

Household peanut consumption as a risk factor for the development of peanut allergy

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Background: Most children with peanut allergy (PA) react on first known oral exposure to peanut. Recent data suggest cutaneous exposure as a route of sensitization.

Objectives: This study aimed to establish the relevant route of peanut exposure in the development of allergy.

Methods: Questionnaires were administered to children with PA and to high-risk controls (with egg allergy) and controls without allergy. Questionnaires were completed before subjects were aware of their PA status, avoiding recall bias. Questionnaires recorded maternal peanut consumption during pregnancy, breast-feeding, and the first year of life. Peanut consumption was determined among all household members, allowing quantification of environmental household exposure (household peanut).

Results: Median weekly household peanut in the 133 PA cases was significantly elevated (18.8 g) compared with 150 controls without allergy (6.9 g) and 160 high-risk controls (1.9 g). There were no differences in infant peanut consumption between groups. Differences in maternal peanut consumption during pregnancy (and lactation) were significant but become nonsignificant after adjusting for household peanut. A dose-response relationship was observed between environmental (nonoral) peanut exposure and the development of PA, which was strongest for peanut butter. Early oral exposure to peanut

in infants with high environmental peanut exposure may have had a protective effect against the development of PA.

Conclusions: High levels of environmental exposure to peanut during infancy appear to promote sensitization, whereas low levels may be protective in atopic children. No effect of maternal peanut consumption during pregnancy or lactation is observed, supporting the hypothesis that peanut sensitization occurs as a result of environmental exposure. (*J Allergy Clin Immunol* 2009;123:417-23.)

Key words: Allergy, children, food allergy, peanut allergy, sensitization, peanut consumption, cutaneous exposure, environmental exposure

Peanut allergy (PA) is one of the most serious of the food hypersensitivities.¹ It has been argued that PA, and food allergy in general, are the result of early consumption of food allergens. However, 72% to 81% of presentations of PA occur on first known exposure to peanut.²⁻⁴

Public health measures to prevent peanut and other food allergies in the United States and United Kingdom (UK) have focused on allergen exclusion by the mother during pregnancy and lactation, and by the child in the first 3 years of life.^{5,6} Despite this advice, there is evidence to suggest that PA continues to rise in these countries,⁷ and randomized interventional studies have not shown an effect on preventing PA by avoiding ingestion during gestation, lactation, or infancy.^{8,9}

Infants can be exposed to peanut by a number of routes (*in utero*, via breast milk,¹⁰ via infant dietary consumption, or via environmental exposure). The relevant routes of exposure through which sensitization to peanut allergens is acquired remain unknown. Environmental exposure may result from cutaneous contact or vapor inhalation of allergen.

Recent data support the possibility of environmental sensitization through low-dose cutaneous exposure. In rodent models, low-dose epicutaneous exposure to peanut leads to allergy.¹¹ In human beings, the presence of inflamed skin and the application of *Arachis* (peanut) oil-containing creams are independent risk factors for the development of PA.¹² However, a high incidence of PA is still found in countries where there is little use of peanut-containing creams, and the rise of PA in the UK has not been prevented by the removal of *Arachis* oil from commonly used preparations. This could be explained if environmental exposure to peanut also occurs through cutaneous contact with family members who have eaten peanut, particularly in households where large quantities of such foods are consumed.¹³

The main purpose of this study was to investigate the relevant routes of exposure to peanut that lead to PA.

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Abbreviations used

EA: Egg allergy
PA: Peanut allergy
SPT: Skin prick test
UK: United Kingdom

METHODS**Study design**

This was a questionnaire-based case-control study including children with PA and both high-risk and low-risk controls, conducted between September 2004 and September 2005 within 1 large London pediatric department. To avoid differential recall bias, parents of cases and high-risk controls completed the questionnaire before knowing whether their child had PA. All children were younger than 48 months at recruitment. The power calculation detailed in our protocol called for 150 children in each of the 3 groups. For pragmatic reasons, we closed the study after recruiting 133 cases, 160 high-risk controls, and 150 low-risk controls.

Ethical approval was obtained from the St Mary's Hospital Ethics Committee

Cases and high-risk controls

Children recruited were referred to our food allergy clinic predominantly because of eczema. On arrival at the clinic, parents were asked whether they suspected the child to be allergic to any foods. If they suspected PA, the family was excluded, thus avoiding potential bias in responses.

