

# Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants

Scott H. Sicherer, MD,<sup>a</sup> Robert A. Wood, MD,<sup>b</sup> Donald Stablein, PhD,<sup>c</sup> Robert Lindblad, MD,<sup>c</sup> A. Wesley Burks, MD,<sup>d</sup> Andrew H. Liu, MD,<sup>e</sup> Stacie M. Jones, MD,<sup>f</sup> David M. Fleischer, MD,<sup>e</sup> Donald Y. M. Leung, MD, PhD,<sup>e</sup> and Hugh A. Sampson, MD<sup>a</sup> New York, NY, Baltimore and Rockville, Md, Durham, NC, Denver, Colo, and Little Rock, Ark

**Background:** Peanut allergy is typically severe, lifelong, and prevalent.

**Objective:** To identify factors associated with peanut sensitization.

**Methods:** We evaluated 503 infants 3 to 15 months of age (mean, 9.4 months) with likely milk or egg allergy but no previous diagnosis of peanut allergy. A total of 308 had experienced an immediate allergic reaction to cow's milk and/or egg, and 204 had moderate to severe atopic dermatitis and a positive allergy test to milk and/or egg. A peanut IgE level  $\geq 5$  kU<sub>A</sub>/L was considered likely indicative of peanut allergy.

**Results:** A total of 140 (27.8%) infants had peanut IgE levels  $\geq 5$  kU<sub>A</sub>/L. Multivariate analysis including clinical, laboratory, and

demographic variables showed frequent peanut consumption during pregnancy (odds ratio, 2.9; 95% CI, 1.7-4.9;  $P < .001$ ), IgE levels to milk ( $P = .001$ ) and egg ( $P < .001$ ), male sex ( $P = .02$ ), and nonwhite race ( $P = .02$ ) to be the primary factors associated with peanut IgE  $\geq 5$  kU<sub>A</sub>/L. Frequency of peanut consumption during pregnancy and breast-feeding showed a dose-response association with peanut IgE  $\geq 5$  kU<sub>A</sub>/L, but only consumption during pregnancy was a significant predictor. Among 71 infants never breast-fed, frequent consumption of peanut during pregnancy was strongly associated with peanut IgE  $\geq 5$  kU<sub>A</sub>/L (odds ratio, 4.99, 95% CI, 1.69-14.74;  $P < .004$ ). **Conclusion:** In this cohort of infants with likely milk or egg allergy, maternal ingestion of peanut during pregnancy was strongly associated with a high level of peanut sensitization. (J Allergy Clin Immunol 2010;■■■■:■■■■-■■■■.)

**Key words:** Food allergy, sensitization, atopy, peanut allergy

From <sup>a</sup>the Jaffe Food Allergy Institute, Mount Sinai School of Medicine, New York; <sup>b</sup>the Johns Hopkins University School of Medicine, Baltimore; <sup>c</sup>the EMMES Corp, Rockville; <sup>d</sup>the Duke University Medical Center, Durham; <sup>e</sup>National Jewish Health, Denver; and <sup>f</sup>the University of Arkansas for Medical Sciences.

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Reprint requests: Scott H. Sicherer, MD, Division of Allergy/Immunology, Mount Sinai Hospital, Box 1198, One Gustave L. Levy Place, New York, NY 10029-6574. E-mail: scott.sicherer@mssm.edu.

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Peanut allergy is often severe, is typically lifelong, affects approximately 1% of children,<sup>1-6</sup> and may have increased in prevalence among children over the last decade.<sup>1-4,6</sup> With the goal of preventing peanut allergy, the Committee on Toxicology in the United Kingdom (UK) and the American Academy of Pediatrics from 1998 to 2000 recommended that mothers at risk for atopy avoid peanut during pregnancy and lactation.<sup>7</sup> However, this advice was based on extremely limited evidence and has been recently called into question.<sup>8</sup> In 2008, the American Academy of Pediatrics rescinded their recommendation and replaced it with a statement that the efficacy of this practice remains unproven.<sup>9</sup> As a result of limited studies, a European expert panel also recommended no maternal dietary restrictions during pregnancy or lactation.<sup>10,11</sup>

The Consortium of Food Allergy Research has enrolled infants with likely egg or milk allergy but without previously known peanut allergy in an observational study to address the immunologic, genetic, and environmental factors that affect the course of food allergy.<sup>12</sup> A surprisingly high rate of peanut sensitization ( $>0.35$  kU<sub>A</sub>/L), 69%, was observed at the time of enrollment. Here we report clinical, demographic, and immunologic factors influencing an elevated ( $\geq 5$  kU<sub>A</sub>/L) peanut-specific IgE level observed at the time of enrollment, with emphasis on the role of maternal ingestion of peanut, a potentially modifiable risk factor.

