in food sensitization rates were first observed at age 3 years, these differences between the 2 folate groups were not statistically significant until age 6 years. Because of the modest sample size, we were unable to determine whether the risk of food sensitization was also borne out as an increased risk in likely food allergy.

The mechanisms underlying our observations are unclear. Although folate has a myriad of biologic effects, one current hypothesis posits that it may promote DNA methylation since it serves as a methyl donor, thereby suppressing the expression of key immune regulatory genes.[1,8] Although these findings point to the potential for folate to act via an epigenetic mechanism in early childhood, folate has many roles in cellular function so that it may act on the pathogenesis of allergic sensitization by other mechanisms.

Other potential confounding factors may include breast-feeding, consumption of high-folate-containing (or folate-fortified) foods. In this study, we found no significant difference between breast-feeding in both clusters (data not shown). Although we cannot ascertain exactly what role diet may have contributed to variability in our findings, in this study dietary folic acid intake would not be considered a true confounder as it is present in the causal pathway; since dietary intake is the major driver of plasma folate levels, our use of plasma folate levels already captures the dietary intake of folic acid. However, it is possible that plasma folate levels are simply a marker in general of a healthy diet and that some other component of a healthy diet—such as another micronutrient—could be the true driver of allergic sensitization risk rather than folate. The observational study design does not allow for the evaluation of this question, and so this limitation could not be controlled for in a natural history study such as Childhood Origins of Asthma.

In summary, we found in a high-risk birth cohort that higher folate levels in early childhood were significantly associated with the increased incidence of both food and aeroallergen sensitization, suggesting that folate may confer the risk of allergy not only *in utero* but also in the first few years of life. These findings suggest that modification of folate intake in early childhood could reduce the risk of allergic sensitization and support the conduct of larger prospective studies to determine whether these findings are reproducible and whether folate affects the risk of allergic disease as well as the risk of allergic sensitization.

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This study was funded by National Institutes of Health grants M01 RR03186, R01 HL61879, 1UL1RR025011, and P01 HL70831 5P50ES015903 P01 ES018176-5R01AI070630.

Disclosure of potential conflict of interest: R. F. Lemanske, Jr has received research support from the National Institutes of Health (NIH), National Heart, Lung, and Blood Institute, and Pharmaxis; has received consultancy fees from Merck, Sepracor, SA Boney and Associates, GlaxoSmithKline, American Institute of Research, Genentech, Double Helix Development, and Boehringer Ingelheim; is employed by the University of Wisconsin School of Medicine and Public Health; has received lecture fees from the Michigan Public Health Institute, Allegheny General Hospital, the American Academy of Pediatrics, West Allegheny Health Systems, California Chapter 4 AAP, the Colorado Allergy Society, the Pennsylvania Allergy and Asthma Association, Harvard Pilgrim Health, the California Society of Allergy, NYC Allergy Society, the World Allergy Organization, and the American College of Chest Physicians; has received payment for manuscript preparation from the AAAAI; and receives royalties from Elsevier and UpToDate. D. J. Jackson has received research support from the NIH, Pharmaxis, and AAAAI/GlaxoSmithKline and has received consultancy fees from Gilead. M. D. Evans has received research support from the NIH. R. A. Wood has received consultancy fees from the Asthma and Allergy Foundation of America; is employed by Johns Hopkins University; has provided expert testimony for the NIH; and receives royalties from UpToDate. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Hollingsworth JW, Maruoka S, Boon K, Garantziotis S, Li Z, Tomfohr J, et al. In utero supplementation with methyl donors enhances allergic airway disease in mice. J Clin Invest 2008;118:3462-9.
2. Haberg SE, London SD, Stigum H, Nafstad P, Nystad W. Folic acid supplements in pregnancy and early childhood respiratory health. Arch Dis Child 2009;94:180-4.
3. Haberg SE, London SJ, Nafstad P, Nilsen RM, Ueland PM, Vollset SE, et al. Maternal folate levels in pregnancy and asthma in children at age 3 years. J Allergy Clin Immunol 2011;127:262-4, 264.e1.
4. Whitrow MJ, Moore VM, Rumbold AR, Davies MJ. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. Am J Epidemiol 2009;170:1486-93.
5. Magdelijns FJ, Mommers M, Penders J, Smits L, Thijs C. Folic acid use in pregnancy and the development of atopy, asthma, and lung function in childhood. Pediatrics 2011;128:e135-44.
6. Bekkers MB, Elstgeest LE, Scholtens S, Haveman A, de Jongste JC, Kerkhof M, et al. Maternal use of folic acid supplements during pregnancy and childhood respiratory health and atopy: the PIAMA birth cohort study. Eur Respir J 2012;39:1468-74.
7. Matsui EC, Matsui W. Higher serum folate levels are associated with a lower risk of atopy and wheeze. J Allergy Clin Immunol 2009;123:1253-9.e2.
8. Nadeau K, McDonald-Hyman C, Noth EM, Pratt B, Hammond SK, Balmes J, et al. Ambient air pollution impairs regulatory T-cell function in asthma. J Allergy Clin Immunol 2010;126:845-852.e10.