Once eligible families completed the questionnaire, they received routine care including consultation with an allergist and allergy testing. Cases were those who subsequently had a firm diagnosis of PA. Diagnosis required a skin prick test (SPT) wheal diameter of >8 mm, a specific IgE antibody level of >15 kU/L, or a positive double-blind placebo-controlled food challenge result. These threshold values were based on validation of a >95% predictive value in 14,000 children (Avon Longitudinal Study of Parents and Children cohort) and validated in our own clinic population.¹⁴

High-risk controls were those with a firm diagnosis of egg allergy (EA; based on allergy testing, as for PA) who were not sensitized to peanut. Children with EA are highly atopic and at high risk of coexisting PA, with approximately 20% to 30% demonstrating sensitization to peanut on SPT (data from Avon Longitudinal Study of Parents and Children cohort).

Low-risk controls

Low-risk controls were recruited from children attending general pediatric clinics with a nonallergic complaint.

Questionnaire

Families were asked detailed questions about peanut consumption by all household members during the child's first year of life and by the mother during pregnancy and lactation using a Food Frequency Questionnaire. Each family member was asked to recall which peanut-containing foods they had consumed from a comprehensive list, how many times per week they had consumed them, and the portion size. Food Frequency Questionnaires have been shown to be a valid method of estimating maternal consumption of food allergens.¹⁵ The questionnaire used in our study has been validated for accuracy of recall over a 2-year period.¹⁶ Weekly consumption of peanut protein for each family member was calculated from data on precise peanut protein content of different foods. Total weekly household peanut consumption (referred to as *household peanut*) for the first year of life was calculated by adding the weekly consumption of all family members resident in the household during this period. Mothers had provided 2 weekly peanut consumption figures for the period of the infant's first year of life: one during the period that they were breast-feeding and another for any remaining period of the infant's first year. A composite maternal value was calculated by using a weighted average dependent on the proportion of the year spent breast-feeding.

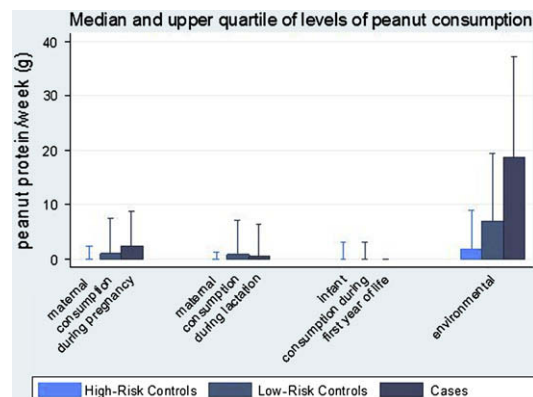


FIG 1. Levels of peanut exposure by different routes during first year of life in cases and controls. Maternal peanut consumption during pregnancy = average weekly peanut protein consumed by mother during course of entire pregnancy. Maternal peanut consumption during lactation = average weekly peanut protein consumed by mother during lactation. Infant consumption during first year of life = average weekly peanut protein consumed by infant over their entire first year of life (derived from age at first exposure and regular consumption from that point). Environmental exposure = average weekly peanut protein consumed by all family members living in the household during first year of life. Maternal component based on appropriately weighted composite of her consumption during lactation and during period of first year of life after breast-feeding has ceased.

Statistical analyses

Cases were compared with high-risk and low-risk controls. Where medians are cited, *P* values are based on the Wilcoxon rank-sum test. Formal comparisons adjusting for multiple risk factors and possible confounding were made using logistic regression. Odds ratios for peanut exposure are relative to 0 g exposure unless otherwise stated. In Fig 2, the logistic curve and confidence intervals were obtained by including the x-axis variable (linearly) in a logistic regression. The other smooth curve is obtained by using a running line smoother.

All analyses were carried out in Stata 8.0 for Windows (StataCorp, College Station, Tex).

RESULTS**Study population**

The groups were similar for age, sex, socioeconomic status, and breast-feeding (not shown). Eczema in the first year of life was very prevalent among both cases (91.7%) and high-risk controls (88.1%) but significantly less so among normal controls (42%), in whom the eczema was also significantly later in onset and less severe ($P < .0001$).