## METHODS

### Subjects

The cohort includes 512 infants enrolled at 3 to 15 months of age (mean age, 9.4 months; median age, 9 months) at 5 sites: Mount Sinai School of Medicine, New York, NY; Duke University Medical Center, Durham, NC;

**Abbreviations used**

AD: Atopic dermatitis  
 OR: Odds ratio  
 ROC: Receiver operating characteristic  
 Rs: Spearman rank correlation coefficient  
 SPT: Skin prick test  
 UK: United Kingdom

Johns Hopkins University School of Medicine, Baltimore, Md; National Jewish Health, Denver, Colo; and the Arkansas Children's Hospital, Little Rock, Ark. Enrollment criteria included atopic children at risk to develop peanut allergy as previously described.<sup>12</sup> Briefly, enrollment required (1) a history of a convincing immediate allergic reaction to cow's milk (and/or egg) and a positive skin prick test (SPT; 3 mm larger than the negative control) to cow's milk (and/or egg, if the clinical reaction was to egg), and/or (2) moderate to severe atopic dermatitis (AD), and a positive SPT to milk and/or egg. The study aimed to observe the development of peanut allergy longitudinally, so children were not enrolled if they had a known allergy to peanut or had a peanut-specific IgE antibody level  $\geq 5$  kU<sub>A</sub>/L performed before study enrollment. In total, 308 children had experienced an immediate clinical reaction to cow's milk and/or egg consisting of urticaria and/or angioedema, respiratory distress, wheezing, and/or vomiting, and had a positive SPT to the trigger food. The remaining 204 had moderate to severe AD<sup>13</sup> and a positive SPT to milk and/or egg. The study was approved by the participating sites' institutional review boards, and written informed consent was obtained.

Atopic disease history in parents of the enrolled infants was based on previously published definitions and was recorded by parental report.<sup>14</sup> Dietary, social, and environmental histories were obtained by using questionnaires completed during enrollment interviews. Maternal ingestion of peanut was queried for each pregnancy trimester and during breast-feeding and recorded as avoided, ingested <2 times/wk, ingested  $\geq 2$  times/wk but less than daily, ingested daily, or unknown. Categorical analysis of maternal ingestion defines "frequent" as twice or more per week. Peanut consumption in the third trimester was selected as an independent variable for analyses, as the period least susceptible to recall bias.

## Tests for IgE sensitization

Skin prick tests (were performed on the infant's back using the GreerPick and standard skin test reagents (egg, milk, peanut, dust mites, mold, and cockroach; Greer Labs, Lenoir, NC). The size of the longest wheal diameter (mm) and its longest perpendicular were averaged. A positive SPT is defined by a mean wheal diameter of 3 mm or greater after subtraction of the saline control. The concentration of specific IgE antibody to egg, milk, and peanut were measured from plasma at a single central laboratory by using the Phadia ImmunoCAP system (Uppsala, Sweden) reported in kU<sub>A</sub>/L. A level  $\geq 0.35$  kU<sub>A</sub>/L was considered positive. The concentration of IgG and IgG<sub>4</sub> antibodies to peanut were also measured from plasma samples by using the Phadia ImmunoCAP system. The detection limits for IgG and IgG<sub>4</sub> are 0.02 and 0.07 mg/L, respectively.

## Statistics

We sought to estimate a peanut-specific IgE level signifying a high likelihood of peanut allergy. Oral food challenges are not typically performed to peanut in this age group, and therefore, diagnostic properties of the test have not been determined in infants.<sup>15,16</sup> There are no studies correlating peanut specific IgE levels with clinical outcomes in a cohort of infants such as those described in this study. We selected a peanut IgE  $\geq 5$  kU<sub>A</sub>/L as an endpoint of interest because several studies of older children evaluated for a variety of reasons indicated an increased likelihood (>70%) of peanut allergy above this value.<sup>15-17</sup> We examined clinical and laboratory variables with potential influence on this outcome by using the  $\chi^2$  test. To identify the factors with the greatest association with peanut-specific IgE  $\geq 5$  kU<sub>A</sub>/L, logistic regression was

used with a stepwise selection procedure retaining variables that were significant ( $P < .05$ ) in the resulting multivariate model. Variables that had the greatest predictive influence on peanut IgE outcomes were examined simultaneously by using receiver operator characteristics<sup>18</sup> (ROCs) (eg, comparing the sensitivity vs 1-specificity) to evaluate the predictive quality of the model combining these factors. Trend tests to evaluate the association of maternal ingestion with the primary outcome used logistic regression with a single slope parameter and equally spaced ingestion categories.

Additional analyses of peanut specific IgE sensitization ( $\geq 0.35$  kU<sub>A</sub>/L) and linear regression modeling was performed. Food-specific IgE and IgG values were log base 10-transformed, and 0 values were scored below the lowest detected value (ie, as 0.001 kU<sub>A</sub>/L for IgE, 0.005 mg/L for both IgG and IgG<sub>4</sub>). The IgE to IgG ratio is presented as the antilog of the log ratio. Standard descriptive statistics were used including the Spearman rank correlation coefficient (Rs). Immunoglobulin levels were compared with the Wilcoxon or Kruskal-Wallis test depending on the number of grouping levels.