Available online October 4, 2012.
http://dx.doi.org/10.1016/j.jaci.2012.08.015

Anaphylaxis caused by hidden soybean allergens in pillows

To the Editor:

Pillow stuffing can contain polyester, feathers, down, or, more recently, soy-based materials. Component-resolved diagnosis and microarray technology might be useful in patients with food-sensitized allergies or anaphylaxis caused by hidden allergens.

We report 4 patients with repeated anaphylaxis, which was defined as a decrease in blood pressure and possibly life-threatening adverse reactions[1] during sleep at home but not in other places. Patient 1 was a 64-year-old woman with previous nocturnal rhinitis who began to experience anaphylaxis during sleep. Patient 2 was a 58-year-old man with progressive rhinitis, asthma, and anaphylaxis after changing his bedroom furniture and bed linen. Patient 3 was a 64-year-old woman with previous sensitization to *Anisakis simplex* and nocturnal pharyngeal angioedema unrelated to eating fish or other sources of *A simplex* who experienced severe anaphylaxis during sleep. Patient 4 was a 69-year-old woman with nocturnal anaphylaxis for 1 year before diagnosis.

All patients had food-related rhinitis and asthma, although the sources were not clear.

Patient 4 also had severe anaphylaxis after eating soy sauce in a Japanese restaurant, which led to our initial suspicion. All patients had negative skin prick test (SPT) responses and IgE determination (ImmunoCAP Assay; Phadia, Uppsala, Sweden) to conventional aeroallergens and foods, including soybean.

APPENDIX

A wheezing respiratory illness during the first 3 years of life was defined as meeting 1 or more of the following criteria: (1) physician-diagnosed wheezing at an office visit; (2) an illness for which the child was prescribed short- or long-acting beta-agonists and/or controller medications; or (3) an illness given the following specific diagnoses: bronchiolitis, wheezing illness, reactive airway disease, asthma, or asthma exacerbation. Children were diagnosed as having asthma at age 6 years if they fulfilled 1 or more of the following criteria: physician-diagnosed asthma, frequent albuterol use for coughing or wheezing episodes prescribed by physician more than 2 times per week or more than 2 nights per month, use of a prescribed daily controller medication, an implemented step-up plan with albuterol or inhaled corticosteroids during illness as prescribed by a physician, or used prescribed oral prednisone for an asthma exacerbation. Allergic sensitization was determined by fluorenzyme immunoassay at age 6 years. Any single result of 0.35 kU/L or more was considered as positive. For fluorenzyme immunoassay testing, we collected blood, isolated plasma, utilized the UniCap system to measure IgE levels, and evaluated the following perennial and seasonal allergens—dust mite, cat, dog, birch, timothy grass, alternaria, ragweed, peanut, and egg.

Sensitization was defined as 1 or more positive (>0.34) specific IgE results at the annual blood draw. Foods included milk/egg/peanut for years 1 to 3 and egg/peanut for years 5+. Perennial allergens included dog, cat, *Alternaria alternata*, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farinae*. Cockroach was added to the panel of allergens starting at age 5 years. Seasonal allergens were tested starting at age 5 years and included ragweed, timothy grass, and silver birch.[E1]

Plasma folate levels were available in a total of 138 children at age 2, 4, 6, and 8 years. These levels were measured by the Johns Hopkins Hospital Clinical Laboratory.

There were also no differences in sample storage time between the 2 clusters ($P = .90$, .78, .88, and .70 for years 2, 4, 6, and 8, respectively). Biosample quality, analyses, and batch type were also similar. Further information regarding the model-based clustering methods can be found in Fraley et al.[E2,E3]

REFERENCES

E1. Lemanske RF Jr. The Childhood Origins of Asthma (COAST) study. Pediatr Allergy Immunol 2002;13:38-43.

E2. Fraley C, Raftery AE. MCLUST Version 3 for R: Normal Mixture Modeling and Model-based Clustering, Technical Report No. 504, Department of Statistics, University of Washington, September 2006 (revised December 2009).

E3. Fraley C, Raftery AE. Model-based clustering, discriminant analysis, and density estimation. J Am Stat Assoc 2002;97:611-31.

TABLE E1. Comparison of included and excluded subjects

	Percent not included (n = 147)	Percent included (n = 138)	*P* value
Male gender	55	58	.63
White	85	88	.40
Maternal asthma	40	43	.61
Paternal asthma	33	28	.40
Maternal allergy	80	85	.27
Paternal allergy	80	79	.80
Income <$20,000	94	96	.54
Exclusive breast-feeding first 6 mo	28	36	.13
Asthma year 6	26	30	.39
Aeroallergen sensitization year 3	32	24	.18

Total n = 285 subjects who were in the study through the first year of life.