Maternal peanut protein consumption during pregnancy and lactation

Weekly maternal peanut consumption during pregnancy was compared. The median for cases was 2.4 g peanut protein per week, which was significantly higher than for high-risk controls (0.0 g/week; $P < .0001$) and nonsignificantly higher than in low-risk controls (median 1.1 g/week; $P = .32$; Fig 1).

Ninety percent (398/443) of mothers breast-fed their children. This did not differ significantly between the groups. Twelve (9%) children with PA were not breast-fed. Duration of breast-feeding was similar in both cases (mean duration 8.1 + 5.8 months) and high-risk controls (mean duration 8.1 + 5.7 months), which was significantly longer than the low-risk controls (mean duration

TABLE I. Relative risk of PA

Exposure to peanut-protein (g/wk)	Cases vs high-risk controls						Cases vs low-risk controls		
	OR univariate	95% CI		OR adjusted (1)	95% CI		OR univariate	95% CI	
Environmental									
0	1			1			1		
0.1-3.75	1.5	0.5	4	1.23	0.4	3.7	1.57	0.5	4.6
3.75-15	5.7	2.5	13.1	5.79	2.3	14.3	2.77	1.2	6.5
15+	21.5	9.2	49.9	22.81	8.9	58.6	6.09	2.7	13.8
Pregnancy									
0	1			1			1		
0.1-3.75	1.9	1.1	3.5	2.11	0.9	4.8	1.28	0.7	2.3
3.75-15	2.3	1.3	4.4	1	0.4	2.4	1.55	0.8	2.9
15+	5.2	2.1	12.6	2.25	0.7	7.1	1.19	0.6	2.4
Lactating									
Not applicable	2.6	1	6.7	1.63	0.5	5.2	0.6	0.3	1.3
0	1			1			1		
0.1-3.75	1.4	0.8	2.6	0.8	0.3	1.9	0.98	0.5	1.9
3.75-15	2.4	1.2	4.8	0.7	0.3	1.8	1.02	0.5	1.9
15+	4.7	1.4	15.5	0.63	0.1	2.7	0.89	0.4	2.2

Odds ratios (ORs) for environmental exposure are adjusted for maternal consumption during pregnancy and lactation. ORs during pregnancy and lactation are adjusted for each other and household exposure.

6.4 + 4.6 months). Weekly maternal peanut-protein consumption during lactation was significantly greater in cases (median 0.6 g) than in high-risk controls (0.0 g; $P = .0009$). Although low-risk controls (median 0.9 g/week) did not differ significantly from the cases, they were significantly higher than high-risk controls ($P = .0002$). The same pattern of results emerged when consumption during lactation was adjusted for the duration of breast-feeding.

Household peanut exposure during infancy

Weekly peanut protein consumption by all family members during the child's first year of life was calculated and is referred to as *household peanut*. The median household peanut for cases with PA (18.8 g/week) was 10-fold higher than for high-risk controls (1.9 g/week; $P < .0001$; Fig 1). The low-risk controls also had significantly lower household peanut (median 6.9 g/week) than the cases ($P < .0001$). A similar pattern was found for episodes of peanut consumption.

Relative importance of different routes of exposure

The most important difference in exposure to peanut protein among the 3 groups is household peanut exposure (Fig 1). Overall household peanut is correlated with maternal peanut consumption both during pregnancy (correlation coefficient 0.45) and during lactation (correlation coefficient 0.51), so adjusted analyses are needed to separate the effects of different routes.

Although maternal peanut consumption during pregnancy, maternal peanut consumption during breast-feeding, and household peanut during infancy are all strongly associated with PA in children with allergy, only household peanut is associated with PA when using low-risk controls (Table I). Further, after logistic regression was used to adjust for household peanut, maternal consumption during neither pregnancy nor lactation was associated with PA in high-risk children. By contrast, household peanut remains strongly associated with PA even after adjusting for maternal consumption (during pregnancy and lactation; Table I).

