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SHORT TITLE:

Nut allergy prevalence amongst children at primary school entry in Victoria, Australia.

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ABSTRACT:

Background

Asian infants born in Australia are 3 times more likely to develop nut allergy than non-Asian infants and rates of challenge-proven food allergy in infants have been found to be unexpectedly high in metropolitan Melbourne. To further investigate risk factors for nut allergy we assessed the whole of State prevalence distribution of parent-reported nut allergy in 5 year old children entering school.

Methods

Using the 2010 School Entrant Health Questionnaire administered to all 5 year old children in Victoria, Australia, we assessed the prevalence of parent-reported nut allergy (tree nut and peanut) and whether this was altered by region of residence, socioeconomic status, country of birth or history of migration. Prevalence was calculated as observed proportion with 95% confidence intervals (CI). Risk factors were evaluated using multivariable logistic regression and adjusted for appropriate confounders.

Results

Parent-reported nut allergy prevalence was 3.1% (95%CI 2.9-3.2) amongst a cohort of nearly 60,000 children. It was more common amongst children of mothers with higher education and socioeconomic index and less prevalent amongst children in regional Victoria than in Melbourne. While children born in Australia to Asian-born mothers (aOR 2.67 95%CI 2.28, 3.27) were more likely to have nut allergy than non-Asian children, children born in Asia who subsequently migrated to Australia were at decreased risk of nut allergy (aOR 0.1 95%CI 0.03, 0.31).

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Conclusion

Migration from Asia after the early infant period appears protective for the development of nut allergy. Additionally, rural regions have lower rates of nut allergy than urban areas.

Key words: food allergy, migration, nut allergy, peanut allergy, prevalence, tree-nut allergy

Abbreviations:

SEHQ School Entrant health Questionnaire

OFC: oral food challenge

SPT: skin prick test

IgE: immunoglobulin E

Introduction

Food allergy is thought to be on the rise although population data are sparse with little known about what environmental factors may be contributing to the rise. The rise appears highest in young children with a 5-fold increase in food-induced anaphylaxis in children aged 0 to 4 years between 2005-2012 in Australia [1]. Peanuts and tree nuts are two of the most common foods that cause allergic reactions [2], are the food allergies that are most likely to persist [3] and also have the highest lifetime risk for both anaphylaxis and anaphylaxis mortality [4].

We have previously shown unexpectedly high rates of nut allergy in a population-based cohort, the HealthNuts study, in Melbourne Australia with 3% (95%CI 2.4-3.8) of one year old infants demonstrating challenge-proven peanut allergy [5]. We have also shown that infants born in Australia to Asian-born parents are at significantly higher risk of nut allergy

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than those born to Australian-born parents [6, 7]. It is not clear whether this finding is an effect of ethnicity or migration. Here, we extend this work by exploring the role of migration and timing of migration (before or after birth of the child) from Asian and other countries to Australia.

Using a whole of state School Entrant Health Questionnaire (SEHQ) administered to 60,000 children at school entry (average age 5 years), we aimed to assess the prevalence of peanut, tree nut and combined nut allergy in Victoria, Australia in 2010. We also aimed to explore the role of geographical region of residence, socioeconomic status and migration to Australia on nut allergy prevalence in young children at the population level.

Methods

The population in this analysis consists of children beginning primary school in the state of Victoria, Australia, during 2010 (January-December school year).

1. *School Entrant Health Questionnaire (SEHQ)*

The School Entrant Health Questionnaire (SEHQ) is a parent or guardian report instrument that records information about children's health and wellbeing as they begin primary school in Victoria, Australia. It was developed in 1996-97 [8] and has since been annually administered to parents and guardians of preparatory grade children through the Victorian Primary School Nursing Program (VPSNP) of the Department of Education and Early Childhood Development. (DEECD). The parent - completed questionnaires were scanned and converted to an excel file which was then converted to STATA for statistical analysis.

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Definitions

An affirmative response to the question *'have you ever been told by a doctor that your child has an allergy problem*?' was classified as a parent-reported allergy. Parents reporting any allergy were asked to specify to which food, using a checkbox which included milk, peanut, egg, tree nuts, soy, wheat, and fish/shellfish. These were the only questions about allergy that were included in the SEHQ and no further information relevant to food allergy was collected.

