

Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy

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Background: Despite guidelines recommending avoidance of peanuts during infancy in the United Kingdom (UK), Australia, and, until recently, North America, peanut allergy (PA) continues to increase in these countries.

Objective: We sought to determine the prevalence of PA among Israeli and UK Jewish children and evaluate the relationship of PA to infant and maternal peanut consumption.

Methods: A clinically validated questionnaire determined the prevalence of PA among Jewish schoolchildren (5171 in the UK and 5615 in Israel). A second validated questionnaire assessed peanut consumption and weaning in Jewish infants (77 in the UK and 99 in Israel).

Results: The prevalence of PA in the UK was 1.85%, and the prevalence in Israel was 0.17% ($P < .001$). Despite accounting for atopy, the adjusted risk ratio for PA between countries was 9.8 (95% CI, 3.1-30.5) in primary school children. Peanut is introduced earlier and is eaten more frequently and in larger quantities in Israel than in the UK. The median monthly consumption of peanut in Israeli infants aged 8 to 14 months is 7.1 g of peanut protein, and it is 0 g in the UK ($P < .001$). The median number of times peanut is eaten per month was 8 in Israel and 0 in the UK ($P < .0001$).

Conclusions: We demonstrate that Jewish children in the UK have a prevalence of PA that is 10-fold higher than that of Jewish children in Israel. This difference is not accounted for by differences in atopy, social class, genetic background, or peanut allergenicity. Israeli infants consume peanut in high quantities in the first year of life, whereas UK infants avoid peanuts. These findings raise the question of whether early introduction of peanut during infancy, rather than avoidance, will prevent the development of PA. (*J Allergy Clin Immunol* 2008;122:984-91.)

Key words: Allergy, children, food allergy, peanut allergy, prevalence, allergy prevention, oral tolerance, weaning, peanut consumption

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The prevalence of peanut allergy (PA) in children in the United Kingdom (UK) and North America has doubled in 10 years and approximates 1.8% and 1.2%, respectively.^{1,2} PA presents during early childhood, is infrequently outgrown, and can cause anaphylaxis.³⁻⁷ Dietary avoidance of peanut during pregnancy, breastfeeding, and early life has been recommended in the UK and Australia and, until recently, also in the United States.⁸⁻¹¹ Studies eliminating food allergens during pregnancy, lactation, and infancy have consistently failed to prevent IgE-mediated food allergy.¹²⁻¹⁴

There are 2 hypothetical explanations for the failure of these studies. First, sensitization does not occur through oral exposure but through other routes. Second, early oral exposure might be required to induce tolerance.¹⁵

Allergic sensitization can occur through the skin. The risk of food allergies increases with the severity of eczema in infancy.^{16,17} Moreover, application of topical preparations containing peanut oil on infants with eczema was associated with a high risk of PA (odds ratio, 6.8).¹⁶ However, not all countries with an increased prevalence of PA use such preparations. In those countries cutaneous exposure to other peanut products could lead to

Abbreviations used

FAQ: Food Allergy Questionnaire
FFQ: Food Frequency Questionnaire
PA: Peanut Allergy
RR: Relative risk
SA: Sesame allergy
TNA: Tree nut allergy
UK: United Kingdom

sensitization. Environmental exposure to peanut is 10-fold higher during the first year of life in infants with PA compared with that seen in atopic infants without PA.¹⁸ Indeed, peanut allergen is detectable in significant quantities in saliva and on hands after exposure to peanut products.^{19,20} Other foods (egg, milk, and fish) have also been detected in house dust.^{21,22}

There is also evidence to support the second explanation. Oral tolerance is well recognized in murine models. Numerous studies demonstrate that early high-dose oral exposure confers both immunologic and clinical tolerance to food allergens. A single oral dose of allergen (β -lactoglobulin, ovalbumin, or peanut) is sufficient to achieve tolerance and prevent subsequent allergic sensitization.²³⁻²⁵ In human subjects cutaneous exposure to nickel during childhood leads to sensitization and nickel allergy, but oral exposure to nickel through orthodontic braces before ear piercing protects against nickel allergy.^{26,27} Similarly, subjects exposed to pancreatic extract by means of inhalation or contact have IgE-mediated allergic reactions, whereas subjects exposed orally do not.²⁸ Furthermore, in a large observational cohort of children, Poole et al²⁹ demonstrate that delaying the initial exposure to cereal grains until after 6 months might increase the risk of IgE-mediated wheat allergy.