We also analyzed the relationship between PA and peanut consumption when the maternal consumption is quite different from that in the rest of the family (Fig 2). Fig 2, A, I, shows the

relationship between likelihood of PA and environmental exposure (household peanut), whereas Fig 2, B, I, shows the relationship between likelihood of PA and maternal peanut consumption during pregnancy in all children with food allergy ($n = 293$). In Fig 2, A, 2, in households where there was no maternal peanut consumption during pregnancy, the relationship between PA and household peanut persists, whereas in Fig 2, B, 2, in households where there was no household peanut during first year of life, the relationship between PA and maternal peanut consumption during pregnancy disappears.

Furthermore, there is no significant relationship between PA and maternal consumption during pregnancy when the household peanut in infancy exceeded a moderate amount (Fig 2, B, 3, illustrates the relationship between maternal peanut consumption during pregnancy and PA in children for whom household peanut exceeded the equivalent of 2 peanut butter sandwiches per week, 7 g peanut protein/week; $P = .55$). There is no effect of maternal peanut consumption during pregnancy on PA even if the household peanut is more than 1 peanut butter sandwich per week ($P = .15$). In contrast, the strong relationship between household peanut and PA persists when one restricts the analysis to children with at least 7 g/week maternal consumption during pregnancy (Fig 2, A, 3).

Different peanut-containing foods are associated with different risks of PA

The relative importance of different sources of peanut was considered by separating the total household peanut consumption into 3 sources: peanut butter, peanut-containing chocolate bars, and whole peanuts. A significantly greater proportion of peanut was consumed in the form of peanut butter among families of cases, relative to high-risk controls ($P < .0001$). In a multivariate logistic regression model for PA including these 3 sources, peanut-containing chocolate consumption was not significant, but peanut butter and whole peanut consumption were highly significant ($P < .0001$). Fig 3 illustrates the estimated odds ratios for PA for the consumption of each food (expressed as categorical factors) relative to zero consumption of that food group. None of

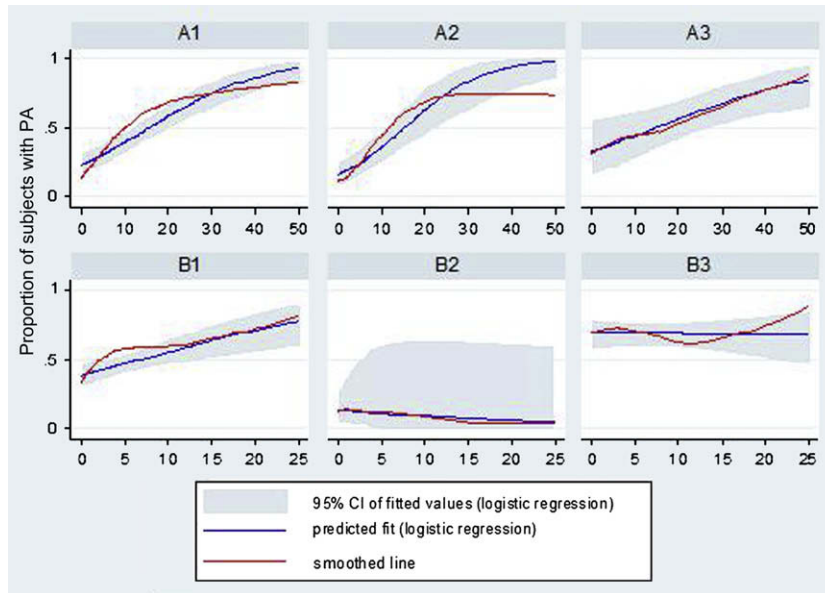


FIG 2. Proportion of allergic children with peanut allergy (**A**) as a function of household peanut consumption during infancy, and (**B**) as a function of maternal peanut consumption during pregnancy (grams of peanut protein per week). **A, 1, and B, 1:** All children with food allergy ($n = 293$). **A, 2,** children with no maternal consumption in pregnancy ($n = 134$). **B, 2,** Children with no household consumption during infancy ($n = 66$). **A, 3,** Children with maternal consumption of >7 g peanut protein per week during pregnancy ($n = 66$). **B, 3,** Children with household consumption of >7 g peanut protein per week during infancy ($n = 152$).

the odds ratios for peanut-containing chocolate are significantly different from 1, whereas at 3.76 to 7.5 g and more than 7.5 g/week, the odds ratios for both peanut butter and whole peanuts are highly significant.

