The prevalence, natural history and time trends of peanut allergy over the first 10 years of life in two cohorts born in the same geographical location 12 years apart

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Running Title: Time trends in peanut allergy

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Abstract

Background: The aim of this study was to explore the natural history of peanut allergy in childhood in two birth cohorts from the same geographical region in the South of England.

Methods: The FAIR birth cohort was established on the Isle of Wight (UK) between 2001-2002 (n = 969). Children were followed up prospectively, skin prick tested (SPT) to peanut allergens at 1, 2, 3 and 10 years and food challenges performed. The Isle of Wight (IOW) Birth cohort was established in 1989 (n = 1456). SPTs were performed at 1, 2, 4 and 10 years. Peanut allergy was based on positive SPT and a good clinical history.

Results: In the FAIR cohort, the prevalence of sensitization to peanut was 0.4%, 2.0%, 2.0% and 2.4% at 1,2,3 and 10 years respectively. At 10 years of age, 12/828 (1.5%) children were diagnosed with peanut allergy. One child (8%) outgrew her peanut allergy between 3 and 10 years and two children (15%) presented with new onset peanut allergy. Over the first ten years of life, 13/934 (1.4%) children were diagnosed with peanut allergy. In the IOW cohort, 6/1034 (0.58%) were diagnosed with peanut allergy at 10 years. We found no significant differences between the FAIR and the IOW birth cohort for any of the time points studied.

Conclusion: Peanut allergy appears to be stable over the first ten years of life in our cohorts. There was no significant difference in peanut sensitization or clinical peanut allergy between 1989 and 2001.

Key words: birth cohort, food allergy epidemiology, peanut allergy, prevalence, time trends

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Introduction

Prevalence, incidence and time trends of peanut allergy in older children remain unclear. Furthermore, it is not known if the prevalence and/or natural history of peanut allergy during childhood has changed in the last decade, although sensitization rates to peanut are reported to be stable (1). A systematic review reported an overall pooled estimate for all age groups of food-challenge-defined peanut allergy of 0.2% (0.2–0.3) (2). In the USA a systematic review (3) based their prevalence figures of 0.6% in 6-10 year olds and 0.2% in 11-17 year olds, mainly on data by Sicherer et al. (4,5).

In terms of the natural history of peanut allergy, we know from cohorts recruited from hospital based clinics, that a small proportion (20%) of children with peanut allergy outgrow it by adolescence and occasionally a relapse may occur (6). Less is known however about the natural history of peanut allergy in unselected, population based birth cohorts (7). Recently, Peters et al. (8) reported a prevalence rate of 1.47% at 4 years in the HealthNuts study. However this was not a birth cohort as children were recruited at 1 year.

We recently reported prevalence of peanut allergy (0.58%) and sensitization (1.3%) at 10 years of age in a cohort born in 1989 (Isle of Wight (IOW) birth cohort) (7). In another cross-sectional study, peanut sensitization rates of 3.7% was reported on the Isle of Wight at 11 years (9). These children (different from the two birth cohorts analyzed in this study) were born in 1991/1992 and assessed at only 11 years of age during a school visit. We have also reported on the time trends of peanut allergy using data from three different cohorts on the Isle of Wight when followed up between the ages of 3-4 years (10), who were born in 1989 (IOW Birth cohort), 1994–1996 (FAB cohort), and 2001–2002 (FAIR birth cohort). Skin prick test (SPT) positivity to peanut and clinical peanut allergy in children aged between 3-4 years increased significantly from 1993 to 1998/2000, but with no significant change was seen from 1998/2000 to 2004/2005. We now present prevalence and natural history data of peanut allergy up to 11 years of age in the FAIR birth cohort, born in 2001-2002. In order to describe time trends of peanut allergy, we have compared the FAIR

cohort to the IOW birth cohort (born in 1989-90) at 1, 2, 3-4 and 10 years of age.

