

## Letter to the Editor

**Winter birth in inner-city asthmatic children is associated with increased food allergen sensitization risk**

To the Editor:

Food allergies affect as many as 1 in 13 children in the United States,<sup>1</sup> and estimates suggest that the prevalence is increasing.<sup>2</sup> Understanding factors that affect the development of food allergy is a particular area of interest, with theories including timing of food introduction, season of birth, environmental exposures, and both excess and deficiency of vitamin D.<sup>3</sup> Season of birth may affect the development of food allergy by several mechanisms, including infectious exposures, indoor allergen exposure, and vitamin D status during the first year of life. Vitamin D has been postulated to have a role in the allergic response primarily by means of inhibition of the inflammatory response of innate immune cells.<sup>4</sup> Using previously collected serum samples and historical information from an Inner-City Asthma study,<sup>5</sup> we sought to uncover the potential role of season of birth, and because of the capability of measuring vitamin D status in the population, the potential effect of serum vitamin D on the development of food allergen sensitization in an inner-city asthmatic cohort.

Four hundred twenty-four samples from the National Institutes of Health-National Cooperative Inner-City Asthma Study<sup>5</sup> were available for analysis of serum 25-hydroxyvitamin D levels.

Vitamin D was characterized as both a continuous variable and as a dichotomous variable using 20 ng/mL as a cutoff on the basis of the distribution of vitamin D within the population. The Pearson  $\chi^2$  test was used for comparison of categorical data, and the Kruskal-Wallis test was used for testing between quantitative and categorical data: for example, food and environmental allergen sensitization. The relationship between food allergen sensitization and season of birth (winter—December, January, and February; spring—March, April, and May; summer—June, July, and August; fall—September, October, and November) was also examined. Season of birth was analyzed as a proxy for vitamin D levels in the first year of life.<sup>6</sup> Because of known differences in vitamin D status and race,<sup>7</sup> analyses were performed on the black portion of the population because the overwhelming majority of our population was black ( $n = 340$ ; Table I). Statistical analyses were performed using R (<http://www.r-project.org/>).

This inner-city asthmatic population, the overwhelming majority of which was from northern latitudes (96%), was 64% male, with a median age of 6 years (Table I); 82% of the individuals were black and 13% Hispanic. Participants were sensitized to foods and select environmental allergens, as shown in Table E1 of this article's Online Repository at [www.jacionline.org](http://www.jacionline.org).

No significant relationship was detected between vitamin D status and food allergen sensitization, environmental allergen sensitization (Table E1), environmental allergen exposure, or likelihood of clinically relevant food allergy on the basis of established predictive values for allergic reactivity to milk, egg, or peanut (data not included). A trend toward significance was noted for egg sensitization and vitamin D status ( $P = .07$ )

**TABLE I.** Population characteristics

| Characteristic                       | N = 427          |
|--------------------------------------|------------------|
| Sex: male                            | 270 (64)         |
| Race                                 |                  |
| Black                                | 340 (82)         |
| Hispanic                             | 54 (13)          |
| Other                                | 21 (5)           |
| Age (y)                              | 6 (5-8)          |
| Site                                 |                  |
| Boston                               | 43               |
| Bronx                                | 43               |
| Chicago                              | 9                |
| Others                               | 4                |
| Body mass index (kg/m <sup>2</sup> ) | 16.7 (15.5-18.6) |
| Season                               |                  |
| Fall                                 | 25               |
| Winter                               | 25               |
| Spring                               | 25               |
| Summer                               | 25               |
| 25-Hydroxyvitamin D (ng/mL)          | 18.0 (12.9-23.2) |

Values are n (%), percentages, or medians with (interquartile ranges).

(Table E1), although we do not have an explanation for this trend. In models adjusting for the current vitamin D level, a significant relationship was detected between winter birth and increased likelihood of sensitization to egg white, peanut, or soy and a trend toward significance for wheat sensitization ( $P = .06$ ) (Fig 1). Data were also analyzed adjusting for time of year when the blood sample was drawn, and no changes in results were observed (data not included).

Investigators have reported various associations between food allergen sensitization and either fall or winter birth. Keet et al<sup>6</sup> recently reported a strong relationship between fall birth and an increased likelihood of developing food allergy in a white cohort of children from the National Health and Nutrition Examination Survey III database, and Mullins et al<sup>8</sup> have shown significantly higher rates of food allergy in Australian children born in fall/winter than in spring/summer. We are the first to report a positive correlation between winter birth and sensitization to egg, peanut, and soy in a predominantly black, inner-city population.