Importantly, in the Middle East, Southeast Asia, and Africa, where peanut is consumed in high amounts during infancy, PA is reportedly rare.³⁰⁻³² However, different rates of food allergies in the UK compared with those in Asia and Africa might be due to genetic differences or the generally lower rates of atopic disease in developing countries, possibly resulting from differences in microbial exposure.^{33,34}

We therefore compared Jewish children (who have a similar genetic background) in the UK and Israel. The UK and Israel are industrialized countries with high levels of atopy.³⁵ The aim of this study was to determine the PA prevalence among Israeli and UK Jewish children and evaluate the relationship of PA to infant and maternal peanut consumption.

METHODS

Questionnaires

Two validated questionnaires were used. Questionnaires recorded categorical answers only.

The Food Allergy Questionnaire. The Food Allergy Questionnaire (FAQ) was distributed in schools in the UK and Israel. In the UK eligible Jewish schools in the greater London region were identified from the UK Jewish Board of Deputies. In Israel schools were identified by the Israel Ministry of Education and were located within the Mehoz Merkaz Region of Tel Aviv. This region was selected because it was thought to represent comparable residential environments (ie, both urban and suburban) to those found in North London. Schools with more than 100 pupils were targeted. It asked about allergies to cow's milk, hen's egg, sesame, peanut, and tree nuts (including the nature and timing of symptoms after exposure to these foods);

asthma; hay fever; and eczema. Parental occupation was used as a surrogate for social class (by using the Standard Occupational Classification System, UK Office of National Statistics, 2000). The questionnaire was completed by high school pupils and by parents on behalf of primary school pupils. Repeat sampling was performed by means of postal reminders or telephone. The FAQ was validated against rigorous clinically confirmed diagnostic criteria for the diagnosis of allergy or tolerance to peanut.

The Food Frequency Questionnaire. The Food Frequency Questionnaire (FFQ) is a validated consumption questionnaire that was distributed to mothers of Jewish infants aged 4 to 24 months.³⁶ The infants and mothers were chosen by consecutive registration (Tipat Halav clinics in Israel and general practitioner clinics in the UK). An information sheet was handed out to all parents attending the clinic. We explained in the information sheet that we wanted dietary history from Jewish children. The information was obtained by researchers (GZH in Israel and HF in the UK) from mothers in the waiting room. The FFQ made a detailed determination of peanut, sesame, and other solid-food consumption during the child's first year and through the mother (during pregnancy and lactation). The FFQ included a comprehensive list of peanut products available in both countries. Additional questions concerned breast-feeding, infant formula, weaning, and introduction of other solid foods. Consumption was compared between countries for infants aged 8 to 14 months. In both countries infants were identified in nurseries and well-baby clinics. Questionnaires were completed over the period March 2004 to 2005.

Definition of PA and other allergic disease

By using the FAQ, individual food allergies were defined as a history of at least 1 of the following within 2 hours of eating the food: itchy rash, wheezing, vomiting, diarrhea, and swelling.

The following questionnaire-based definitions for allergic disease were used: (1) physician-diagnosed asthma and use of short-acting β_2 -agonist and use of an inhaled corticosteroid; (2) physician-diagnosed eczema and use of corticosteroid applications or use of topical calcineurin inhibitor preparations; and (3) physician-diagnosed hay fever and use of antihistamines or an intranasal corticosteroid.

Validation of the FAQ-based diagnosis of PA

All children with a questionnaire-based diagnosis of PA were invited for allergy testing. PA was confirmed if allergy test results (skin prick tests, specific IgE measurements, or both) were greater than 95% positive predictive values³⁷⁻³⁹ or if children had a positive oral peanut challenge result.³⁷

Comparison of the protein content and allergenicity of peanut-containing foods

Total protein content of the foods was determined by using LECO nitrogen analysis (LECO Corp, St Joseph, Mich). Anti-peanut ELISA assays were used to determine the percentage of peanut protein in each product. The products were all normalized according to peanut protein content and subjected to SDS-PAGE, Western blotting, and slot-blot analysis with anti-peanut and anti-Ara h 1, 2, and 3 antibodies and pooled sera from individuals with PA.

Statistical analysis

Statistical Analysis was performed with Stata statistical software (release 8.0; StataCorp, College Station, Tex). For food allergy comparison, formal comparisons were made for all children and for primary school children. Risk ratios and 95% CIs of food allergy in the UK compared with those in Israel were calculated and stratified on confounding factors by using Mantel-Haenszel procedures. We further investigated the effects of socioeconomic class on food allergy in a nested case-control study. Kaplan-Meier estimates of weaning patterns and the age at introduction of particular food types in the 2 countries were calculated and compared by using the log-rank test. Peanut and

TABLE I. Prevalence of food allergies and atopic disease in Israel and the UK: Number (percentage of all children)