Demographic and environmental exposures known to be associated with allergic disease from the HealthNuts cohort [9] and in other literature were considered in our analysis. The following relevant variables could be extracted from the SEHQ: child's age and gender, mother's country of birth, child's country of birth, postcode of residence, mother's level of education, and Local Government Area (LGA) of residence. The Australian Statistical Geography Standard (ASGS) was used to give a measure of remoteness based on geographical region. Australian states and territories are divided into five Remoteness Areas (RAs) based on relative access to services: Inner Regional Australia, Major Cities of Australia, Outer Regional Australia, Remote Australia and Very Remote Australia. Postcodes of residence were converted to RAs (Australian Statistical Geography Standard (ASGS): Volume 5 - Remoteness Structure, July 2011 (cat. no. 1270.0.55.005)).

The country of birth variable for mother and child was collapsed into 8 categories: Australia, East Asia, England, NZ, India, USA and South Africa and unknown. East Asian countries included China, the Philippines, South Korea and Hong Kong. The group termed 'unknown' comprised participants for whom country of birth data were "missing".

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To determine socio-economic status, postcodes of residence were matched with data from the Australian Bureau of Statistics, Socio-economic Indexes for Areas (SEIFA) to obtain the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) for each child [10]. This Index takes into account economic and social conditions of people and households within an area, including both relative advantage and disadvantage measures.

2. *Statistical analysis*

Prevalence of parent reported allergy using SEHQ: The prevalence of individual allergies (to any food and separately for each of the seven individual foods/food groups), eczema and asthma were calculated as the observed proportion with 95% confidence intervals (CI) for the population prevalence calculated assuming a binomial sampling distribution. Figures were mapped for Victorian regions and metropolitan Melbourne by region and individual Local Government Areas.

Risk factors for nut allergy: For these analyses, "peanut allergy" and "tree nut allergy" were combined as a single category of "nut allergy". Although peanuts are technically legumes or groundnuts, tree nut and peanut allergies are clinically similar and often co-exist [11]. Multivariable logistic regression was used to examine the association between the three exposures of interest: (1) location (LGA region); (2) socioeconomic status (SEIFA, maternal education), (3) maternal country of birth and child country of birth (as a marker of migration), and the risk of nut allergy in the child. All three factors were included in a single regression model so estimated odds ratios measure the association between the exposure and the risk of the outcome adjusted for the other two exposures. All models were additionally adjusted for sex of child.

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Based on our previous findings, we hypothesised that the prevalence of nut allergy in the child would be modified by the relationship between maternal country of birth and by the child's country of birth e.g. children with a mother born in Asia would have a lower prevalence of food allergy if the child was also born in Asia, compared with the child being born in Australia. We examined this hypothesis by fitting interaction terms in the multivariable logistic regression model. There was strong evidence of an interaction between child's county of birth, mother's country of birth and nut allergy (p=0.001). We therefore investigated the relationship between the child's country of birth and the risk of nut allergy, stratified by maternal country of birth. For this model, the country of birth variables (child and maternal) were collapsed further with East Asia and India combined into one category termed 'Asia'.

The results of the statistical modelling described above are presented in the tables of estimated odds ratios and 95% confidence intervals (CIs). Data were analysed using Stata version 13.1 (StataCorp, College Station, Texas, USA).

Ethics Approval

Ethics approval was granted by the human research ethics committees of the Royal Children's Hospital (HREC# 34168) and approved by the Victorian Department of Education and Early Childhood Development.

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Results

In 2010, 66,444 children were enrolled in preparatory grade of which 57,005 (85.8%) parents returned the SEHQ (2010-2012 preparatory enrolments were provided by the Performance and Evaluation Division, Department of Education and Early Childhood Development). The mean age of participating children was 4.9 years (SD 0.44 years, median age 5 years), 51.2% were male, 34.5% of mothers had a tertiary degree, 70.4% were born to Australian born mothers and 90.2% of children were born in Australia (Table 1). More than 90% of the parents reported that their child's overall health was very good or excellent. Major cities comprised 73.1% of the SEHQ sample with inner regional comprising 20.7% and outer regional, remote and very remote contributing 6.2%.