A common hypothesis linking the season of birth with the development of allergen sensitization implies that vitamin D deficiency in a neonate may be responsible.<sup>9</sup> Season of birth may affect vitamin D status during infancy, a period of time when the developing immune system may be particularly susceptible to the acquisition of allergen sensitivities. One limitation of our analysis is that samples in our cohort were taken in later childhood, after sensitization had likely occurred in most of the individuals, and thus current vitamin D status may not have a bearing on preexisting sensitivities. Thus, we used season of birth as a proxy for vitamin D status in the first year of life, which has previously been shown to be reflective of seasonal associations with food allergy,<sup>6</sup> though this is clearly not a precise measurement. In addition to the effect of season of birth on vitamin D status, one must consider its effects on infectious exposures (eg, winter viruses) and indoor allergen exposures, factors we were not able to measure in the first year of life in our cohort.

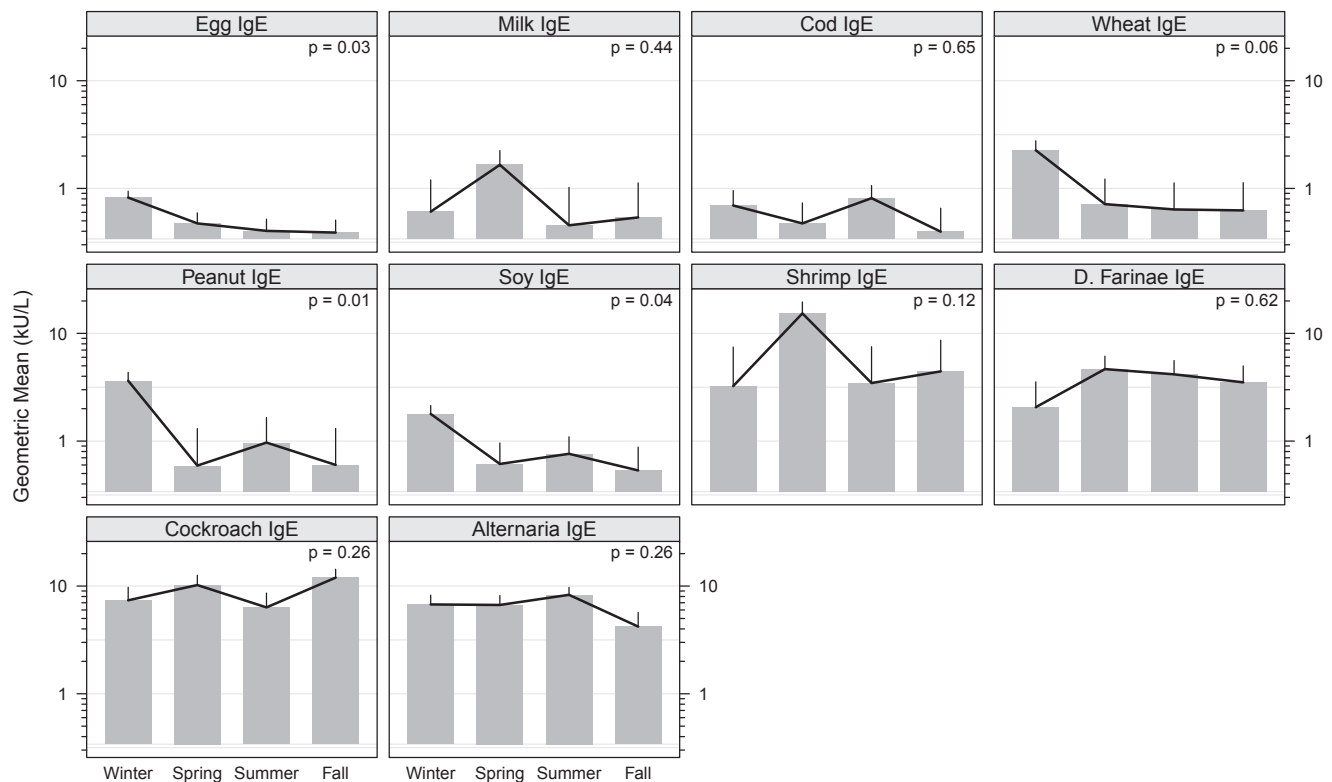


**FIG 1.** Association between specific IgE values and season of birth for black participants. Each bar represents the geometric mean and vertical lines the standard error of the mean.

Another limitation to the interpretability of vitamin D status and food allergen sensitization in our cohort may be that most of the individuals were either vitamin D deficient or insufficient at the time of serum acquisition (see Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)), which limits interpretability based on the lack of normal controls within the population. However, we also saw no relationship of food sensitivity to vitamin D levels when analyzed as a continuous variable (data not shown).