	Individuals with food allergy											
	All individuals		Peanut		Sesame		Tree nuts		Egg		Milk	
	Israel	UK	Israel	UK	Israel	UK	Israel	UK	Israel	UK	Israel	UK
All	4657	3943	8 (0.17)	73 (1.85)	6 (0.13)	31 (0.79)	6 (0.13)	77 (1.95)	20 (0.43)	58 (1.47)	52 (1.12)	85 (2.16)
Sex*												
Male	2278	1994	4 (0.18)	37 (1.86)	3 (0.13)	18 (0.90)	4 (0.18)	39 (1.96)	15 (0.66)	34 (1.71)	21 (0.92)	54 (2.71)
Female	2279	1910	4 (0.18)	36 (1.88)	3 (0.13)	13 (0.68)	2 (0.09)	38 (1.99)	5 (0.22)	24 (1.26)	30 (1.32)	30 (1.57)
Age†												
4-12 y	1992	2395	3 (0.15)	56 (2.34)	4 (0.20)	27 (1.13)	3 (0.15)	58 (2.42)	10 (0.50)	49 (2.05)	33 (1.66)	77 (3.22)
12-18 y	2573	1458	5 (0.19)	15 (1.03)	2 (0.08)	3 (0.21)	3 (0.12)	17 (1.17)	10 (0.39)	7 (0.48)	19 (0.74)	17 (1.17)
Food allergies‡												
Peanut	8	73	8 (100.00)	73 (100.00)	2 (25.00)	18 (24.66)	4 (50.00)	43 (58.90)	2 (25.00)	12 (16.44)	1 (12.50)	7 (9.59)
Sesame/ other nut	10	86	5 (50.00)	45 (52.33)	6 (60.00)	31 (36.05)	6 (60.00)	77 (89.53)	2 (20.00)	17 (19.77)	0 (0.00)	9 (10.47)
Egg	20	58	2 (10.00)	12 (20.69)	1 (5.00)	11 (18.97)	2 (10.00)	14 (24.14)	20 (100.00)	58 (100.00)	1 (5.00)	9 (15.52)
Milk	52	85	1 (1.92)	7 (8.24)	0 (0.00)	4 (4.71)	0 (0.00)	7 (8.24)	1 (1.92)	9 (10.59)	52 (100.00)	85 (100.00)
Any other	81	224	6 (7.59)	49 (24.50)	3 (3.85)	27 (12.27)	5 (6.25)	51 (25.76)	3 (4.69)	21 (11.23)	2 (6.45)	15 (9.74)
No other	4576	3719	2 (0.04)	24 (0.64)	3 (0.07)	4 (0.11)	1 (0.02)	26 (0.69)	17 (0.37)	37 (0.99)	50 (1.08)	70 (1.85)
Atopic disease§												
Asthma	458 (9.8)	544 (13.8)	6 (1.31)	29 (5.33)	2 (0.44)	17 (3.13)	3 (0.66)	36 (6.62)	8 (1.75)	23 (4.23)	9 (1.97)	33 (6.07)
Eczema	127 (2.7)	619 (15.7)	1 (0.79)	40 (6.46)	1 (0.79)	22 (3.55)	1 (0.79)	42 (6.79)	3 (2.36)	26 (4.20)	4 (3.15)	29 (4.68)
Hay fever	117 (2.5)	341 (8.64)	4 (3.42)	21 (6.16)	2 (1.71)	9 (2.64)	2 (1.71)	25 (7.33)	3 (2.56)	14 (4.11)	6 (5.13)	16 (4.69)
Any	620 (13.3)	1144 (29.0)	6 (0.97)	52 (4.55)	3 (0.48)	27 (2.36)	3 (0.48)	57 (4.98)	9 (1.45)	36 (3.15)	17 (2.74)	48 (4.20)
None	4037 (86.7)	2799 (71.0)	2 (0.05)	21 (0.75)	3 (0.07)	4 (0.14)	3 (0.07)	20 (0.71)	11 (0.27)	22 (0.79)	35 (0.87)	37 (1.32)

UK, United Kingdom.

*Sex could not be determined for 2 children with milk allergy (1 in the UK and 1 in Israel); hence these 2 children were not included in the analysis.

†Age could not be determined for several children in the UK, and hence these children were not included in the analysis.

‡Individual food allergies were defined as a history of at least 1 of the following within 2 hours of eating the food: itchy rash, wheezing, vomiting, diarrhea, and swelling.