## RESULTS

### Relationship of peanut sensitization to clinical, demographic, and dietary characteristics

Of the 512 subjects enrolled, blood samples were obtained in 503 and analyzed further. Overall, 270 of 503 children (53.7%) had a positive SPT to peanut, 305 (60.6%) had detectable ( $\geq 0.35$  kU<sub>A</sub>/L) IgE to peanut, and 346 (68.8%) had sensitization detected by at least 1 of the test methods at enrollment. There were 140 (27.8%) children with peanut-IgE levels  $\geq 5$  kU<sub>A</sub>/L. The association of key categorical clinical and demographic factors with elevated peanut IgE levels  $\geq 5$  kU<sub>A</sub>/L are shown in Table I without adjustment for multiple analyses. Several variables that reflect stronger atopic phenotypes, such as AD severity, having more than 1 food allergy, or being enrolled with both AD and a food reaction, were expected significant variables influencing peanut IgE in the univariate analysis. In addition to variables shown in Table I, no significant associations were found between peanut IgE levels  $\geq 5$  kU<sub>A</sub>/L and age (months) at enrollment (odds ratio [OR], 1.03; 95% CI, 0.96-1.09;  $P = .45$ ), age when introducing formula (OR, 1.05; 95% CI, 0.97-1.14;  $P = .22$ ) or solid foods (OR, 1.03; 95% CI, 0.89-1.18;  $P = .71$ ), household income, parental educational level, parental atopic disease, use of soy formula, whether a child was breast-fed, mode of delivery at birth, or lifetime antibiotic courses. Univariate analyses were also performed for detectable peanut IgE ( $\geq 0.35$  kU<sub>A</sub>/L), and results showed similar trends and conclusions as those for peanut IgE  $\geq 5$  kU<sub>A</sub>/L. Univariate analysis of peanut IgE  $\geq 5$  kU<sub>A</sub>/L according to sensitization to allergens is shown in Table II. Peanut IgE levels were highly correlated with egg ( $r = 0.68$ ;  $P < .001$ ) and milk ( $r = 0.52$ ;  $P < .001$ ) IgE levels.

A multivariate model including all of the clinical variables and results of egg and milk sensitization showed peanut consumption during pregnancy, race, and sex to be the primary clinical and demographic factors associated with peanut IgE  $\geq 5$  kU<sub>A</sub>/L (Table III). Multivariate analyses were also performed examining sensitized subjects (peanut specific IgE  $\geq 0.35$  kU<sub>A</sub>/L). In the model including clinical, laboratory (milk and egg IgE) and milk and egg SPT, for both IgE categories ( $\geq 5$  and  $\geq 0.35$  kU<sub>A</sub>/L), the top 3 significant variables were frequent peanut consumption during pregnancy, egg-specific IgE levels, and milk-specific IgE levels. The variables in Table III were evaluated for their ability to predict peanut sensitization when tested in a model that combines all 5 variables. The ROC analysis showed a very good predictive ability, with the area under the ROC of 0.86 and 0.85 for peanut IgE  $\geq 5$  and  $\geq 0.35$  kU<sub>A</sub>/L, respectively.

**TABLE I.** Results of univariate analysis of key clinical and demographic factors in relation to peanut IgE  $\geq 5$  kU<sub>A</sub>/L (additional factors described in text)