Prevalence of parent-reported peanut and tree nut allergy

The overall prevalence of parent-reported food allergy was 5.07% (95%CI 4.89-5.25) (Table 2). The prevalence of parent-reported peanut allergy was 2.68% (95%CI 2.55-2.82) and tree nuts was 1.67 % (95%CI 1.57-1.78). The prevalence of any nut allergy was 3.09% (95%CI 2.95 - 3.23).

Differences in nut allergy prevalence by region and socioeconomic status

Figure 1a displays the distribution and prevalence of nut allergy in the 30 Local Government Areas (LGAs) amongst the four geographical regions of metropolitan Melbourne. The overall prevalence of nut allergy in the metropolitan area was 3.4% (95%CI 3.22-3.58).

Figure 1b shows the distribution and prevalence of nut allergy across the five non-metropolitan Victorian regions (Loddon Mallee (n=3585), Grampians (n=2615), Barwon South West (n=4198), Hume (n=3199) and Gippsland (n=2910)). Overall the prevalence of

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nut allergy across these non-metropolitan regions was 2.38% (95%CI 2.16-2.60), varying from 1.82% in Gippsland to 2.55% in Barwon South West.

After adjusting for maternal and child country of birth, nut allergy was more commonly reported amongst children of mothers with higher education levels and higher socioeconomic index (Table 3). When these two factors were included in the model there was little difference in nut allergy prevalence between the nine Victorian regions.

In a separate model using a classification of region based on remoteness, the ASGC Remoteness Area Index, there was some evidence of less nut allergy amongst children residing in inner regional Victoria (OR 0.8 95%CI 0.67-0.95) and outer regional Victoria (OR 0.51 95%CI 0.51-1.03) than in major cities in adjusted logistic regression models for socioeconomic status and maternal education.

Relationship between migration and nut allergy

The prevalence of nut allergy amongst children by child and maternal country of birth is presented in Figure 2a.

Children born to Asian mothers were less likely to have nut allergy if they were born in Asia and subsequently migrated to Australia (aOR 0.1 95%CI 0.03, 0.31) than children born in Australia to Asian mothers (aOR 2.67 95%CI 2.28, 3.27) (figure 2b). There were no differences related to country of birth of the child for risk of nut allergy if mothers migrated from England or New Zealand. A sub-analysis of the migration results was performed on the groups separately, however this did not change the overall result. For peanut allergy only children born to Asian mothers were less likely to have nut allergy if they were born in Asia

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and subsequently migrated to Australia (aOR 0.08 95%CI 0.01, 0.57) than children born in Australia to Asian mothers (aOR 2.90 95%CI 2.17, 3.89). The results are similar for tree nut allergy with children born to Asian mothers in Australia being more likely to have tree nut allergy (aOR 1.35 95%CI 073, 2.47) than those children born to Asian mothers in Asia.

Discussion

In this whole of state study of 57,000 children with a mean age of 4.9 years, 3.1% had a parent-reported nut allergy (2.7% to peanut and 1.7% to tree nuts) with a lower prevalence in rural versus urban regions. We also found that postnatal migration from Asia appeared protective against nut allergy and confirmed that Australia-born Asian children had higher rates of nut allergy than Australian born non-Asian children.

The strengths of this study are the large population-based dataset that captured data from the majority of children who began primary school in Victoria in 2010. The main limitation is that food allergy was reported by parents which can lead to overestimation due to confusion with other conditions associated with adverse reactions to food. However, nut allergies are most commonly IgE-mediated and reactions are usually immediate (within 5-10 minutes), which provides greater confidence that parent-report is likely to correlate with challenge-proven outcomes [12]. The use of self-reported nut allergy data to examine risk factors may have contributed to the association between socioeconomic factors and nut allergy. Mothers from a higher socioeconomic index, with a higher education level and from metropolitan areas might be more likely to seek medical advice for a food reaction, and may therefore be more aware of their child's nut allergy status.