§The following questionnaire-based definitions for allergic disease were used: (1) physician-diagnosed asthma and use of short-acting β_2 -agonist and use of an inhaled corticosteroid; (2) physician-diagnosed eczema and use of corticosteroid applications or use of topical calcineurin inhibitor preparations; and (3) physician-diagnosed hay fever and use of antihistamines or an intranasal corticosteroid.

sesame consumption levels for all children and for children aged 8 to 14 months were compared between countries, and odds ratios comparing any with no consumption of food are reported. Furthermore, odds ratios comparing groups (based on consumption amount) with no consumption at all between the countries are calculated.

Ethics

The study was approved by the St Mary's Hospital Research Ethics Committee and the Ethics Committee of Assaf-Harofeh, Tel Aviv University. Consent was obtained from participating school principals and school-parent authorities and the Ministry of Education and Ministry of Health and Nutrition in Israel.

RESULTS

Questionnaire response rate

FAQ. The FAQs were distributed to 10,786 children in 24 schools (13 in the UK and 11 in Israel). Eight thousand eight hundred twenty-six were returned, resulting in an overall response rate of 81.8% (80.2% [4148/5171] in the UK and 83.2% [4672/5615] in Israel). Two hundred twenty-six FAQs were excluded from analysis (220 were outside the age range [ie, <4 or ≥ 19 years of age], 2 were duplicates, and 4 had an incorrect school code). Of the 8826 returned FAQs, 7880 were returned after initial sampling (early responders), and 946 were returned after a reminder. The demographics and rate of PA (and other allergies) were not significantly different between the early and late responders.

FFQ. One hundred seventy-six FFQs were returned by mothers of infants aged 4 to 24 months (median, 12 months; 99 from Israel

and 77 from the UK). No mothers declined participation. The age of first introduction of peanut (and other weaning foods) was determined. A more detailed analysis of peanut (and sesame) was made for infants aged 8 to 14 months at FFQ completion (86 in Israel and 50 in the UK). Age distributions for both countries within this subgroup were similar.

Prevalence of PA

The questionnaire-determined prevalence of PA in the UK was 1.85% (73/3943), and it was 0.17% (8/4657) in Israel ($P < .001$, Table I). The unadjusted relative risk (RR) for PA between the countries was 10.8 (95% CI, 5.2-22.3) for all children and 17.4 (95% CI, 5.5-55.6) for primary school children (Table II).

Even after adjusting for atopy, age, and food allergy, the RRs for PA in the UK remained high at 5.8 (95% CI, 2.87-11.8) for all children and 9.8 (95% CI, 3.1-30.5) for primary school children (Table II). In the nested case-control study, adjustment for social class made little difference.

In contrast, the adjusted RRs for egg and milk allergy were only 1.8 (95% CI, 1.0-3.1) and 1.3 (95% CI, 0.9-1.9), respectively (Table II). Even when the analysis of PA was confined to children at high risk for the development of PA, such as those with eczema, the prevalence of PA remained significantly higher in the UK (6.46%) compared with that seen in Israel (0.79%, $P = .024$).

Significant differences in the prevalence of tree nut allergy (TNA) and sesame allergy (SA) are also observed between the 2 countries, with an increased RR in the UK both before (Table I) and after adjustment (Table II). In both countries TNA and SA were independently associated with PA. Among children with

TABLE II. The ratio of the risk of food allergies in the UK compared with Israel

	Peanut		Sesame		Tree nuts		Egg		Milk	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
All individuals										
Unadjusted	10.8 (5.2-22.3)	<.001	6.1 (2.5-14.6)	<.001	15.2 (6.6-34.7)	<.001	3.4 (2.1-5.7)	<.001	1.9 (1.4-2.7)	<.001
Adjusted for age group* and sex§	10.4 (4.8-22.2)	<.001	5.3 (2.2-13.0)	<.001	14.0 (6.0-32.5)	<.001	3.1 (1.8-5.2)	<.001	1.7 (1.2-2.4)	.008
Adjusted for age group,* sex,§ food allergy,† and atopy‡	5.8 (2.8-11.8)	<.001	2.7 (1.1-7.0)	.057	8.4 (3.6-19.5)	<.001	1.8 (1.0-3.1)	.054	1.3 (0.9-1.9)	.33
Primary school										
Unadjusted	17.4 (5.5-55.6)	<.001	6.3 (2.2-18.0)	<.001	17.4 (5.5-55.6)	<.001	4.8 (2.4-9.4)	<.001	1.7 (1.1-2.5)	.012
Adjusted for sex§	16.9 (5.3-53.5)	<.001	6.1 (2.2-17.6)	<.001	16.5 (5.3-51.8)	<.001	4.6 (2.3-9.0)	<.001	1.6 (1.1-2.4)	.046
Adjusted for sex,§ food allergy,† and atopy‡	9.8 (3.1-30.5)	<.001	3.6 (1.1-12.1)	.045	9.5 (3.0-29.5)	<.001	2.5 (1.3-4.9)	.011	1.2 (0.8-1.9)	.47

Food allergy is defined as at least 1 symptom of itchy rash, swelling, wheeze, vomiting, or diarrhea within 2 hours of eating the food.