| Variable                                         | Total (N) no. of subjects | No. with Peanut IgE $\geq 5$ kU <sub>A</sub> /L (%) | OR        | 95% CI     | P value |
|--------------------------------------------------|---------------------------|-----------------------------------------------------|-----------|------------|---------|
| Site                                             |                           |                                                     |           |            | .002    |
| Denver, Colo                                     | 96                        | 22 (22.9)                                           | 0.92      | 0.47-1.79  |         |
| Durham, NC                                       | 101                       | 22 (21.8)                                           | 0.86      | 0.44-1.67  |         |
| Baltimore, Md                                    | 108                       | 47 (43.5)                                           | 2.38      | 1.30-4.36  |         |
| New York, NY                                     | 104                       | 26 (25.0)                                           | 1.03      | 0.54-1.96  |         |
| Little Rock, Ark                                 | 94                        | 23 (24.5)                                           | Reference |            |         |
| Sex                                              |                           |                                                     |           |            | .007    |
| Male                                             | 342                       | 108 (31.6)                                          | 1.86      | 1.19-2.92  |         |
| Female                                           | 161                       | 32 (19.9)                                           | Reference |            |         |
| Race                                             |                           |                                                     |           |            | .003    |
| Black                                            | 79                        | 29 (36.7)                                           | 1.87      | 1.11-3.13  |         |
| Asian                                            | 39                        | 19 (48.7)                                           | 3.05      | 1.56-5.98  |         |
| Other                                            | 14                        | 4 (28.6)                                            | 1.29      | 0.39-4.20  |         |
| White                                            | 371                       | 88 (23.7)                                           | Reference |            |         |
| Parental allergy/asthma                          |                           |                                                     |           |            | .339    |
| No known                                         | 83                        | 28 (33.7)                                           | Reference |            |         |
| Maternal                                         | 120                       | 36 (30.0)                                           | 0.84      | 0.46-1.53  |         |
| Paternal                                         | 83                        | 24 (28.9)                                           | 0.80      | 0.41-1.54  |         |
| Both                                             | 217                       | 52 (24.00)                                          | 0.62      | 0.36-1.08  |         |
| AD severity                                      |                           |                                                     |           |            | .005    |
| None                                             | 40                        | 2 (5.0)                                             | Reference |            |         |
| Mild                                             | 50                        | 10 (20.0)                                           | 5.00      | 1.03-24.3  |         |
| Moderate                                         | 253                       | 72 (28.5)                                           | 7.76      | 1.83-32.95 |         |
| Severe                                           | 160                       | 56 (35.0)                                           | 10.50     | 2.44-45.1  |         |
| Milk, egg, or both allergies (clinical reaction) |                           |                                                     |           |            | <.0001  |
| Egg                                              | 162                       | 32 (19.8)                                           | 0.37      | 0.23-0.59  |         |
| Milk                                             | 99                        | 11 (11.1)                                           | 0.19      | 0.10-0.37  |         |
| Both                                             | 242                       | 97 (40.1)                                           | Reference |            |         |
| Enrolled with AD or clinical reaction            |                           |                                                     |           |            | .003    |
| AD                                               | 196                       | 56 (28.6)                                           | 0.81      | 0.53-1.23  |         |
| Clinical reaction                                | 90                        | 12 (13.3)                                           | 0.31      | 0.16-0.61  |         |
| Both                                             | 217                       | 72 (33.2)                                           | Reference |            |         |
| Stomach acid control agents                      |                           |                                                     |           |            | .036    |
| Yes                                              | 74                        | 13 (17.6)                                           | 0.51      | 0.27-0.96  |         |
| No                                               | 429                       | 127 (29.6)                                          | Reference |            |         |
| Breast-fed                                       |                           |                                                     |           |            | .811    |
| Yes                                              | 174                       | 48 (27.6)                                           | 0.85      | 0.46-1.55  |         |
| Before enrollment                                | 258                       | 70 (27.1)                                           | 0.83      | 0.47-1.47  |         |
| Never                                            | 71                        | 22 (31.00)                                          | Reference |            |         |
| Peanut present in house during breast-feeding    |                           |                                                     |           |            | .270    |
| Yes                                              | 373                       | 107 (28.7)                                          | 1.72      | 0.86-3.44  |         |
| No                                               | 58                        | 11 (19.00)                                          | Reference |            |         |
| Soy formula                                      |                           |                                                     |           |            | .143    |
| Yes                                              | 243                       | 75 (30.9)                                           | 1.34      | 0.91-1.98  |         |
| No                                               | 260                       | 65 (25.0)                                           | Reference |            |         |
| Peanut consumption— pregnancy                    |                           |                                                     |           |            | .002    |
| Frequent ( $\geq 2 \times /wk$ )                 | 211                       | 74 (35.1)                                           | 1.85      | 1.25-2.74  |         |
| Infrequent ( $< 2 \times /wk$ )                  | 292                       | 66 (22.6)                                           | Reference |            |         |
| Peanut consumption during breast-feeding         |                           |                                                     |           |            | .039    |
| Frequent ( $\geq 2 \times /wk$ )                 | 129                       | 45 (34.9)                                           | 1.57      | 1.02-2.42  |         |
| Infrequent ( $< 2 \times /wk$ )                  | 374                       | 95 (25.4)                                           | Reference |            |         |

### Additional analysis of maternal diet

The frequency of peanut consumption during the third trimester and during breast-feeding (Fig 1) revealed a dose-dependent association of maternal peanut ingestion with the outcome of peanut IgE  $\geq 5$  kU<sub>A</sub>/L, which was significant only for pregnancy consumption ( $P$  trend = .001). There were a total of 188 infants who consumed formula only or who were breast-fed while their mothers avoided peanut; among these, 27% had peanut IgE  $\geq 5$

kU<sub>A</sub>/L. The histogram in Fig 1 shows these 2 groups (maternal avoidance while breast-feeding or formula-fed) separately. Maternal ingestion of peanut was essentially constant from the first through third trimesters of pregnancy with concordance on the 4 levels of ingestion (eg, avoid, ingested less than twice a week, twice a week or more but less than daily, or daily) of at least 92% for each of the pairwise relationships. Analyses of data relating peanut consumption during each trimester separately to

