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

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.3,4 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.5-11 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...
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. Indeed, peanut allergen is detectable in significant quantities in saliva and on hands after exposure to peanut products. Other foods (egg, milk, and fish) have also been detected in house dust.

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 (κ-lactoglobulin, ovalbumin, or peanut) is sufficient to achieve tolerance and prevent subsequent allergic sensitization. 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. Similarly, subjects exposed to pancreatic extract by means of inhalation or contact have IgE-mediated allergic reactions, whereas subjects exposed orally do not. Furthermore, in a large observational cohort of children, Poole et al demonstrated 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. 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.

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. 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 Mezho 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. 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 β2-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 values or if children had a positive oral peanut challenge result.

**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
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 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 sixty-two children 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**

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

<table>
<thead>
<tr>
<th></th>
<th>Peanut</th>
<th>Sesame</th>
<th>Tree nuts</th>
<th>Egg</th>
<th>Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P value</td>
<td>RR (95% CI)</td>
<td>P value</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>All individuals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>10.8 (5.2-22.3)</td>
<td>&lt;.001</td>
<td>6.1 (2.5-14.6)</td>
<td>&lt;.001</td>
<td>15.2 (6.6-34.7)</td>
</tr>
<tr>
<td>Adjusted for age group* and sex§</td>
<td>10.4 (4.8-22.2)</td>
<td>&lt;.001</td>
<td>5.3 (2.2-13.0)</td>
<td>&lt;.001</td>
<td>14.0 (6.0-32.5)</td>
</tr>
<tr>
<td>Adjusted for age group,* sex,§ food allergy,‡ and atopy†</td>
<td>5.8 (2.8-11.8)</td>
<td>&lt;.001</td>
<td>2.7 (1.1-7.0)</td>
<td>.057</td>
<td>8.4 (3.6-19.5)</td>
</tr>
<tr>
<td>Primary school</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>17.4 (5.5-55.6)</td>
<td>&lt;.001</td>
<td>6.3 (2.2-18.0)</td>
<td>&lt;.001</td>
<td>17.4 (5.5-55.6)</td>
</tr>
<tr>
<td>Adjusted for sex§</td>
<td>16.9 (5.3-53.5)</td>
<td>&lt;.001</td>
<td>6.1 (2.2-17.6)</td>
<td>&lt;.001</td>
<td>16.5 (5.3-51.8)</td>
</tr>
<tr>
<td>Adjusted for sex,§ food allergy,‡ and atopy†</td>
<td>9.8 (3.1-30.5)</td>
<td>&lt;.001</td>
<td>3.6 (1.1-12.1)</td>
<td>.045</td>
<td>9.5 (3.0-29.5)</td>
</tr>
</tbody>
</table>

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 did not provide consent). Of the children who did not undergo assessment, 6 had with certainty outgrown their PA by the time of assessment. The proportion of UK mothers not consuming peanuts during pregnancy 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, 1.3-3.1), 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...
with a stringent diagnosis of eczema, the difference in PA between countries remained high (6.5% in the UK and 0.8% in Israel, \( P = 0.024 \)).

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

![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.](image-url)
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, we observed a strong association between PA, TNA, and SA in Israeli children could be due to cross-tolerance among 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.43,44 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.

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 infants. The differences in TNA between the 2 populations cannot be accounted for by differences in consumption of tree nut. As reported previously, we observed a strong association between PA, TNA, and SA.43,44 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.

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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 (47) 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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