Methods

FAIR birth cohort

A birth cohort born on the Isle of Wight (UK) (n = 969) between 2001-2002 was followed up prospectively (11). Children were clinically examined and SPT were performed to milk, wheat, egg, cod, peanut and sesame (ALK Abello) at 1, 2, 3 and 10 years of age. Children were invited for food challenges when indicated at three and ten years of age. The Committee on Toxicity advice (UK)(12), which recommended the avoidance of peanut until 3 years in high risk families, was still relevant at the time. Children were therefore first challenged to peanut at 3 years of age.

Peanut allergy was defined as a positive food challenge or a positive SPT and a thorough clinical history, as previously reported (7). At 10 years sensitization was also measured using specific IgE to whole peanut protein and individual components (ThermoFisher, Uppsala, Sweden). Lupin sensitization and allergy was determined at 10 years only, using Stallergens SPT solution.

The IOW Birth cohort

The IOW birth cohort was born in 1989 (13) . SPTs were performed at 1, 2, 4 and 10 years of age using ALK Abello diagnostic extracts. 1034 children were seen at 10 years of age (7). Peanut allergy was defined as a positive SPT and a thorough clinical history (14).

In both cohorts SPT was performed using standardised allergen reagents and methodology by the same research team (15). Allergic sensitization was defined by a positive SPT, indicated by a mean wheal diameter of 3 mm or greater than the negative control (saline).

Specific IgE tests in the FAIR cohort

All children in the FAIR cohort were invited to undergo a blood test, n=246 consented. Specific IgE tests to peanut were performed using ImmunoCap

(ThermoFisher). Component resolved diagnostic (CRD) tests using ImmunoCap (ThermoFisher) were performed in all children with a positive specific IgE test to peanut; these included: Ara h1, Ara h2, Ara h3, Ara h8 and Ara h9 components.

Food challenges in the FAIR cohort

Food challenges were performed with 2.5g of peanut protein at 3 years of age followed by a normal age-appropriate portion, calculated from national consumption data for young children from the UK National Diet and Nutrition Survey databases (16). At 10 years of age, the PRACTALL (17) recommendations were in place, therefore challenge doses were adapted to comply with these (i.e. 3.443g of protein). At younger ages in the FAIR cohort, challenges were performed as double blind placebo controlled food challenge, however at age 10 parents consented to open food challenges only as their children already had prior diagnosis of peanut allergy. Food challenges were considered positive based on an adapted version of the PRACTALL (17) recommendations, which is used as standard clinical practice at the David Hide Asthma and Allergy Clinic on the Isle of Wight.

Statistical methods

All data were double entered by different operators on SPSS versions 20 and 21 and were verified (SPSS Inc, Chicago, USA). Prevalence rates were computed, together with 95% confidence intervals, using the method of Clopper and Pearson. Numbers indicating loss of follow-up were clearly stated. Fisher's exact tests, Odds Ratio and Mann Whitney tests were used to assess risk factors for the development of peanut allergy. A logistic regression model was used to assess factors that could independently determine development of peanut allergy.

Ethical approval for the FAIR study was obtained from the NRES South Central - Southampton B Research Ethics Committee (REF 10/H0504/11). Ethical approval for the IOW study was obtained from the Isle of Wight Local Research Ethics Committee (Ref 18/98). All parents consented and children provided assent.

Results

Prevalence and cumulative incidence of peanut allergy in the FAIR birth cohort

969 children were recruited and 900/969 (92.9%), 858/969 (88.5%), 891/969 (91.6%) and 827/969 (85%) were assessed at 1, 2, 3 and 10 years of age. Prevalence of sensitization to any of the predefined foods was 1.9%, 3.8%, 4.5% and 2.7% at these ages. Prevalence of sensitization to peanut at these ages was 0.4%, 2.0%, 2.0% and 2.4% (Table 1).

At 3 years of age 11/891 (1.2%; 95% CI: 0. 6 – 2.2%) children were diagnosed with peanut allergy. At 10 years of age, 12/828 (1.5%; 95% CI: 0. 8 – 2.5%) children were diagnosed with a peanut allergy. SPT at either 1, 2, 3 or 10 years was available for 849 children. Over the first ten years of life, 27/849 (3.2%; 95% CI: 2.0% - 4.4%) children were sensitized to peanut. Information on peanut allergy was available for 934 children at either 1, 2, 3 or 10 years. 13/934 (1.4%; 95% CI: 0.6 - 2.2%) children were diagnosed with a peanut allergy over the first ten years.