**TABLE II.** Univariate association of immune factors with peanut IgE  $\geq 5$  kU<sub>A</sub>/L

| Variable                     | Total | OR   | 95% CI    | P value |
|------------------------------|-------|------|-----------|---------|
| Log <sub>10</sub> (milk IgE) | 503   | 2.46 | 1.97-3.06 | <.0001  |
| Log <sub>10</sub> (egg IgE)  | 503   | 4.98 | 3.51-7.06 | <.0001  |
| Milk SPT                     | 502   | 1.11 | 1.07-1.16 | <.0001  |
| Egg SPT                      | 502   | 1.15 | 1.10-1.21 | <.0001  |
| Peanut SPT                   | 503   | 1.37 | 1.30-1.46 | <.0001  |
| Cat SPT                      | 495   | 1.11 | 1.03-1.20 | .007    |
| Dog SPT                      | 494   | 1.13 | 1.02-1.25 | .016    |

Additional allergens tested by SPTs that did not reach significance included mold, dust mite, and cockroach.

**TABLE III.** Multivariate analysis of predictors of peanut-specific IgE  $\geq 5$  kU<sub>A</sub>/L

| Effect                                              | OR   | P value | 95% Confidence limits |      |
|-----------------------------------------------------|------|---------|-----------------------|------|
| Sex (male vs female)                                | 1.92 | .024    | 1.09                  | 3.37 |
| Race vs white                                       |      | .019    |                       |      |
| Black                                               | 2.32 |         | 1.20                  | 4.51 |
| Asian                                               | 2.85 |         | 1.18                  | 6.87 |
| Other                                               | 1.18 |         | 0.29                  | 4.87 |
| Pregnancy peanut consumption frequent vs infrequent | 2.93 | <.001   | 1.76                  | 4.88 |
| Log <sub>10</sub> (milk IgE)                        | 1.55 | .001    | 1.19                  | 2.01 |
| Log <sub>10</sub> (egg IgE)                         | 3.87 | <.001   | 2.59                  | 5.78 |

Stepwise, multivariate logistic regression was performed by using variables from Tables I and II. Model intercept is -1.44. A significance level of <.05 was required to stay in the model.

outcome of peanut IgE  $>5$  kU<sub>A</sub>/L also showed a similar association, with trimester-specific elevated peanut IgE rates ranging from 35.4% to 36.4% for the frequent consumption group. Compared with third trimester peanut consumption, breast-feeding mothers reported the same (67.9%), decreased (23.3%), or increased (7.8%) consumption of peanut during breast-feeding.

To explore the association of peanut exposure during pregnancy without any influence of maternal peanut ingestion during breast-feeding on peanut IgE, we analyzed 71 children who were never breast-fed. Frequent consumption of peanut during pregnancy (vs infrequent) was strongly associated with peanut IgE  $\geq 5$  kU<sub>A</sub>/L (OR, 4.99; 95% CI, 1.69-14.74;  $P < .004$ ) in this subgroup.

Additional analyses were performed to test the result of the multivariate model with respect to maternal ingestion of peanut. To address further the relative association of maternal consumption of peanut during pregnancy compared with breast-feeding on dichotomized peanut IgE outcomes, frequent versus infrequent consumption was analyzed simultaneously with only these 2 variables as predictors of peanut IgE  $>5$  kU<sub>A</sub>/L in a logistic regression model. This analysis revealed consumption of peanut during pregnancy to be significant ( $P = .002$ ) and peanut consumption during breast-feeding to have no discernable association with peanut IgE ( $P > .8$ ) in the joint model. In addition, the data were analyzed with peanut IgE levels as a continuous variable. In a linear regression analysis of log peanut IgE levels, after adjusting for egg IgE, milk IgE, AD severity, sex, study site, and race, only peanut ingestion during pregnancy significantly predicted peanut IgE levels ( $P < .001$ ). This analysis was consistent with the importance of peanut consumption during pregnancy,

relative to breast-feeding consumption, because the latter variable was not significant when added to the model ( $P > .40$ ), whereas the pregnancy consumption variable maintained its significance. Thus, these additional analyses support the results of the multivariate model identifying maternal pregnancy consumption as a significant predictor of peanut IgE outcomes.

To explore further the impact of maternal diet during pregnancy, we analyzed egg consumption. There were 143 mothers with infrequent egg ingestion and 356 with frequent egg ingestion in the third trimester. Frequent ingestion of egg in the third trimester was associated with an increased risk for egg IgE  $\geq 2$  kU<sub>A</sub>/L (OR, 1.53; 95% CI, 1.03-2.25;  $P = .03$ ), which was a level associated with immediate-type allergic reactions in 1 study of children under age 2 years suspected of egg allergy.<sup>19</sup> In multivariate analysis, consumption of egg, after adjusting for milk and peanut specific IgE levels, still remained a significant predictor of egg IgE  $\geq 2$  kU<sub>A</sub>/L (OR, 1.75;  $P = .026$ ). We could not analyze milk consumption because too few mothers had infrequent milk consumption ( $n = 37$ ).