High household peanut consumption in subgroup of high-risk controls

If sensitization occurs through environmental exposure in atopic individuals, one would not expect to find children in the high-risk control group (EA but not PA) with substantial environmental exposure to peanut. The high levels of environmental peanut exposure would have been expected to lead them to develop PA. Surprisingly, although the median environmental peanut exposure in this group was very low, 11% had a high household consumption of more than 20 g/week, and in 1.9% it was extremely elevated, more than 50 g/week. Why did these atopic children exposed to high levels of peanut not develop PA?

One possible explanation is that these children had milder eczema, and peanut was unable to penetrate the skin barrier. However, there was no difference in eczema severity or age of onset of eczema between this subgroup (>20 g/week) and the other high-risk controls, who had lower exposure.

Another explanation is that early introduction of peanut into the diet of these children with EA may have tolerized these infants, protecting them from PA, despite high household peanut. **Fig 4** illustrates how the strong relationship between PA (in high-risk children) and household peanut breaks down in the subgroup of children who themselves ate peanuts by 12 months. It is noteworthy that 5 of the 15 children with EA who ate peanuts by 1 year had household peanut of more than 20 g/week. Twenty-nine percent (2/7) of children who ate peanuts by 1 year and whose household peanut was more than 20 g/week had PA compared with 82% (60/73) of those who did not eat peanuts by 1 year ($P = .0012$).

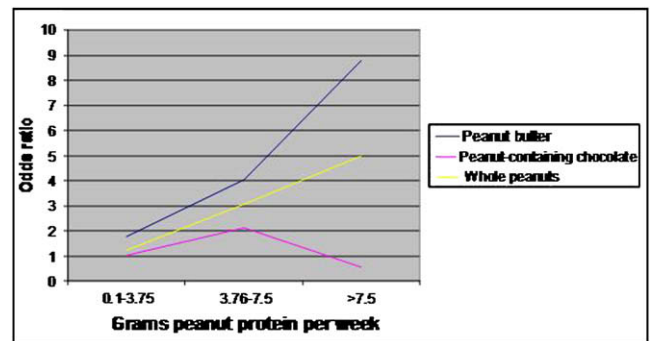


FIG 3. Odds ratio of PA according to source of peanut protein.

DISCUSSION

An understanding of routes of exposure leading to either allergic sensitization or immunologic tolerance is required for the development of effective prevention strategies.¹⁷

Recently, we showed that exposure to preparations containing *Arachis* oil was a risk factor for the development of PA.¹² Almost 91% of the children with PA had been exposed topically to creams containing *Arachis* oil in the first 6 months of life. Moreover, children with PA were exposed to significantly more preparations containing *Arachis* oil than were controls. Eczema was also identified as a risk factor, raising the possibility that exposure to low doses of peanut antigen through inflamed skin causes allergic sensitization.

However, topical preparations may represent only 1 component of environmental exposure. Cutaneous contact may occur when a tolerant household member eats allergen-containing food and then touches or kisses someone naive to that allergen or when the infant touches a surface contaminated with peanut. After peanut

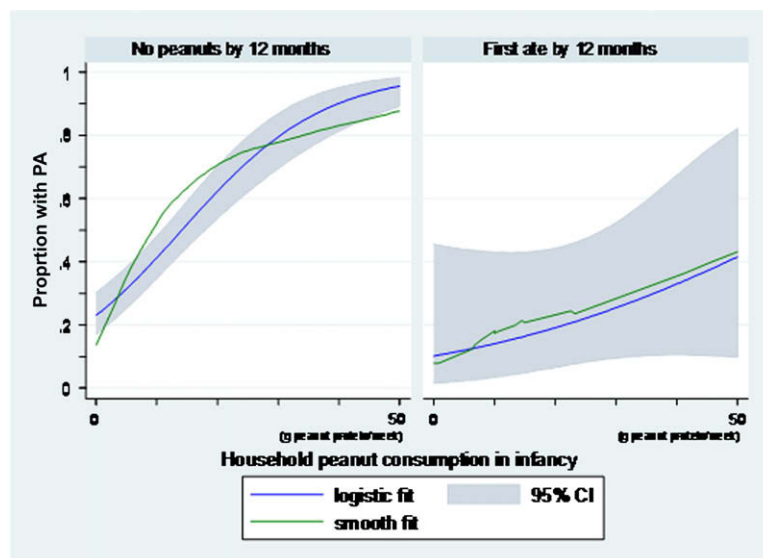


FIG 4. Peanut allergy among children with food allergy ($n = 293$) as a function of environmental exposure depending on whether child first ate peanuts by 12 months.