*Age group is determined by whether a child attends primary or secondary school.

†Any atopy is defined as 1 or more of asthma, eczema, or hay fever, as previously defined.

‡Food allergy adjusted is for egg/milk allergy when considering peanut, sesame, and nuts and any nuts/seeds when considering egg/milk allergy.

§All analyses involving sex include only those individuals for whom sex was provided.

PA, 58.9% (43/73) in the UK and 50% (4/8) in Israel had TNA, whereas 25% (18/73 in the UK and 2/8 in Israel) in both countries had SA (Table I).

Clinical validation of FAQ diagnosis of PA

Eighty-one children (73 in the UK and 8 in Israel) met the FAQ definition of PA. Sixty-three percent had urticaria, 69% had angioedema, 37% had wheeze, and 30% had vomiting. Ninety-one percent of allergic reactions occurred within 1 hour of exposure.

Forty-seven of the 81 children with a questionnaire-based diagnosis of PA underwent clinical assessment. By using the study definition for PA, 36 (77%) had PA, and 11 children were peanut tolerant. All but 4 of the tolerant children had TNA, and 2 had with certainty outgrown their PA by the time of assessment. Thirty-four children did not undergo assessment (school or parent declined clinical assessment for 31 children, and 3 families could not be contacted).

Dietary assessments

Information on weaning was analyzed for 176 infants aged 4 to 24 months. The Kaplan-Meier plots for the age of introduction of solid foods were similar in both countries (Fig 1). The introduction of egg, soya, wheat, vegetables, fruit, and tree nuts was similar in both countries. Small but significant differences were observed for the introduction of cow's milk (infant formula, dairy solids, or both), breast-feeding, and exclusive breast-feeding. The largest and most significant difference in weaning between the UK and Israel was observed in the age of introduction of peanut ($P < .0001$). By 9 months of age, 69% of Israelis were eating peanut compared with only 10% of UK infants. The earlier introduction of peanut in Israel is reflected by a higher median monthly consumption of peanut in the first year of life (7.1 g of peanut protein in Israel and 0 g in the UK, $P < .0001$). The median episodes of peanut consumption per month were 8 in Israel and 0 in the UK ($P < .001$). The differences in consumption are shown in Table III. At every level, there was greater consumption in Israel. Although

sesame was also introduced earlier in Israel, the differences in consumption were not as striking as for peanut.

The proportion of UK mothers not consuming peanuts during breast-feeding was significantly greater than in Israel ($P = .004$); the difference during pregnancy was in the same direction but not significant ($P = .06$, Table III).

Comparison of the peanut protein content and allergenicity of commonly consumed peanut foods in Israel and the UK

In Israeli infants peanut protein is mainly consumed as one of 2 snacks, both of which are derived from roasted peanut butter; in the UK peanut butter serves as the main source of peanut protein during infancy. Peanut protein content, major peanut allergen content, and IgE binding were therefore compared between these products. After adjustment for peanut protein content, we demonstrated similar content of major peanut allergens (Ara h 1, 2, and 3) in products from both countries and similar levels of IgE binding between the products (Fig 2).

DISCUSSION

Using a questionnaire-based study of 8600 schoolchildren, we have shown that the prevalence of PA is 10-fold higher in Jewish children in the UK compared with that seen in Jewish children in Israel (1.85% and 0.17%, respectively). Furthermore, the prevalence of PA appears to be increasing in the UK, whereas in Israel it remains stable among all age groups. These differences cannot be explained by differences in age, sex, ancestry, atopy, or socioeconomic class. After adjustment for atopy, other food allergies, age, and sex, the RR for PA in the UK remained high at 5.8 (95% CI, 2.8-11.8), whereas the RRs for egg and milk allergy were low, at 1.3 (95% CI, 0.9-1.9) and 1.8 (95% CI, 1-3.1), respectively, suggesting an allergen-specific effect. The biggest difference in PA was observed in the primary schools (aged 4-12 years), where the prevalence was 2.05% in the UK and 0.12% in Israel ($P < .001$). Even after adjustment, the RR for PA among UK primary school children was 9.8 (95% CI, 3.1-30.5). Even confining the analysis to the very high-risk subgroup of children