The ratio of food specific IgE to IgG is noted to decrease in persons achieving natural tolerance to a food and in those undergoing oral immunotherapy.<sup>20</sup> Conversely, a higher IgE to IgG ratio may reflect a higher risk of clinical allergy. Therefore, we explored the relationship of the infant's peanut-specific IgE, IgG, and IgG<sub>4</sub> to maternal ingestion of peanut. Although we found substantial correlation of PN-IgE with peanut specific IgG (Rs 0.61;  $P < .001$ ) and IgG<sub>4</sub> (Rs 0.58;  $P < .001$ ), the relative concentrations were affected by peanut consumption. Infants of mothers with frequent, compared with infrequent, ingestion of peanut during pregnancy and during breast-feeding had significantly higher levels of all 3 immunoglobulin subtypes but had a stronger relative increase in IgE compared to IgG and IgG<sub>4</sub> (Table IV). The relationship was also noted in those who were never breast-fed (data not shown).

Household exposure to peanut was not a significant predictor of peanut IgE outcomes as indicated in Table I, and this variable did not survive the multivariate model. Because there is interest in the influence of environmental exposure to peanut on sensitization, we also reviewed the relationship of exposure to peanut-specific IgE/IgG ratios. In a linear regression analysis of log<sub>10</sub> IgE/IgG ratios, considering the key variables of maternal ingestion during pregnancy, maternal ingestion during breast-feeding, and exclusion of peanut from the home during breast-feeding, only pregnancy consumption remained in the model as a significant predictor, with an effect size of -0.45.

## DISCUSSION

We found that maternal ingestion of peanut during pregnancy had a dose-dependent association with peanut sensitization and likely peanut allergy in infants with likely egg or milk allergy. Our result is in accordance with a previous small study.<sup>21</sup> In that study, 25 children with IgE to peanut were compared with 18 who had positive tests to milk or egg but not peanut. Ingestion of peanut more than once per week during pregnancy trended toward being a risk for peanut sensitization (OR, 3.97;  $P = .063$ ). This small study was potentially biased by dietary recall because children were as old as 3 years and their peanut allergies were already known. One additional study implicated maternal ingestion of peanut as a risk factor for peanut allergy. Hourihane et al<sup>22</sup> used a questionnaire to evaluate 622 individuals with peanut allergy

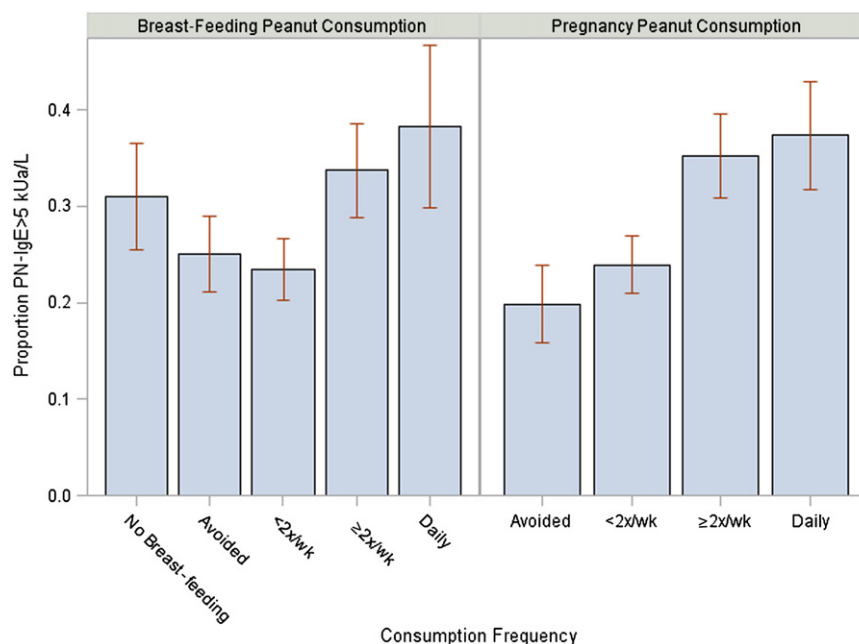


**FIG 1.** Proportion of children with elevated peanut specific IgE  $\geq 5$  kU<sub>A</sub>/L by maternal peanut ingestion status. There was a significant dose-response relationship of peanut consumption during pregnancy with outcomes of elevated peanut IgE ( $P$  trend = .001), which was not the case for peanut consumption during breast-feeding ( $P$  trend = .10; see text).