Looking at peanut specific IgE levels at 10 years, 29 children were sensitized to peanut using a cut off of 0.35 kUA/l, 31 using 0.2 kUA/l as a cut off point[17] and 36 using 0.1 kUA/l[17] as a cut off point. All children with a positive SPT to peanut (n = 14) who consented to a blood test (n = 10) showed levels of specific IgE above 0.35 kUA/l.

Natural history of peanut allergy in the FAIR birth cohort over the first 10 years of life

Table 2 summarizes all 27 children who were sensitized to peanut at some point during their first 10 years of life. They showed a variable time course, from early sensitization to late sensitization, with some cases of sensitization in specific time points only. Table 3 summarizes the 13 children with clinical peanut allergy over the first 10 years of life, and their sensitization status measured by SPT, as well as specific IgE. One child (8%) outgrew peanut allergy between 3 and 10 years of age. Two children (15%) presented with new onset peanut allergy. The CRD results of these children showed 5 of the 8 children having levels of Ara h2 >

0.35 kUA/l. Of the 12 children diagnosed with peanut allergy at age 10 years, five children had positive Ara h2 levels > 0.35 kUA/L, two children had Ara h2 levels < 0.35 kUA/l and five children did not have blood tests.

Time trends in peanut allergy in the FAIR and IOW birth cohorts

Although both sensitization and clinical allergy were clearly higher in the FAIR cohort, the differences were not statistically significant. Looking at peanut allergy in the two cohorts the data shows a prevalence of 0.62% versus 1.2% at 3-4 years and 0.58% vs. 1.5% at 10 -11 years (Figures 1 and 2).

210 Table 1: Sensitization patterns in the FAIR cohort over the first ten years of life

Sensitisation	1 year (n=763)	2 years (n=658)	3 years (n=642)	10 years (n=588)	Specific IgE at 10 years (n=246)
	n (%)	n (%)	n (%)	n (%)	n (%)
Any of the predefined allergens	20 (2.6)	54 (8.2)	76 (11.8)	145 (24.7)	124 (50.4)
Any of the predefined food allergens (milk, egg, cod, wheat, peanut, sesame)	17 (1.9)	25 (3.8)	29(4.5) 23 (3.6)	87 (14.6) 16 (2.7%)	fx5 56 (22.8)
Any of the predefined aero-allergens	8 (1.1)	42 (6.4)	70 (10.9)	99 (16.8%)	Aero-allergen 113 (45.9)
Peanut	3 (0.4)	13 (2.0)	13 (2.0)	14(2.4)	29/57 (50.9) Ara h8: 6/33 (18.2) Ara h1:2/33 (6.1) Ara h2: 6/33 (18.2) Ara h3: 2/33 (6.1) Ara h9: 1/33 (3.03)
Lupin				4 (0.68)	3/57 (5.3)

Table 2: Natural history of sensitization and clinical allergy in 27 children of the FAIR cohort over the first 10 years of life

Participant	Sensitized at 1 year	Sensitized at 2 years	Sensitized at 3 years	Peanut allergic at 3 years	Sensitized at 10 years	Peanut allergic at 10 years
1	No	Yes	Yes	Yes	Yes	Yes
2	No	NA	Yes	Yes	NA	Yes
3	No	Yes	Yes	Yes	Yes	Yes
4	NA	Yes	Yes	Yes	NA	Yes
5	NA	NA	Yes	Yes	Yes	Yes
6	NA	NA	Yes	Yes	Yes	Yes
7	No	No	No	No	Yes	Yes
8	No	Yes	Yes	Yes	Yes	Yes
9	No	No	Yes	Yes	NA	Yes
10	No	Yes	Yes	Yes	Yes	Yes
11	No	Yes	NA	Yes	No	No
12	No	NA	No	No	Yes	Yes
13	Yes	Yes	Yes	Yes	Yes	Yes
14	Yes	No	No	No	No	No
15	Yes	Yes	No	No	No	No
16	NA	Yes	No	No	No	No
17	No	Yes	Yes	No	No	No