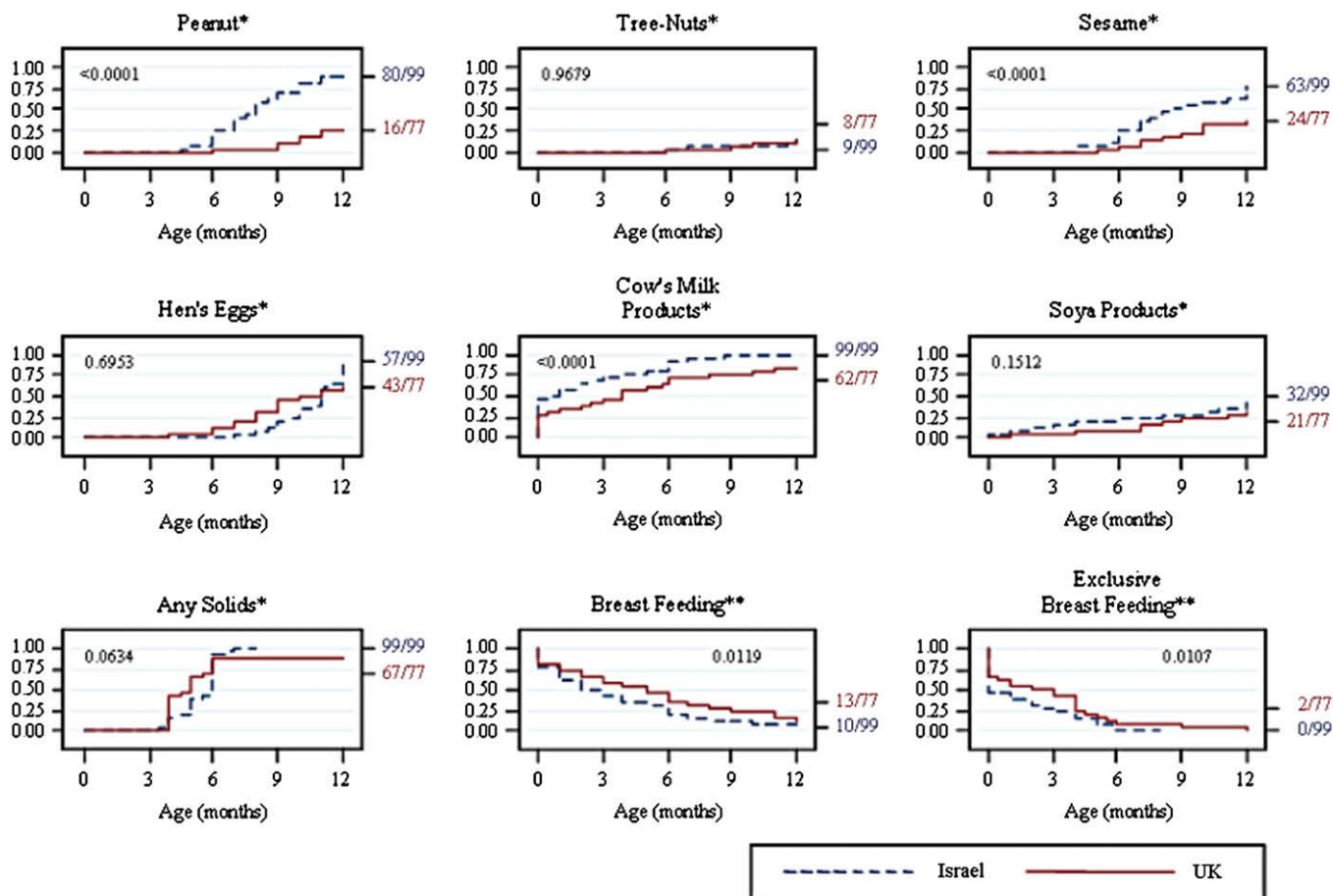


FIG 1. Kaplan-Meier estimates for age at which foods are introduced and duration of breast-feeding and exclusive breast-feeding according to country. *The y-axis represents proportions who have consumed food by age (in months). **The y-axis represents the proportion still breast-feeding/exclusively breast-feeding at various ages (in months). *P* values are derived by using the log-rank test.

with a stringent diagnosis of eczema, the difference in PA between countries remained high (6.5% in the UK and 0.8% in Israel, *P* = .024).

The most obvious difference in the diet of infants in both populations occurs in the introduction of peanut. Israeli infants are introduced to peanut during early weaning and continue to eat peanut more frequently and in higher amounts than UK infants, who avoid peanut, as per Department of Health recommendations.⁴⁰

The observed differences in PA between the UK and Israel are unlikely to be explained by genetic differences. Although ethical considerations did not allow for questions regarding Ashkenazi or Sephardic ancestry in Israel, a nested case-control analysis of 159 of the UK children (103 without food allergy and 56 with food allergy) showed no effect of Sephardic, Ashkenazi, or mixed background on food allergy. Furthermore, the difference in composition of the Israeli and UK populations as a whole is too small to explain the large differences in PA between the 2 populations. Even if there were no Ashkenazi children in our Israeli sample, ancestry could not account for the differences in PA between the 2 countries.