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Our findings regarding migration and food allergy are unlikely to be attributed to differential reporting of allergy by maternal country of birth since we observed the same patterns using challenge-confirmed allergy in the HealthNuts cohort. We reported a higher prevalence of peanut allergy in children with either one or two East Asian parents, with a higher prevalence in those with two East Asian parents [6]. Unfortunately no information on paternal country of birth was available in the SEHQ cohort.

We have previously shown high rates of peanut allergy in a population-based cohort study of 1 year old infants in metropolitan Melbourne, Australia in which 3% had challenge-proven peanut allergy [5]. This is in the context of a high population level of food sensitisation, with 9% sensitised to peanut [5]. Our 4-5 year old SEHQ cohort (2.7% peanut allergy) is comparable with challenge-proven peanut allergy prevalence (3.4%) in 1 year olds in metropolitan Melbourne (HealthNuts study) since we have shown in two separate studies that approximately 20% of infants develop tolerance to peanut between 1-5 years of age [3, 13].

The prevalence of nut allergy in Victoria is high compared to international estimates. Rona *et al*. conducted a meta-analysis of IgE-mediated food allergy prevalence of common food allergens in Europe. Self (parent)-reported peanut allergy varied from 0-2% amongst 0-4 year old children [14]. A further review found that the prevalence of self (parent)-reported tree nut allergy was 0.03-0.2% amongst 0-6 year old children [15]. Our recent tree nut allergy systematic review showed worldwide prevalence of IgE-mediated tree nut allergy was less than 2% for children less than 18 years of age [16]. Although that includes children of all ages and since some outgrow nut allergy with age higher prevalence in younger age groups such as in this study would be anticipated. However, our findings are consistent with other Australian population-based studies, including data from the Australian Capital Territory where parent-reported nut allergy prevalence amongst 5 year old school entrants in 2009 was

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3.8% (95%CI 3.2-4.4%) [17]. Likewise, the prevalence of parent-reported peanut allergy amongst a cohort of 4000 Australian children aged 4-5 years sampled from across each of the states - and along the full latitude gradient of Australia, was found to be 2.9% [18]. Our data contributes to strong and consistent evidence that Australia has a high prevalence of allergic disease, compared with other countries [19].

The question remains as to why Australia has such high rates of nut allergy. Several hypotheses have been proposed which might contribute to this phenomenon, including the hygiene hypothesis [20, 21], the dual allergen exposure [22], and the vitamin D hypothesis [23]. Unique to Australia, rising rates of migration from East Asia coupled with more recently rising rates from India with second generation children born in Australia, may explain at least some of the increase in food allergy, and the unusually high rate of food allergy in Victoria. In 2011, 46.8% of Victorians were either born overseas or had at least one parent born overseas. Of overseas-born Victorians, 15% were born in South East Asia and 13% in Southern and Central Asia with large increases between 2006 and 2011 [24]. Our findings suggest that removal of protective environmental factors present in the Asian environment, or conversely exposure to environmental risk factors in the Australian (Western) environment, uncover a genetically determined risk of food allergy in children of Asian descent. Risk factors associated with migration could include changes to diet, microbial exposure and Ultra Violet Radiation (UVR) exposure with impact on Vitamin D status. Finally changes to humidity and the potential effect on eczema development may also play a role.

Conclusions

Parental migration from Asia to Australia appears to be an important risk factor in the development of nut allergy in the next generation, while being born in Asia is protective even

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with migration to Australia in early life. The finding of an urban-rural difference in Victoria contributes to the concept that early life microbial exposure may be an important key risk factor for persistent IgE-mediated nut allergy.

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Conflict of Interest

Conflict of interest: M.T. is a member of the Medical Advisory Board (Oceania) for Nestle Nutrition Institute, a member of the Medical Advisory Board (Australia New Zealand) for Danone Nutricia and a member of the Scientific Advisory Board for Immunology Allergy (Global) for Danone Nutricia; and has received lecture fees from Danone and Nestle Nutrition Institute; and has received travel fees from APAPARI. K.A has received speaker's honoraria from Abbott, Danone, Nestle and Alphapharm. The rest of the authors declare that they have no relevant conflicts of interest.