18	No	Yes	No	No	No	No
19	No	Yes	No	No	No	No
20	No	NA	Yes	No	NA	No
21	No	NA	Yes	No	NA	No
22	No	No	NA	No	Yes	No
23	No	No	No	No	Yes	No
24	No	No	No	No	Yes	No
25	No	No	No	No	Yes	No
26	No	NA	No	No	Yes	No
27	No	Yes	No	No	No	No

No = negative skin prick test of food challenge. Yes= positive skin prick test or food challenge. NA= not applicable (i.e. declined test)

220 Table 3: Natural history of peanut allergy in the FAIR cohort over the first 10 years of life
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Participant	SPT wheal size (mm) at 1 year	SPT wheal size (mm) at 2 years	SPT wheal size (mm) at 3 years	Peanut allergy at 3 years	SPT wheal size (mm) at 10 years	Peanut allergy over the first 10 years of life	Specific IgE at 10 years (kUA/L)	CRD at 10 years
1	0	7.75	5.5	Yes	6	Yes (Positive OFC)	Fx5 15.2 Peanut 13.5	Ara h8 0.09 Ara h1 0.05 Ara h2 13 .0 Ara h3 0.07 Ara h9 0.28
2	1.75	NA	4.25	Yes	NA	Yes (positive SPT plus history of reactions)	NA	NA
3	0	9.25	8.75	Yes	8.5	Yes (positive OFC in past and SPT > 8 mm)	Fx5 3.5 Peanut 0.4	Ara h8 0.01 Ara h1 0.02 Ara h2 0.32 Ara h3 0.18 Ara h9 0.04
4	NA	9.5	7.75	Yes	NA	Yes (positive SPT > 8 mm plus history of reactions)	NA	NA
5	NA	NA	6	Yes	10.75	Yes (positive SPT > 8 mm plus history of reactions)	Fx5 264 Peanut 264.5	Ara h8 0.07 Ara h1 13.6 Ara h2 138 Ara h3 2.07 Ara h9 0.11

6	NA	NA	10.5	Yes	7.5	Yes (positive SPT > 8 mm plus history of reactions)	NA	
7	0	0	0	No	5	Yes (positive SPT and history of reactions)	Fx5 0.9 Peanut 1.5	Ara h8 0.01 Ara h1 0.07 Ara h2 0.15 Ara h3 0.01 Ara h9 0.01
8	0	0	12	Yes	8.5	Yes (positive SPT > 8 mm plus history of reactions)	Fx5 69 Peanut 49.7	Ara h8 0.00 Ara h1 11.8 Ara h2 29.5 Ara h3 7.79 Ara h9 0.01
9	0	0	3.5	Yes	NA	Yes (Positive OFC in past and still reacting)	NA	NA
10	0	4.75	11	13.25	√	Yes (positive OFC in past and SPT > 8 mm)	NA	NA
11	1.5	0	0	No	10	Yes (positive OFC in past and SPT > 8 mm)	Fx5 1.26 Spec IgE 2.34	Ara h8 1.47 Ara h1 0 Ara h2 1.01 Ara h3 0.001 Ara h9 0.003
12	4.5	8.75	11	Yes	5.5	Yes (Positive OFC)	Fx5 5.03 Spec IgE 4.65	Ara h8 0.01 Ara h1 0.3 Ara h2 4.65

								Ara h3 0.002 Ara h9 0.01
13	0	5.5	NA	Yes	0	X	Fx5 0.75 Spec IgE 1.93	Ara h8 0.03 Ara h1 0.01 Ara h2 0.02 Ara h3 0.17 Ara h9 0.04

√ = positive. NA = Not applicable (i.e. declined blood test). CRD = component resolved diagnostics

Table 4: Factors associated with the development of peanut allergy at age ten years of life in the FAIR cohort