**TABLE IV.** Peanut-specific IgE (kU<sub>A</sub>/L), IgG, and IgG<sub>4</sub> (mg/L) and IgE/IgG ratio in relation to maternal ingestion

| Peanut consumption                  | Peanut IgE (median) | Peanut IgG (median) | Peanut IgG <sub>4</sub> (median) | Peanut IgE/IgG ratio |
|-------------------------------------|---------------------|---------------------|----------------------------------|----------------------|
| During third trimester of pregnancy |                     |                     |                                  |                      |
| Frequent                            | 2.06                | 6.69                | 0.08                             | 0.22                 |
| Infrequent                          | 0.50                | 3.90                | 0.04                             | 0.12                 |
| During breast-feeding               |                     |                     |                                  |                      |
| Frequent                            | 1.74                | 6.68                | 0.08                             | 0.22                 |
| Infrequent                          | 0.54                | 3.74                | 0.03                             | 0.14                 |
| Not breast-fed                      | 0.88                | 7.04                | 0.10                             | 0.19                 |

Frequent consumers have median levels 1.5 to 4 times higher. Each variable differs within the consumption groups (all  $P$  values <.001 except peanut IgE/IgG ratio during breast-feeding,  $P$  = .006).

and noted that probands under 6 years of age were more likely to have mothers who consumed peanut during pregnancy or while breast-feeding than older probands. The onset of peanut allergy was earlier in the younger probands and had increased in prevalence over generations, leading the authors to conclude that maternal ingestion may be a risk factor. However, the study could not control for recall bias and may have been influenced by a general increase in atopic disease over the past 3 decades. In contrast with these 2 studies, our study includes evidence of a dose-response and is not affected by comparing participants from different generations or by a significant potential for dietary recall bias.

In contrast with our data, 2 population-based studies concluded that peanut consumption during pregnancy/lactation was not a risk factor for peanut allergy. Lack et al<sup>23</sup> used a part-retrospective (several years delay for recall for diet) approach

and evaluated a cohort of 13,971 preschool children; data regarding risk factors were limited to analysis of 48 affected children, 23 with confirmed peanut allergy. In a birth cohort of 1218 children followed to age 4 years, Tariq et al<sup>24</sup> also did not identify a relationship between maternal peanut or nut ingestion with sensitization, but only 15 cases were evaluated. It is possible that the low numbers of affected children reduced the power to determine maternal dietary influences in these studies.

The paucity of studies, conflicting results, and their limitations have led to controversies regarding advice to mothers. From 1998 to 2000, the Committee on Toxicology (UK), and the American Academy of Pediatrics (United States)<sup>7</sup> recommended that women with infants at risk for atopy should avoid peanuts during pregnancy and lactation. The outcome of this advice is unclear. Hourihane et al<sup>25</sup> evaluated parent-child pairs in a UK school cohort born after the avoidance advice ( $n$  = 1072). In evaluating children with peanut allergy ( $n$  = 20), 8 mothers had reduced and 1 stopped peanut ingestion during pregnancy. Dean et al<sup>26</sup> followed a birth cohort on the Isle of Wight, UK, born between September 2001 and August 2002, and noted that 65% of 838 children available for follow-up had avoided peanut. A total of 658 were skin-tested to peanut, and 13 were positive; mothers had avoided peanut in 10 of 13 cases (85% of these had a family history of atopy). The authors of both of these studies interpreted their findings to suggest that avoidance of peanut had no discernable effect. Indeed, the number of affected children in both of these studies was low, reducing the ability to draw firm conclusions.

We identified several additional factors associated with strong sensitization to peanut that are not amenable to risk reduction, including male sex, nonwhite race, and elevated milk/egg IgE levels. Studies of food allergies and atopy in children typically disclose a male preponderance, although the pathophysiological reason for this relationship remains unknown.<sup>2</sup> Our observation

that nonwhite subjects, especially Asians, were at higher risk is novel and deserves further study. Last, it is not unexpected that sensitization to milk or egg was a risk factor because strong sensitization to these multiple foods has been noted in previous studies and likely indicates a strong atopic disposition that includes a risk for peanut allergy.<sup>3,27</sup>

Atopic disease is influenced by heredity, and previous studies have noted parental atopic disease to be an influence on outcomes of peanut allergy.<sup>23,28</sup> However, we did not identify atopic disease as a risk factor, possibly because our cohort was preselected for having atopic disease; 67% of mothers and 60% of the fathers were atopic. We also did not find an association with soy ingestion and peanut allergy, a factor identified as an independent risk in a previous population-based study<sup>23</sup> but not confirmed in 2 subsequent studies.<sup>29,30</sup> It has been suggested that the use of acid suppression medications, by reducing protein digestion, may increase the risk of sensitization and reactions to food proteins,<sup>31</sup> but we did not observe this relationship.