Author Contributions

MP, JK, KA developed the concept, facilitated the writing, edited the manuscript and led the writing of specific sections. MP, JK & SD under took the statistical analysis. All the authors contributed to the development of the manuscript and approved the final version.

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Figure Legends

Figure 2a Legend:
NZ=New Zealand
Model also adjusted for Socio-economic Indexes for Areas, (SEIFA, most disadvantaged =1, least disadvantaged =5), maternal education. All factors were included in the model simultaneously.
Maternal country of birth/Child country of birth: Australia/Australia (n=39585), NZ/NZ (n=233), NZ/Australia (n=786), England/England (n=214), England/Australia (n=1144), East Asia/East Asia (n=420), East Asia/Australia (n=1112), India/India (n=583), India/Australia (n=545)

Figure 2b Legend:
NZ=New Zealand
Model also adjusted for Socio-economic Indexes for Areas, (SEIFA, most disadvantaged =1, least disadvantaged =5), maternal education. All factors were included in the model simultaneously.
Maternal country of birth/Child country of birth: Australia/Australia (n=39585), NZ/NZ (n=233), NZ/Australia (n=786), England/England (n=214), England/Australia (n=1144), Asia/Asia (n=1005), Asia/Australia (n=1657)

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Table 1: Demographics of Victorian primary school entrants completing the School Entrant Health Questionnaire (n=57,005)

Variable	N (%)
Age	4.9 ± 0.44 (4.0-7.0)
Mean ± SD (range) years	
Sex of child	
Female	27,169 (48.83)
Male	28,476 (51.17)
Mother's country of birth	
Australia	40,118 (70.38)
New Zealand	1,046 (1.83)
England	1,412 (2.48)
East Asia	1,657 (2.91)
India	1,274 (2.23)
USA	193 (0.34)
South Africa	381 (0.67)
Unknown	9,381 (16.46)
Missing	1,543 (2.71)
Child's country of birth	
Australia	51,439 (90.24)
New Zealand	471 (0.83)
England	512 (0.90)
East Asia	506 (0.89)
India	593 (1.04)
USA	170 (0.30)
South Africa	114 (0.20)
Unknown	2,202 (3.86)
Missing	998 (1.75)
Region	
North (metropolitan)	9,973 (17.49)
West (metropolitan)	6,814 (11.95)
South	13,003 (22.81)
East	10,708 (18.78)
Barwon S/West	4,198 (7.36)
Gippsland	2,910 (5.10)
Grampians	2,615 (4.59)
Hume	3,199 (5.61)
Loddon Mallee	3,585 (6.29)
Mother Education	
Some high school	9,175 (16.10)
Completed high school	12,302 (21.58)
TAFE trade cert/diploma	10,704 (18.78)
Tertiary institute degree	19,684 (34.53)
Other	597 (1.05)
Missing	4,543 (7.97)
SEIFA^	

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1	14,411 (24.59)
2	10,060 (17.17)
3	6,756 (11.53)
4	14,861 (25.36)
5	4,441 (7.58)
Missing	8,067 (13.77)
Child's general health	
Excellent	34,335 (60.23)
Very good	17,376 (30.48)
Good	3,667 (6.43)
Fair	416 (0.73)
Poor	41 (0.07)
Missing	1,170 (2.05)
ASGCS#	
Major cities	31,515 (73.14)
Inner regional	8,910 (20.68)
Outer regional	2,372 (5.50)
Remote	184 (0.43)
Very remote	108 (0.25)

^ Socio-economic Indexes for Areas most disadvantaged =1, least disadvantaged =5
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Table 2: Prevalence of parent-reported allergic disease in Victorian primary school entrants (n=57,005)