This raises the question of whether early consumption of peanuts in Israeli infants leads to oral tolerance. It is unlikely that the difference in PA between the 2 countries can be explained by

nonspecific differences in weaning. The early introduction of frequent and high doses of peanut protein remains the most compelling explanation. The ages of weaning of egg, wheat, soya, meat, fruit, and vegetables are similar for both countries. Although significant differences between countries for cow's milk (earlier introduction in Israel) and breast-feeding (longer in the UK) are noted, these differences are small and unlikely to explain the difference in PA. Furthermore, if the earlier introduction of cow's milk protein in Israel was protective against PA, it ought to prove protective against cow's milk protein allergy as well; however, the adjusted RR for cow's milk protein allergy is only 1.3 (95% CI, 0.9-1.9).

Roasting peanuts enhances the allergenic properties of peanuts, and it has been proposed that different methods of preparing peanut could be responsible for different rates of PA in different countries.⁴¹ This is, however, unlikely to account for the differences in PA between Israel and the UK because commonly consumed peanut-containing foods in both countries are derived from roasted peanut butter. Additionally, we demonstrate equivalent amounts of total protein, major peanut allergen, and IgE binding among these commonly consumed foods.

Interestingly, we observe a greater prevalence of SA in the UK (0.79% vs 0.13% in Israel), with the latter being similar to that reported in Israel in 2002.⁴² The lower levels of SA in Israel could

TABLE III. Percentages of individuals according to monthly peanut and sesame consumption§

	Infancy (aged 8-14 mo)			Pregnancy (all ages)			Breast-feeding (all ages)‡		
	Israel (%) (n = 86)	UK (%) (n = 50)	P value	Israel (%) (n = 99)	UK (%) (n = 77)	P value	Israel (%) (n = 99)	UK (%) (n = 77)	P value
Peanut									
Grams eaten per month									
0	20.9	80.0	<.0001†	21.1	33.8	.06†	40.4	62.3	.004†
>0-7	27.9	10.0	<.0001*	14.1	11.7	.21*	10.1	5.2	.07*
≥7-14	14.0	2.0	.0001*	34.3	18.2	.01*	35.4	15.6	.001*
≥14-28	18.6	6.0	.0001*	13.1	15.6	.56*	8.1	5.2	.17*
≥28	18.6	2.0	<.0001*	17.2	20.8	.55*	6.1	11.7	.70*
Times eaten per month									
0	20.9	80.0	<.0001†	21.2	33.8	.06†	40.4	62.3	.004†
>0-3	11.6	4.0	.0008*	12.1	3.9	.02*	9.1	1.3	.008*
≥3-6	11.6	6.0	.002*	28.3	19.5	.05*	27.3	9.1	.0008*
≥6-9	10.5	4.0	.002*	19.2	9.1	.02*	13.1	7.8	.07*
≥9	45.4	6.0	<.0001*	19.2	33.8	.81*	10.1	19.5	.63*
Sesame									
Grams eaten per month									
0	32.6	48.0	.08†	No information			No information		
>0-7	10.5	19.0	.78*						
≥7-14	5.8	14.0	.45*						
≥14-28	3.5	6.0	.86*						
≥28	47.7	14.0	.0007*						
Times eaten per month									
0	32.6	48.0	.08†	No information			No information		
>0-3	7.0	16.0	.47*						
≥3-6	12.8	8.0	.18*						
≥6-9	7.0	6.0	.048*						
≥9	40.7	22.0	.002*						

*P value associated with odds ratio comparing consumption group with no consumption between countries.

†P value associated with odds ratio comparing any consumption with no consumption between countries.

‡Women only included if breast-fed for at least 1 month.

§Consumption in grams of peanut/sesame protein.

also be explained by higher consumption of sesame observed in Israeli infants. The differences in TNA between the 2 populations cannot be accounted for by differences in consumption of tree nut. As reported previously,^{43,44} we observed a strong association between PA, TNA, and SA. Peanut and sesame contain highly conserved homologous seed storage proteins, and it is possible that cross-sensitization explains their co-occurrence in allergic populations. Indeed, sequence searching of nucleotide and protein databases (Basic Local Alignment Search Tool 2.0; National Center for Biotechnology Information, Bethesda, Md) for peanut, sesame, and tree nut protein indicates areas of homology between the amino acid sequences of these allergens. The low prevalence of PA, TNA, and SA in Israeli children could be due to cross-tolerance induced through the early, high, and frequent consumption of peanut in Israel.

