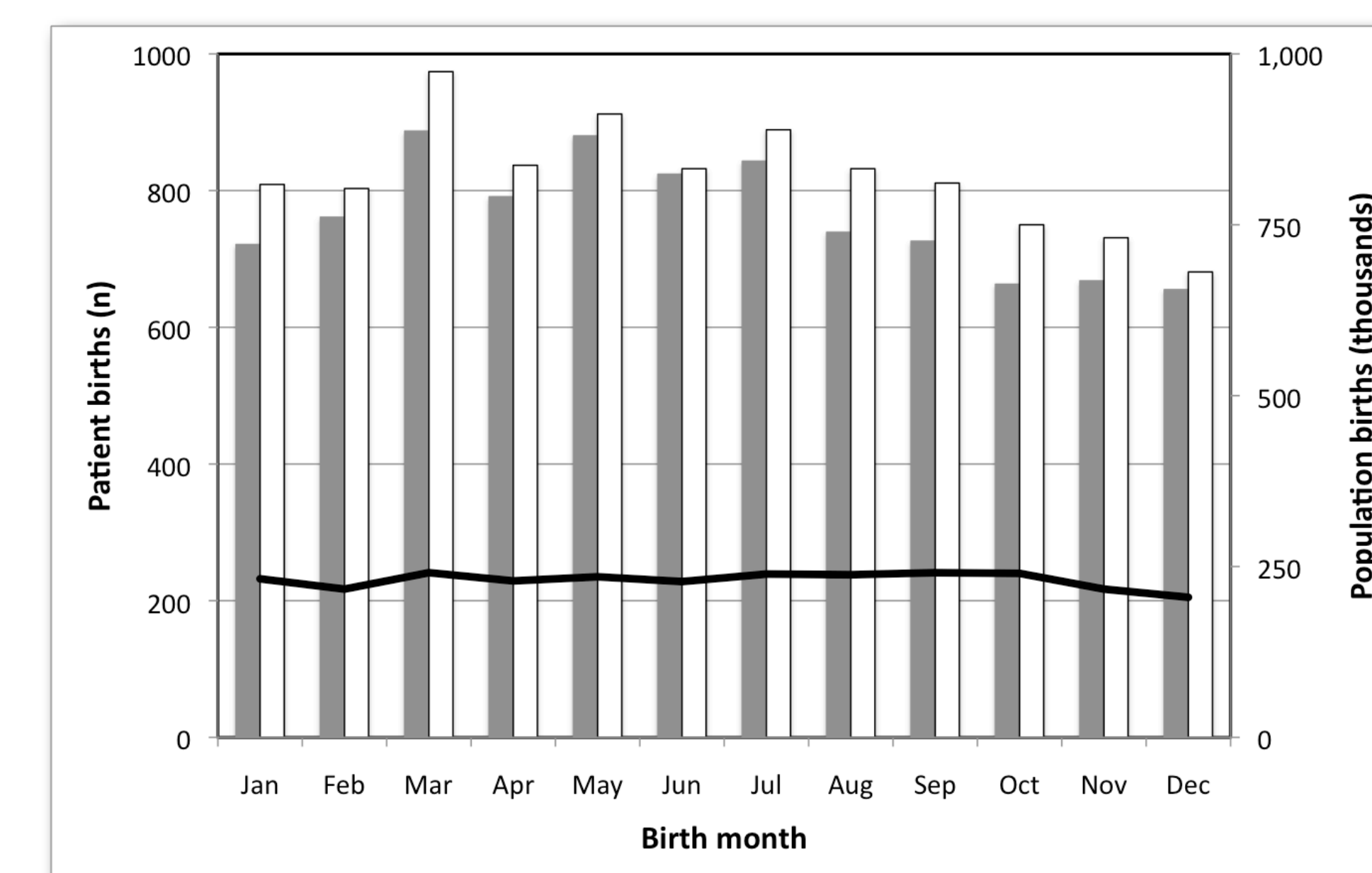


Figure 4. Distribution of Australian children prescribed EpiPen and infant hypoallergenic formula by birth month. The birth month distribution of children prescribed EpiPen during 2007 (aged 0-4 years, grey bars) or infant hypoallergenic formula during 2009 (aged 0-2 years, open bars) is compared with the national distribution of live births between 1997 and 2007 (black line).



REFERENCES

- 1) Camargo CA Jr, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol* 2007; 120: 131-6.
- 2) Mullins RJ, Clark S, Camargo CA Jr. Regional variation in EpiPen prescriptions in Australia: More evidence for the vitamin D-anaphylaxis hypothesis. *Ann Allergy Asthma Immunol* 2009; 103: 488-495.
- 3) Mullins RJ, Clark S, Camargo CA Jr. Regional variation in infant hypoallergenic formula prescriptions in Australia. *Pediatr Allergy Immunol* 2010; DOI: 10.1111/j.1399-3038.2009.00962.x
- 4) Rudders SA, Espinola JA, Camargo CA Jr. North-south differences in US emergency department visits for acute allergic reactions. *Ann Allergy Asthma Immunol* 2010; 104(5):413-6.
- 5) Nwaru BI, Ahonen S, Kaila M, Erkkola M, Haapala AM, Kronberg-Kippili C, Veijola R, Ilonen J, Simell O, Knip M, Virtanen SM. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. *Pediatr Allergy Immunol* 2011; 22: 29-37. DOI: 10.1111/j.1399-3038.2009.00949.x