butter has been consumed, there is residual detectable Ara h 1 on the hands or in saliva, despite washing hands¹³ or cleaning teeth.¹⁸ There are thus many opportunities for an infant to experience cutaneous allergen exposure in households where peanut-containing foods are consumed. Moreover, cutaneous exposure to peanut in 33% of patients with PA causes contact reactions,¹⁹ confirming the bioavailability of peanut allergen through the skin. In animal models, the application of egg white^{20,21} and peanut¹¹ onto abraded skin has led to IgE sensitization.

This study found that total weekly household peanut consumption (household peanut) during the first year of life is significantly higher for infants who developed PA than for those who did not. The median household peanut is more than 10 times greater in the cases than high-risk controls. We have demonstrated a dose-response relationship between household peanut and the risk of later PA that is unaffected by maternal peanut consumption during pregnancy and lactation. Furthermore, the household peanut in the controls with EA is significantly lower than that of the low-risk controls. Children with EA are at high risk of developing PA, so these data suggest that reduced or absent levels of household peanut may exert a protective effect.

One previous study showed a nonsignificant trend toward increased peanut consumption during pregnancy in mothers of children who developed PA.²² Our study shows a significant increase in maternal consumption of peanuts during pregnancy and lactation in mothers of children who develop PA. However, after adjusting for household peanut, maternal consumption becomes insignificant. The increased maternal consumption during pregnancy and lactation is merely a marker of high household peanut: mothers in households with high peanut consumption are more likely to eat peanut because of its availability. However, this maternal consumption appears to be irrelevant. Analyses of households where there is a high peanut consumption (>7 g) show no effect of increasing maternal peanut consumption in the development of PA.

Although it may be premature to attach too much importance to the different possible roles of different forms of peanut products, it is nevertheless of interest that peanut butter consumption in the

home appeared to be a greater risk for PA than other forms of peanut. This could relate to its greater potential role in cutaneous sensitization. If environmental exposure involves the transfer of peanut protein from the hands of those who have consumed it to the skin of the infant, then the likelihood of this happening will differ depending on the nature of the food consumed. Peanut butter is extremely high in peanut protein, which is exposed to the environment and is also sticky. This makes it highly amenable to being transferred between surfaces. In contrast, in a peanut-containing chocolate bar, the peanut protein is encapsulated in chocolate, is less sticky, and is not as readily exposed to the environment.

The presence of a subgroup of high-risk controls who do not have PA despite relatively high levels of environmental peanut exposure challenges our hypothesis regarding sensitization. We would have expected these children to have developed PA unless they had been protected from this exposure by another factor such as a more intact skin barrier. However, this subgroup of children did not differ from other high-risk controls in the severity or age of onset of their eczema but were different inasmuch as a significant proportion had eaten peanut in infancy. The suggestion of an apparent protective effect of early infant peanut consumption raises the possibility that these children had developed oral tolerance. There is evidence that early oral exposure may be required to prevent the development of allergy.^{23,24} Oral tolerance induction is well recognized in murine models²⁵ and even in the human literature.²⁶ Du Toit et al²⁷ demonstrated the association between high infant peanut consumption and low prevalence of PA in Jewish children in Israel compared with the UK. Such data are consistent with early, high-dose peanut consumption inducing tolerance.

