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Relationships between folate and inflammatory features of asthma

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To the Editor

Recent studies suggest that folate may influence the risk of developing atopy and lower respiratory tract disease in children[1] and adults,[2–4] but there have been no studies, to our knowledge, that examine the relationship between folate status and allergic inflammation and asthma control among individuals with established disease. Because population-based data have shown an inverse association between serum folate levels and atopy,[2] wheeze,[2,3] and asthma,[3] it is plausible that serum folate levels may also be inversely associated with these outcomes among individuals with established asthma. In addition, because blacks have lower serum folate levels,[5] lower dietary folate intake,[6] and greater asthma morbidity than do whites,[7] folate status may be especially relevant in this high-risk population. We, therefore, hypothesized that higher serum folate levels would be associated with less atopy, pulmonary inflammation, and asthma morbidity. We tested this hypothesis in a prospective cohort study of predominantly black, urban children and adolescents with asthma.

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One hundred fifty children between the ages of 5 and 17 years with persistent asthma were followed prospectively for 1 year. Serum folate and total IgE levels were measured at baseline. Asthma-related outcomes assessed every 3 months included fractional exhaled nitric oxide (Feno), spirometry, and symptoms and health care encounter data collected by questionnaire. Population characteristics can be found in this article's Online Repository at www.jacionline.org (see Tables E1 and E2).

Nonlinear relationships were observed between folate level and Feno, total IgE level, and the number of positive skin test results (Table I; see Table E3 in this article's Online Repository at www.jacionline.org; Fig 1). Overall, these measures of airway inflammation and atopy were lowest among participants with the lowest folate levels and then peaked among participants with low to moderate folate levels. For example, Feno, total IgE, and the number of positive skin test results were similar in the first folate quartile to those in the third and fourth folate quartiles (Table I and Fig 1, *A*).

Although symptom outcomes tended to decrease in frequency across folate quintiles, these findings were not statistically significant for many of the symptom outcomes (see Table E5 in this article's Online Repository at www.jacionline.org; Fig 1, *B*). There were also no statistically significant differences in lung function (FEV_1/forced vital capacity %: 81.4 ± 9.0, 78.9 ± 8.7, 80.8 ± 9.8, and 81.2 ± 7.8, respectively), hospitalizations (2.8%, 5.6%, 2.8%, and 2.8%, respectively), or acute visits during the 1-year follow-up period (55%, 43%, 63%, 61%, respectively) across folate quartiles.

In a population of urban, predominantly black children and adolescents with asthma, we found "bell-shaped" relationships between serum folate and Feno and total IgE levels. Interestingly, relationships between folate levels and serum levels of T_H2 cytokines were similar to those observed with Feno and total IgE (see Table E4 in this article's Online Repository at www.jacionline.org). The reasons why low folate levels are associated with less allergic inflammation are unclear, but there are biologically plausible mechanisms that could explain this observation. Because folate is critical for optimal lymphocyte function,[8] it is possible that a certain level of serum folate is required to initiate and sustain a T_H2 inflammatory response, so that those with the lowest folate levels are protected from allergic inflammation.

Folate may also influence allergic inflammatory markers through epigenetic mechanisms.[9] In this context, individuals with the lowest folate levels may be protected from developing an allergic phenotype as regulatory T-cell function will be optimal, but with higher folate levels and concomitant methylation of immunoregulatory genes, regulatory T-cell function may be compromised, thereby increasing the risk of an allergic phenotype. Findings from some,[1] but not all,[10] birth cohort studies support this working model as in utero exposure to folic acid has been associated with a greater risk of allergic respiratory disease in offspring.