Environmental, noningestion exposure to peanut, such as contact from skin creams containing peanut, from residual protein on the hands of caregivers or siblings, or in the home has also been cited as a risk factor for peanut allergy because the skin may be a sensitizing route of exposure.<sup>23,32,33</sup> We did not query about skin products containing peanut because these are not typically available in the United States. We did not find having peanuts in the home to be a risk factor for sensitization to peanut; however, we had very few homes that excluded peanut, perhaps limiting power to evaluate this variable.

Our results concerning maternal peanut consumption must be interpreted with caution. This is an observational study, and as such, we do not know whether additional subtle influences affected our findings, especially regarding reporting of dietary habits. To minimize recall bias, we enrolled children between 3 and 15 months of age, and families were not informed of peanut IgE test results at the time of the dietary history; however, we cannot exclude the possibility of subtle reporting biases. Our observational study design excluded enrollment of children with known peanut allergy and/or peanut IgE  $\geq 5$  kU<sub>A</sub>/L before screening for enrollment; the impact of this exclusion on the current analysis is unknown. Nonetheless, maternal peanut consumption during pregnancy was identified as a significant predictive factor for peanut sensitization in our cohort through a variety of analyses, including univariate, multivariate, models focusing on household ingestion, models isolated to maternal consumption, different trimesters, and considering formula-fed infants separately, and was in agreement with our additional novel observation that maternal ingestion of egg during pregnancy was associated with elevated levels of egg-specific IgE in the infants.

One might postulate that maternal ingestion is protective, perhaps stimulating an IgG response and transferring IgG to the infant. We interpret our results of the peanut-specific IgG and IgG<sub>4</sub> data as supporting the notion that maternal ingestion of peanut during pregnancy did not result in favorable IgE/IgG ratios compared with infants whose mothers ingested less peanut. Although we await determination of the final clinical outcomes for these infants, we do not anticipate that the elevated IgE levels are modulated by "protective" levels of IgG. In addition, we did not observe higher peanut-specific IgG levels in the younger infants, which might have indicated passive transfer (data not shown).

We emphasize that this work focused on sensitization to peanut, not clinical allergy. Oral food challenges are not typically

performed to peanut in this age group and, therefore, diagnostic properties of the test have not been determined in infants. We chose a peanut IgE  $\geq 5$  kU<sub>A</sub>/L as an endpoint of interest because several studies<sup>15-17</sup> indicate that this level is associated with a high likelihood of peanut allergy (70% to 85%) in older children evaluated for a variety of reasons. In a large study by Komata et al<sup>34</sup> that addressed milk and egg allergy, younger infants were more likely to react to the tested food than older infants with the same IgE level (eg, an egg-specific IgE concentration of 3 kU<sub>A</sub>/L represented an 80% risk for infants under age 1 year and a 40% risk for children over age 2 years). The study by Komata et al<sup>34</sup> may indicate that the peanut IgE level we selected indicates a higher risk than noted in studies of older children. However, studies in infants with the characteristics of our cohort would be needed to address this possibility specifically.

Longitudinal evaluation of the children in our cohort children will be needed to determine final expression rates of symptomatic peanut allergy. Following standard care, we have suggested not feeding peanut to these young atopic children according to previous guidelines.<sup>7</sup> The influence of this advice on outcomes of peanut allergy remains unknown because early oral exposure may induce tolerance, as suggested by observations that peanut allergy is less common in Israeli Jews whose infants ingest peanut early, compared with a similar population in the UK who delay ingestion.<sup>32,35</sup> A study is currently underway to determine the effects of early feeding of peanut to infants at risk for peanut allergy ([www.leapstudy.co.uk](http://www.leapstudy.co.uk)). The interaction of maternal ingestion of peanut and timing of infant introduction may be complex.

Recent studies in children have estimated the prevalence of peanut allergy to be over 1% and approaching 2%,<sup>4,25,36</sup> indicating an epidemic.<sup>3</sup> Peanut allergy is usually lifelong<sup>37,38</sup> and can be fatal.<sup>39,40</sup> These observations indicate a need for prevention measures. Our study has identified maternal consumption of peanut during pregnancy as a primary modifiable risk factor. Our observation of a dose-dependent response of peanut ingestion during pregnancy on outcomes of peanut IgE  $>5$  kU<sub>A</sub>/L, as well as a parallel association of maternal egg ingestion on outcomes of egg-specific IgE, are striking observations worthy of further exploration in controlled interventional studies.

Additional site investigators: D. Atkins, W. Shreffler, A. Grishin, T. T. Perry, A. M. Scurlock, M. Masilamani, B. Vickery.

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**Clinical implications:** In this observational study, maternal ingestion of peanut during pregnancy was associated with peanut IgE  $\geq 5$  kU<sub>A</sub>/L in infants, implying that maternal avoidance as a strategy to reduce allergy risk is an area worthy of additional study.

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