Our data can be explained by a model wherein the allergic or tolerant outcome of an atopic infant is determined by opposing routes of peanut exposure. High level environmental exposure in the absence of oral infant exposure leads to allergic sensitization, whereas high levels of oral exposure lead to tolerance irrespective of environmental exposure.¹⁷ This model may explain the varying prevalence of PA in different countries. Where infants do not eat peanut but environmental exposure is high because of high adult

consumption (eg, UK, United States, Canada), the outcome is allergic sensitization. Where neither adults nor infants eat peanut, environmental exposure is low, and the outcome is tolerance. Where both environmental exposure and infant consumption are high, oral tolerance overrides cutaneous sensitization, and the outcome is a low prevalence of PA—for example, Israel.²⁷

One main strength of our study is that peanut exposure was ascertained from the high-risk children before it was known (or even suspected) whether they had PA. Thus, there is no possibility of recall bias to explain the difference we have found. Another advantage of this study over previous studies is the choice of high-risk (EA) and normal controls. Comparison with only normal children may not be adequate to reveal the risk factors and protective factors for PA. The choice of children with EA who did not develop PA is an ideal control because children with EA have a >20% chance of developing PA. Indeed, we found the greatest difference in household peanut between the children with PA and this high-risk group. Furthermore, comparison with the EA group suggests that there are 2 protective factors that prevent the development of PA. Median household peanut in the group with EA was significantly lower than the low-risk group, suggesting that this high-risk group was protected against PA by reduced peanut exposure. Furthermore, the others in this group who were exposed to high household peanut might have been protected against PA through oral exposure.

There are potential limitations to our study design. We did not directly measure environmental exposure to peanut, but used a questionnaire-based approach, which included only the household consumption of peanut-containing foods by family members. Peanut protein is present in foods but also in creams, animal feeds, cosmetics, and plastics, and exposure may occur not only inside the home but also away from it. Studies are currently underway to validate the expected link between household peanut consumption and environmental peanut levels by measuring peanut protein levels in dust samples from homes and comparing these to household peanut consumption. However, although we cannot claim to be making an absolutely accurate measure of environmental peanut exposure, any inaccuracy in our measurement would tend to weaken any associations between the different groups and levels of environmental peanut exposure. Thus the associations observed cannot be explained by inaccurate measurement of environmental exposure or by recall bias, because cases and high-risk controls were naive to their PA status when completing the questionnaires.

Because the Food Frequency Questionnaire used was only validated for recall accuracy over a 2-year period,¹⁶ a subgroup analysis was performed including only children entered into the study at younger than 2 years. This did not significantly alter any of the main outcomes of the study.

A potential disadvantage is that none of the children in the PA group had a history of reaction, but were identified as having PA on the basis of sensitization. Had we included children with a history of reacting to peanuts, familial recall of peanut consumption would inevitably have been biased, especially given current government advice that advises peanut avoidance measures as a means of reducing PA. However, to ensure diagnostic stringency, children were defined as having PA if they had specific IgE or SPT values that were above the 95% positive predictive value or subsequently had a positive peanut challenge result. It has become well established that the magnitude of SPT response/specific IgE levels can predict the outcome of food challenges.²⁸⁻³⁰ Exclusion of

children with positive allergy test results to peanut below the 95% positive predictive value will have resulted in missing some cases who did indeed have PA. We did not analyze consumption data on such children and thus cannot be certain that this did not introduce any bias into our results.

The finding that controls with EA with moderate environmental peanut exposure were more likely than cases to have consumed peanuts in infancy could theoretically be an artefact of the design whereby children with known PA were excluded. Thus those PA children who consumed peanuts under 1 year of age but reacted to them were not included. However, in practice it is uncommon for us to see a child who has reacted to peanut at less than 12 months of age.

Another potential limitation is that children may have been misclassified as high-risk controls with EA, and although testing negative to peanut at entry into the study, could have later gone on to develop PA. This would have been a greater problem had we enrolled a younger group of children (<12 months of age), but because the majority of children were older than 2 years, it is unlikely that a significant proportion would have gone on to develop PA.

Conclusions

These results suggest that in susceptible individuals, increased exposure to peanut by cutaneous contact or inhalation promotes allergy in a dose-dependent manner, whereas low environmental levels may be protective. This supports our hypothesis that peanut sensitization occurs as a result of environmental exposure through cutaneous or inhalational routes rather than from maternal or infant allergen consumption. Our data also raise the possibility of early oral exposure playing an important role in the development of tolerance.¹⁷ If sensitization is indeed occurring through environmental exposure, this has important implications for public health policy. Our findings highlight the need for randomized controlled trials to explore these novel strategies of either reducing environmental peanut exposure during infancy or introducing peanut protein in the diet early to induce oral tolerance.

We are indebted to all of the families who took part in this study.