Allergy outcome	n	% (95% CI)
Any food allergy	2,892	5.07 (4.89, 5.26)
Peanut allergy	1,529	2.68 (2.55, 2.82)
Tree nuts	952	1.67 (1.57, 1.78)
Any nut allergy (peanut and/or tree nut)	1,761	3.09 (2.95, 3.23)
Egg	954	1.67 (1.57, 1.78)
Milk	762	1.34 (1.24, 1.43)
Soy	149	0.26 (0.22, 0.31)
Fish/shellfish	363	0.64 (0.57 - 0.70)
Wheat	241	0.42 (0.37 - 0.48)

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Table 3: Differences in parent-report nut allergy prevalence by region and socioeconomic status

			Univariate logistic regression		Multivariate logistic regression*	
Variable ***reference category***	**Children with nut allergy n=1,761 (3.09%)**	**Children without nut allergy n=55,245 (96.91%)**	**OR (95% CI)**	**P value**	**Adjusted OR (95% CI)**	**P value**
Sex of child						
Female	729 (2.68)	26,440 (97.32)	1.0		1.0	
Male	1,014 (3.56)	27,462 (96.44)	1.34 (1.21, 1.47)	**<0.001**	1.39 (1.25, 1.55)	**<0.001**
Region						
North	325 (3.26)	9,648 (96.74)	1.0		1.0	
West	265(3.89)	6,549 (96.11)	1.20 (1.02, 1.42)	**0.03**	1.18 (0.98, 1.42)	0.08
South	439 (3.38)	12,564 (96.62)	1.04 (0.90, 1.20)	0.62	1.06 (0.89, 1.25)	0.49
East	355 (3.32)	10,353 (96.68)	1.02 (0.87, 1.20)	0.82	0.98 (0.82, 1.17)	0.85
Barwon S/West	107 (2.55)	4,091 (97.45)	0.77 (0.62, 0.97)	**0.02**	0.90 (0.71, 1.16	0.43
Gippsland	53 (1.82)	2,857 (98.18)	0.55 (0.41, 0.74)	**<0.001**	0.73 (0.52, 1.00)	**0.05**
Grampians	64 (2.45)	2,551 (97.55)	0.74 (0.57, 0.98)	**0.03**	0.86 (0.63, 1.17)	0.35
Hume	68 (2.13)	3,131 (97.87)	0.64 (0.49, 0 .84)	**0.001**	0.82 (0.61, 1.10)	0.18
Loddon Mallee	84 (2.34)	3,501 (97.66)	0.71 (0.56, 0.91)	**0.006**	0.82 (0.62, 1.09)	0.18
SEIFA quintile^						
1	381 (2.64)	14,030 (97.36)	1.0		1.0	
2	305 (3.03)	9,755 (96.97)	1.15 (0.99, 1.34)	0.071	1.09 (0.92, 1.29)	0.33
3	245 (3.63)	6,511 (96.37)	1.38 (1.78, 1.63)	**0.000**	1.25 (1.05, 1.50)	**0.01**
4	530 (3.57)	14,331 (96.43)	1.36 (1.19, 1.56)	**0.000**	1.22 (1.03, 1.44)	**0.02**
5	157 (3.54)	4,284 (96.46)	1.35 (1.11, 1.63)	**0.002**	1.22 (0.97, 1.76)	0.09

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Mother Education						
Some high school	211 (2.30)	8,964	1.0		1.0	
Completed high school or equivalent	333 (2.71)	(97.70)	1.18 (0 .99,	**0.06**	1.11 (0.92,	
TAFE trade certificate or diploma	341 3(.19)	11,969	1.41)	**<0.001**	1.33)	0.27
university / tertiary institute degree including post-grad	733 (3.72)	(97.29)	1.40 (1.17,	**<0.001**	1.30 (1.08,	
		10,363	1.66)		1.57)	**0.005**
		(96.81)	1.64 (1.41,		1.49 (1.25,	**<0.001**
		18,951	1.92)		1.76)	
		(96.28)				

* All factors were included in the model simultaneously. Additionally adjusted for maternal and child country of birth

^SEIFA, Socio-economic Indexes for Areas, most disadvantaged =1, least disadvantaged =5

Significant p-values bold

Figure 1a: Prevalence (%) of nut allergy (peanut and/or tree nut) in metropolitan Melbourne only