Our data suggest an important role between season of birth and the development of food allergen sensitization. In addition to vitamin D status, other factors may affect the development of allergen sensitivity for an infant born during winter, including exposure to winter viruses, global geographic location, and indoor allergen exposure. Additional considerations during the first year of life include the effects of breast-feeding and cesarian birth, factors we were not able to analyze in our sample. Given the lack of food allergy history in our population and variability in vitamin D levels with other ethnicities, we caution against drawing firm conclusions with regard to the presence of clinical reactivity and vitamin D status in other ethnicities; however, these data are suggestive of a relationship that warrants further investigation. Future epidemiologic studies should prospectively measure numerous factors, including vitamin D status and the development of allergy, in a diverse population.

J. Andrew Bird, MD<sup>a</sup>

Julie Wang, MD<sup>b</sup>

Cynthia M. Visness, PhD, MPH<sup>c</sup>

Agustin Calatroni, MS<sup>c</sup>

Hugh A. Sampson, MD<sup>b</sup>

Rebecca Gruchalla, MD, PhD<sup>a</sup>

From <sup>a</sup>the University of Texas Southwestern Medical Center, Dallas, Tex; <sup>b</sup>Icahn School of Medicine at Mount Sinai, New York, NY; and <sup>c</sup>Rho Federal Systems Division, Inc, Chapel Hill, NC. E-mail: [NCdrew.bird@utsouthwestern.edu](mailto:NCdrew.bird@utsouthwestern.edu).

The National Cooperative Inner-City Asthma Study was supported by grants U01 A1-30752, A1-30752, A1-30756, A1-30772, A1-30773-01, A1-30777, A1-30779, A1-30780, and N01-A1-15105. Funding for this analysis was provided by the Dedman Family Scholar in Clinical Care funds.

Disclosure of potential conflict of interest: J. A. Bird has received research support from DBV Technologies, Allergen Research Corporation, and Food Allergy Research and Education and has received payment for lectures from Nutricia North America. J. Wang has consultant arrangements with Merck, is employed by Icahn School of Medicine at Mount Sinai, has received research support from the National Institutes of Health, receives royalties from UpToDate, and has stock/stock options with JDP Therapeutics. C. M. Visness and A. Calatroni have received research support from the National Institutes of Health-National Institute of Allergy and Infectious Diseases. H. A. Sampson has received research support from the National Institute of Allergy and Infectious Diseases, the National Institutes of Health, and Food Allergy Research and Education; has received travel expenses as Chair of PhARF Award review committee; has consultant arrangements with Allertein Therapeutics, Regeneron, and Danone Research Institute; and has received payment for lectures from ThermoFisher Scientific, UCB, and Pfizer. R. Gruchalla has received research support from the National Institutes of Health-National Institute of Allergy and Infectious Diseases and the National Institutes of Health-Inner City Asthma Consortium and is employed by the Food and Drug Administration.

## REFERENCES

- Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128:e9-17.
- Branum AM, Lukacs SL. Food allergy among U.S. children: trends in prevalence and hospitalizations. *NCHS Data Brief* 2008;1-8.
- Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;121:1331-6.

4. Dimeloe S, Nanzer A, Ryanna K, Hawrylowicz C. Regulatory T cells, inflammation and the allergic response—the role of glucocorticoids and vitamin D. *J Steroid Biochem Mol Biol* 2010;120:86-95.
5. Wang J, Visness CM, Sampson HA. Food allergen sensitization in inner-city children with asthma. *J Allergy Clin Immunol* 2005;115:1076-80.
6. Keet CA, Matsui EC, Savage JH, Neuman-Sunshine DL, Skripak J, Peng RD, et al. Potential mechanisms for the association between fall birth and food allergy. *Allergy* 2012;67:775-82.
7. Mansbach JM, Ginde AA, Camargo CA Jr. Serum 25-hydroxyvitamin D levels among US children aged 1 to 11 years: do children need more vitamin D? *Pediatrics* 2009;124:1404-10.
8. Mullins RJ, Clark S, Katelaris C, Smith V, Solley G, Camargo CA Jr. Season of birth and childhood food allergy in Australia. *Pediatr Allergy Immunol* 2011;22:583-9.
9. Vassallo MF, Banerji A, Rudders SA, Clark S, Camargo CA Jr. Season of birth and food-induced anaphylaxis in Boston. *Allergy* 2010;65:1492-3.