	Peanut allergy at age 10 years (n=12)	No peanut allergy at age 10 years (n=935)*	Odds ratio (95% confidence interval)	Fisher's exact test
Sensitization to any allergen over 10 years (n=186)	12/12	174/835	Inf	p=0.000
Sensitization to any aero-allergen over 10 years (n=175)	10/13	165/671	Inf	p=0.000
Senitization to any FA over 10 years (n=41)	12/12	29/934	Inf	p= 0.000
Ever sensitized to grass (n=108)	8/12	100/835	16.727 (4.603 – 65.852)	p=0.001
Any IgE mediated Food Allergy (n=31)	12/12	19/934	Inf	p=0.000
Egg allergy at one year (n=16)	3/13	13/875	22.436 (4.245 – 106.953)	p=0.001
Ever suffered from asthma (n =101)	5/10	96/503	4.2 (1.041 – 17.278)	p=0.029
Ever suffered from eczema (n=258)	10/12	248/815	11.43 (2.486-52.55)	p=0.001
Ever suffered from hayfever (n=233)	7/12	226/815	3.649 (1.146-11.614)	p=0.045
Family history of allergy (n=790)	9/13	781/806	Inf	p=0.241
Any breast feeding (n= 598)	7/12	591/855	0.540 (0.142- 2.061)	p=0.000

* n=947 children have been seen at some point over the 10 years. Inf = infinite

Factors associated with the development of peanut allergy

In the FAIR cohort, the following factors were associated with the development of peanut allergy at age 10 years (Table 4): sensitization over the first ten years of life to any allergen, any aero-allergen, any food allergen and grass; ever suffered from asthma, eczema or hayfever, any breastfeeding, as well as egg allergy at one year. A family history of allergy was not however not associated with the development of peanut allergy.

Logistic regression was performed to assess the impact of a number of factors on the likelihood of developing peanut allergy. The model, containing four variables (breastfeeding, family history, egg allergy and sensitization to any food allergen) was statistically significant, predicting 98.9% of participants' peanut allergic status correctly, α^2 (6, N = 854) = 75.94, $p < 0.01$. The model as a whole explained between 8.5% (Cox and Snell R squared) and 66.1% (Nagelkerke R squared) of the variation. Although this model was very specific, correctly predicting 99.9% of non-peanut allergic participants; it had low sensitivity, correctly predicting only 27% of those with peanut allergy. None of the variables made a unique statistically significant contribution to the model. Sensitization to any food allergen made the strongest contribution, explaining 20.8% of the variation.

Discussion

We have shown that in the FAIR cohort at 10 years of age, 2.4% of children were sensitized to peanut and 1.5% clinically allergic. Between the ages of 3 and 10 years, one child outgrew peanut allergy and two children had new onset peanut allergy, leading to a cumulative incidence of peanut allergy over the first ten years of life of 3.0%. Comparing peanut sensitization and peanut allergy in two cohorts of children born 12 years apart, we found no significant difference in the prevalence of peanut sensitization at 1, 2, 3-4 and 10 years of age or peanut allergy at 3-4 or 10 years of age. A number of factors played a role in the development of peanut allergy, such as egg allergy and eczema in early life. Family history of allergy and breastfeeding did not independently affect the risk although they were both contributing factors in a multivariate logistic regression model.

We found a sensitization rate to peanuts at 10 years of 1.8% in the IOW birth cohort and 2.4% in the FAIR cohort. We have also described the prevalence of peanut sensitization in a different IOW school cohort (9) to be 3.7%, which may indicate either higher rates in that particular cohort or some selection bias as only 47.4% of the total cohort was recruited. Very few studies have looked at peanut sensitization in children of this age. Mustayev et al.(18) described the prevalence of sensitization to peanut at 11 years of age in Turkish children as 0.7%. Asarnoj et al. (19) report a higher rate of peanut sensitization of 7.4% at age eight years in a Swedish birth cohort, whilst McGowan et al (1) reported a higher rate again of 10.5% in a cross sectional US population of 6-19 year old children and adolescents.