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Figure 1b: Prevalence of nut (peanut and/or tree nut) allergy in non-Metropolitan regions in State of Victoria, Australia. (Dark shaded area represents Melbourne Metropolitan region)

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Figure 2a: % Prevalence (95%CI) of nut allergy by maternal and child country of birth

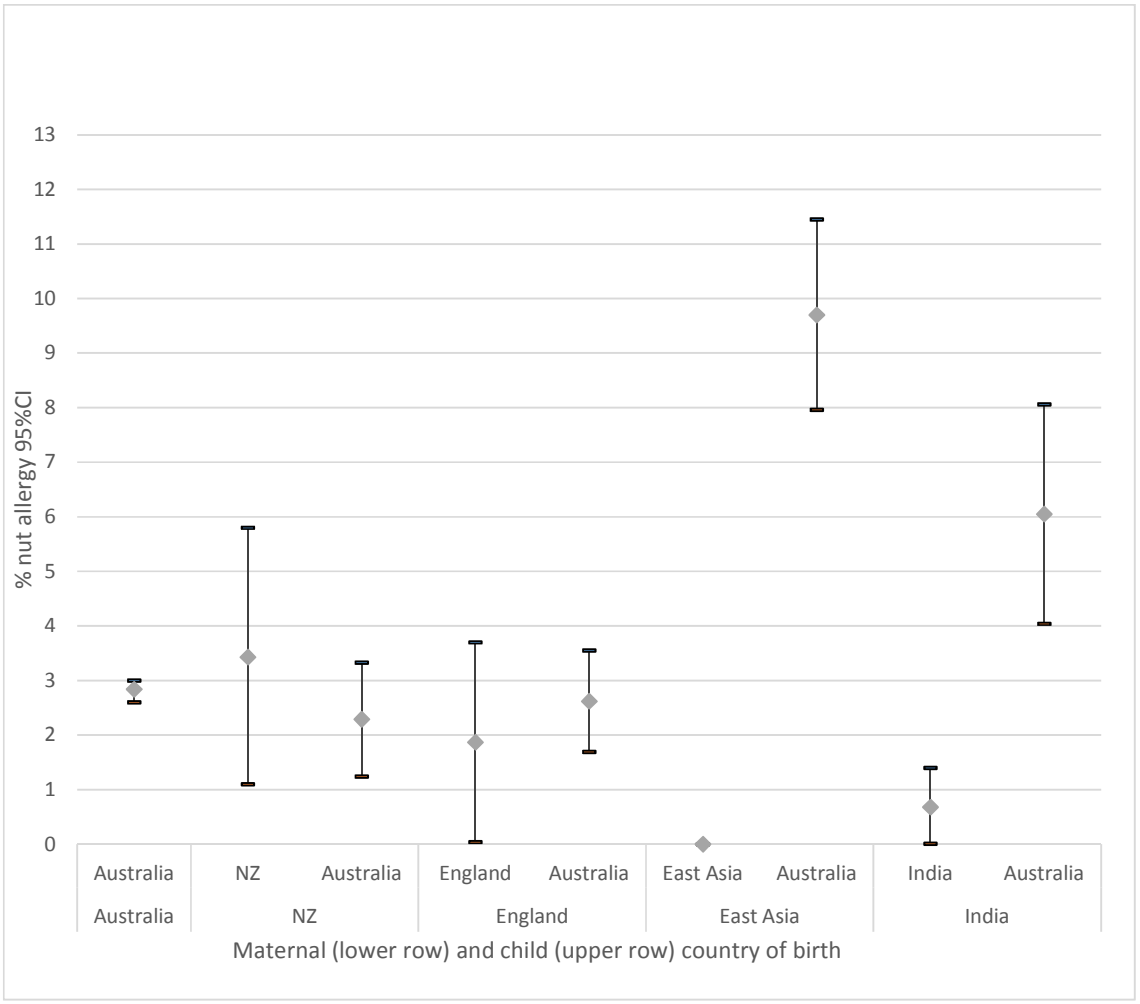

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Figure 2b: Adjusted Odds Ratios for nut allergy: child country of birth by maternal country of birth