<http://dx.doi.org/10.1016/j.jaci.2014.05.002>

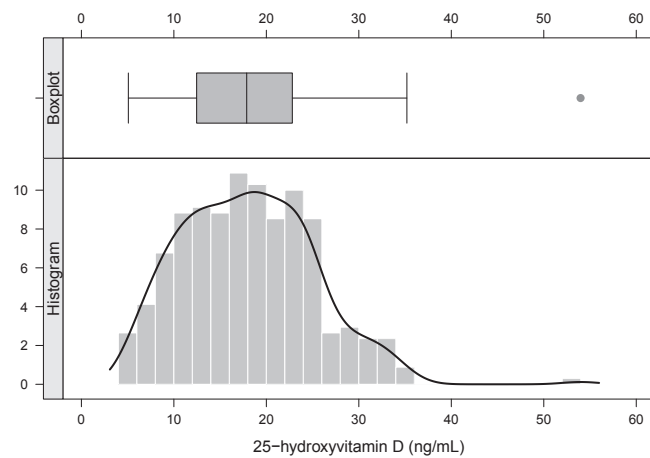


**FIG E1.** Distribution of 25-hydroxyvitamin D (ng/mL) among black participants ( $n = 340$ ). In the box plot, *boxes* represent the IQR, which contains data between the 25th and 75th percentiles. *Whiskers* extend to the 1.5 IQR beyond each box. *Circles* represent extreme observations. The median is represented by a vertical line within the box. In the histogram, the superimposed *solid line* over the histogram corresponds to the Gaussian theoretical curve for the distribution. *IQR*, Interquartile range.

**TABLE E1.** Association between specific IgE and total 25-hydroxyvitamin D for black participants

| Allergen                               | Category of specific IgE (kU/L) | All (n = 340)  | 25-Hydroxyvitamin D (ng/mL) |                 | P value |
|----------------------------------------|---------------------------------|----------------|-----------------------------|-----------------|---------|
|                                        |                                 |                | 5-20 (n = 209)              | 20-54 (n = 131) |         |
| Egg (kU/L)                             | Negative 0.34                   | 290 (85.3)     | 172 (82.3)                  | 118 (90.1)      | .07     |
|                                        | Positive 0.35-32.3              | 50 (14.7)      | 37 (17.7)                   | 13 (9.92)       |         |
| Milk (kU/L)                            | Negative 0.34                   | 269 (79.1)     | 162 (77.5)                  | 107 (81.7)      | .43     |
|                                        | Positive 0.35-99.3              | 71 (20.9)      | 47 (22.5)                   | 24 (18.3)       |         |
| Cod (kU/L)                             | Negative 0.34                   | 314 (92.4)     | 192 (91.9)                  | 122 (93.1)      | .83     |
|                                        | Positive 0.35-94.8              | 26 (7.65)      | 17 (8.13)                   | 9 (6.87)        |         |
| Wheat (kU/L)                           | Negative 0.34                   | 260 (76.5)     | 161 (77.0)                  | 99 (75.6)       | .86     |
|                                        | Positive 0.35-81.3              | 80 (23.5)      | 48 (23.0)                   | 32 (24.4)       |         |
| Peanut (kU/L)                          | Negative 0.34                   | 282 (83.2)     | 178 (85.6)                  | 104 (79.4)      | .18     |
|                                        | Positive 0.35-75.3              | 57 (16.8)      | 30 (14.4)                   | 27 (20.6)       |         |
| Soy (kU/L)                             | Negative 0.34                   | 281 (82.6)     | 176 (84.2)                  | 105 (80.2)      | .42     |
|                                        | Positive 0.35-48.6              | 59 (17.4)      | 33 (15.8)                   | 26 (19.8)       |         |
| Shrimp (kU/L)                          | Negative 0.34                   | 242 (71.2)     | 145 (69.4)                  | 97 (74.0)       | .42     |
|                                        | Positive 0.35-646               | 98 (28.8)      | 64 (30.6)                   | 34 (26.0)       |         |
| <i>Dermatophagoides farinae</i> (kU/L) | Negative 0.34                   | 235 (69.1)     | 147 (70.3)                  | 88 (67.2)       | .62     |
|                                        | Positive 0.35-100               | 105 (30.9)     | 62 (29.7)                   | 43 (32.8)       |         |
| Cockroach (kU/L)                       | Negative 0.34                   | 205 (60.3)     | 126 (60.3)                  | 79 (60.3)       | .99     |
|                                        | Positive 0.35-100               | 135 (39.7)     | 83 (39.7)                   | 52 (39.7)       |         |
| Alternaria (kU/L)                      | Negative 0.34                   | 207 (60.9)     | 129 (61.7)                  | 78 (59.5)       | .77     |
|                                        | Positive 0.35-100               | 133 (39.1)     | 80 (38.3)                   | 53 (40.5)       |         |
| Total IgE (kU/L)                       |                                 | 196 (71.3-522) | 197 (73.2-521)              | 195 (69.7-514)  | .84     |

Values are n (%) or medians with (interquartile ranges).