Gupta et al.(20) described the prevalence of self-reported doctor's diagnosed peanut allergy in 11- 13 year olds from the US to be 2.3%. Using similar methodology in children 11-17 years of age, Sicherer et al. (4,5) reported prevalences of 0.2% and 1.7%. In our cohort, 1.4% of children reported a problem with consuming peanut, but not necessarily based on a doctor's diagnosis. Only one previous study has reported peanut allergy in a prospective cohort study based on oral food challenges, SPTs, and specific IgE measurements (21). The HealthNuts study recruited 12 month old infants in Australia, born between 2006-2009 (n = 5276). Of the 156 participants diagnosed with peanut allergy at age 12 months (2.95% of cohort), 78% had persisting allergy at age 4 years. This is therefore a higher initial diagnosis rate and resolution rate than observed in either the FAIR or IOW cohorts. In the HealthNuts study, Ara h2, tree nut, and house dust mite sensitization, coexisting food allergies, eczema and asthma were not predictive of persistent peanut allergy at age 4 years. In the FAIR cohort, we reported that sensitization over the first ten years of life to any allergen, ever having asthma, eczema, hayfever or egg allergy at one year *were* associated with the development of peanut allergy by 10 years. Overall the differences between studies are difficult to disentangle given the different sampling time periods, ages at recruitment and factors reported. Future

publications from the HealthNuts study reporting data at age ten years will enable more direct comparisons to be made.

In terms of development of peanut allergy, our data confirm that egg allergy and eczema are significant risk factors for peanut allergy, as reported previously by Lack et al. (22), the recent LEAP study (23) and the HealthNuts study (21). Nicolau et al. (24) reported that asthma, eczema, and food allergies were more common among subjects with peanut allergy, whereas hayfever was more common in peanut-tolerant children. With respect to diet during pregnancy and infancy as risk factors for development of peanut allergy, our group has previously demonstrated that government advice to atopic mothers to avoid peanut during pregnancy was misunderstood and did not lead to a reduction in peanut allergy prevalence (25). It remains to be seen whether changes to national UK infant feeding guidelines will be made following the publication of the LEAP (23) and Enquiring About Tolerance (EAT) studies (26).

Comparing SPT or specific IgE testing, we found SPT was a better indicator of peanut allergy: 29 children had a positive specific IgE to peanut, 14 had a positive SPT, with 12 found to be peanut allergic at age 10. For specific IgE, a cut off of > 0.35 kUA/l performed better than 0.1 kUA/l. This is despite the fact that a 0.35 kUA/l cut off point reported by ThermoFisher was due to the initial analytic ability of the test, and does not have a clinical basis. This cut off was reduced to 0.1 kUA/l as lower detection levels are now possible, but these are not clinical diagnostic levels(27).

Children with a clinical peanut allergy were sensitised to a range of peanut components. The majority was sensitised to Ara h2 as all eight children showed a level of sensitisation to Ara h2; (n=7 above 0.1 kUA/l; n=5 above 0.35 kUA/l). This is similar to data reported by Nicolau et al.(24) who reported that Ara h2 was the most important predictor of peanut allergy. However, it may not be true in all populations as Restani et al. (28) identified Ara h3 as the major allergen in a group of peanut allergic children.

A limitation of our study was that the IOW birth cohort were not challenged to peanut, rather the diagnosis was based on a thorough clinical history and positive SPT. Although all the children in the FAIR cohort at the age of 10 years were offered a food challenge, only two consented, both of which were open challenges. Additionally, less than 25% consented to a blood test, which may affect the accuracy of the results. Another limitation is that the sample size was not sufficient to detect statistically significant differences between the two cohorts. Based on our data, we would require a sample size of 4207 children in each group at 3 years and 1908 children per group at 10 years of age to detect a difference with 80% power. Theoretically, if we use these sample sizes and impute our % of peanut allergy we will find a highly significant increase in peanut allergy, both at 3 years (p=0.006) and at 10 years (p = 0.004).

Conclusion

Peanut allergy appears to be stable at 1.5% over the first 10 years of life, with only about 10% of children outgrowing their peanut allergy and approximately 20% developing new onset peanut allergy. In the 12 years between 1989-2011, an increase in both peanut sensitization and clinical peanut allergy was noted but this did not reach statistical significance possibly due to sample size constraints. We acknowledge that in some areas of the world, some food allergies seem to be on the increase (29). It is therefore probably safe to assume that with sufficient numbers our peanut allergy prevalence may be significantly increasing, but it is difficult to say for certain as there is such limited data on the time-trends in food allergy.

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Conflicts of interest: none

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