Other studies have used questionnaires to determine rates of food allergy among unselected subjects or subjects with self-reported food allergy.^{2,45,46} The selection bias inherent in all questionnaire surveys is reduced in this study because we achieved high response rates for both the FAQ (with active resampling) and FFQ in both countries. The demographics and prevalence of PA are similar for both early and late FAQ responders, showing a lack of bias in our responder population. Furthermore, we evaluated our FAQ against rigorous, clinically confirmed diagnostic criteria for the diagnosis of PA and found a diagnostic accuracy of 77% for questionnaire-diagnosed PA. Nevertheless, not all children with suspected PA were assessed clinically, and there could be bias in the group that presented

for clinical assessment. Even if we assume that all children in Israel who were not assessed by means of challenge had PA and all children from the UK who were not assessed did not have PA, we still find that the risk of PA is significantly higher in the UK than in Israel. Thus by making these assumptions, if we look at all children, the unadjusted RR for PA is 5.4 (95% CI, 2.4–12.2), and after adjustment for sex, age, food allergy, and atopy, it is 2.6 (95% CI, 1.2–5.9). If one looks at the group of primary school children in whom PA is more common, the unadjusted RR is 13.5 (95% CI, 3.2–56.7), and after adjustment for the same factors, it remains increased at 6.6 (95% CI, 1.7–24.8).

Consumption questionnaires can be associated with significant recall bias. The FFQ was initially pretested for face and translation validity.³⁶ The FFQ was validated by pediatric dietitians, lay organizations, and a group of 50 families. Criterion validity was assessed against a 7-day consecutive 24-hour food diary, which is considered to be the gold standard (unpublished data). There was extremely close agreement between the FFQ responses and the mean diary response when assessing groups of individuals.

To limit recall bias, we limited the distribution of the FFQ to mothers of young infants and in an unselected population. Finally, even if recall bias cannot be excluded, there is no reason it should be different in the 2 countries.

In conclusion, we demonstrate a strong inverse association between peanut consumption in infancy and the prevalence of PA in childhood. The difference between PA in UK and Israeli

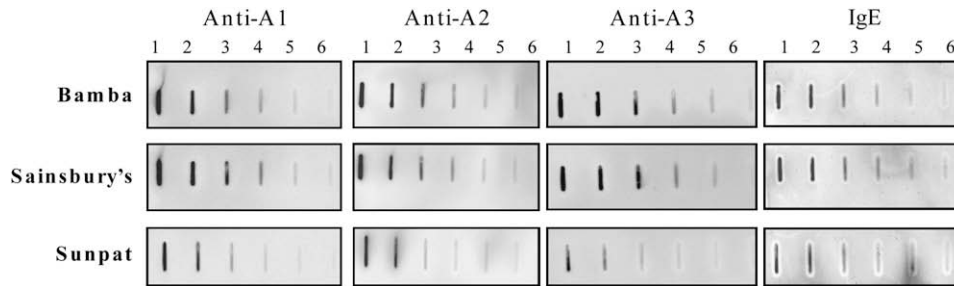


FIG 2. Major allergen content and IgE binding of peanut foods in the UK and Israel. Slot-blot analysis of Israeli peanut snacks and 2 commonly consumed peanut butters from the UK is shown. Serial dilutions of peanut protein from each food can be seen from the highest dilution (lane 1) through the lowest dilution (lane 6). Each of 4 membranes was probed with either anti-Ara h 1 (Anti-A1), anti-Ara h 2 (Anti-A2), or anti-Ara h 3 (Anti-A3) or a pool of 9 patient sera IgE from individuals with PA.

infants cannot be accounted for by differences in atopy, social class, ancestry, or methods of peanut processing in the 2 countries. Our findings raise the question of whether early and frequent ingestion of high-dose peanut protein during infancy might prevent the development of PA through tolerance induction. Paradoxically, past recommendations in the United States and current recommendations in the UK and Australia^{11,40} might be promoting the development of PA and could explain the continued increase in the prevalence of PA observed in these countries.^{1,2,47} Randomized controlled interventional studies, such as the Immune Tolerance Network/National Institutes of Health-funded Learning Early about Peanut Allergy Study (further information is available at www.leapstudy.co.uk/ and <http://clinicaltrials.gov/ct2/show/record/NCT00329784>), are therefore required to determine whether peanut avoidance or the early dietary introduction of peanut will prevent PA. Until such evidence is obtained, current recommendations should remain unchanged.

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Clinical implications: Our study findings raise the question of whether early introduction rather than avoidance of peanut in infancy is the better strategy for the prevention of PA.

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