Clinical implications: High levels of environmental peanut exposure may increase the risk of peanut allergy among atopic infants, whereas low levels may be protective.

REFERENCES

1. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to food. *J Allergy Clin Immunol* 2001;107:191-3.
2. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998;102:e6.
3. Hourihane JO'B, Kilburn SA, Dean TP, Warner JO. Clinical characteristics of peanut allergy. *Clin Exp Allergy* 1997;27:634-9.
4. Ewan PW. Clinical study of peanut and nut allergy in 62 consecutive patients: new features and associations. *BMJ* 1996;312:1074-8.
5. Committee on Toxicity of Chemicals in Food Consumer Products and the Environment. Peanut allergy. London: Department of Health; 1998.
6. American Academy of Pediatrics, Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000;106:346-9.
7. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003;112:1203-7.
8. Zeiger RS, Heller MSN, Mellon MH, Forsythe AB, O'Connor RD, Hamburger RN, et al. Effect of combined maternal and infant food allergen avoidance on development of atopy in early infancy: a randomised study. *J Clin Allergy Immunol* 1989;84:72-89.

9. Zeiger RS, Heller MSN. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995; 95:1179-90.
10. Vadas P, Wai Y, Burks W, Perelman B. Detection of peanut allergens in breast milk of lactating women. *JAMA* 2001;285:1746-8.
11. Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Disruption of the stratum corneum allows potent epicutaneous immunization with protein antigens resulting in a dominant systemic Th2 response. *Eur J Immunol* 2004;34:2100-9.
12. Lack G, Fox D, Northstone K, Golding J. Factors associated with the development of peanut allergy. *N Engl J Med* 2003;348:977-85.
13. Perry TT, Conover-Walker MK, Pomes A, Chapman MD, Wood RA. Distribution of peanut allergen in the environment. *J Allergy Clin Immunol* 2004;113:973-6.
14. Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. *J Allergy Clin Immunol* 2005;115:1291-6.
15. Venter C, Higgins B, Grundy J, Clayton CB, Gant C, Dean T. Reliability and validity of a maternal food frequency questionnaire designed to estimate consumption of common food allergens. *J Hum Nutr Diet* 2006;19:129-38.
16. Fox AT, Meyer R, DuToit G, Syed H, Sasieni P, Lack G. Retrospective recall of maternal peanut consumption using a multiple food-frequency questionnaire. *S Afr J Nutr* 2006;19(4):154-60.
17. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;121:1331-6.
18. Maloney JM, Chapman MD, Sicherer SH. Peanut allergen exposure through saliva: Assessment and interventions to reduce exposure. *J Allergy Clin Immunol* 2006; 118:719-24.
19. Simonte SJ, Ma S, Mofidi S, Sicherer SH. Relevance of casual contact with peanut butter in children with peanut allergy. *J Allergy Clin Immunol* 2003;112:180-2.
20. Hsieh K-Y, Tsai CC, Wu CH, Lin RH. Epicutaneous exposure to protein antigen and food allergy. *Clin Exp Allergy* 2003;33:1067-75.
21. Saloga J, Renz H, Larsen GL, Gelfand EW. Increased airways responsiveness in mice depends on local challenge with antigen. *Am J Respir Crit Care Med* 1994;149:65-70.
22. Frank L, Marian A, Visser M, Weinberg E, Potter PC. Exposure to peanuts in utero and in infancy and the development of sensitization to peanut allergens in young children. *Pediatr Allergy Immunol* 1999;10:27-32.
23. Poole JA, Barriga K, Leung DY, Hoffman M, Eisenbarth GS, Rewers M, et al. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics* 2006;117:2175-82.
24. Kull I, Bergstrom A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. *Allergy* 2006;61:1009-15.
25. Ngan J, Kind LS. Suppressor T cells for IgE and IgG in Peyer's patches of mice made tolerant by the oral administration of ovalbumin. *J Immunol* 1978;120:861-5.
26. Husby S, Mestecky J, Moldoveanu Z, Holland S, Elson CO. Oral tolerance in humans. T cell but not B cell tolerance after antigen feeding. *J Immunol* 1994; 152:4663-70.
27. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki S, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:986-91.
28. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;30:1540-6.
29. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444-51.
30. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005;35:268-73.