However, in contrast to studies showing a linear dose-response relationship between folate levels and allergic disease outcomes, our study suggests that the initial increase in the risk of allergic inflammation that occurs at low to moderate folate levels is attenuated at higher levels of folate, and so folate may confer some protection at higher levels. The relationships

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observed across higher levels of folate and allergic inflammatory outcomes are consistent with findings from the 2005–2006 National Health and Nutrition Examination Surveys[2] as well as a study of atopic Egyptian adults.[4] The mechanisms by which folate may afford protection against inflammation remain unclear; however, the cardiovascular literature suggests that folate reduces oxidative stress by lowering homocysteine levels,[11] and so it is possible that higher folate levels attenuate the allergic inflammatory response by reducing oxidative stress.[12]

Folate's effects—promotion of gene methylation, reduction of oxidative stress by lowering homocysteine levels, or others—may be most biologically relevant under different conditions or in different contexts. For example, folate's effects on allergic inflammatory responses may be dose-dependent. Perhaps folate's effects on regulatory immune gene methylation are more important at low to moderate folate levels while its effects on homocysteine levels and oxidative stress are more important at moderate to high levels. In addition, findings from this study and others[2–4] suggest that the effects of folate differ by the timing of exposure as in utero exposure appears to confer risk while exposure in later childhood and adulthood may be protective.

Low-income minority populations are at the greatest risk for folate deficiency, and so our findings lend insight into the potential public health implications of lower folate levels on minority populations with asthma. However, whether our findings are applicable to other populations of asthmatic patients remains unclear. We also do not know how diet may have influenced serum folate levels in this population. Our findings are derived from a modestly sized study population, and although the contrast in relationships between folate levels and inflammatory outcomes versus folate levels and symptoms outcomes is clear, the relationships between folate levels and symptoms in particular were marginal, and so these findings must be replicated in other populations. Because we did not have data or samples available to examine potential mechanisms, future studies should incorporate assessment of homocysteine levels, oxidative stress, methylation of immunoregulatory genes, and folate metabolism-related gene polymorphisms.

Serum folate levels were associated with markers of allergic inflammation and, in larger study populations, may prove to be associated with asthma symptoms as well. Future studies should examine relationships between folate status and asthma control and severity as well as elucidate mechanisms of action. Should these findings be replicated, clinical trials involving folic acid supplementation in asthmatic patients with low folate levels would be indicated to assess the clinical efficacy of folic acid supplementation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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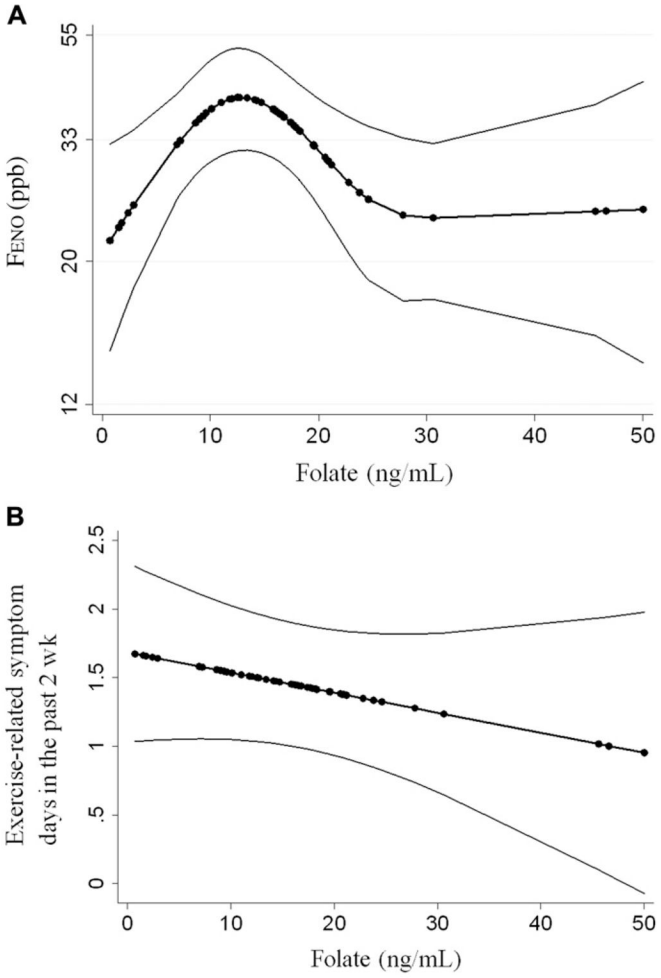

FIG 1.

Predicted Feno **(A)** and exercise-related days of symptoms **(B)** are depicted on the *y-axes*, respectively. Serum folate levels are depicted on the *x-axes*. 95% CIs are indicated by *shaded areas*. Figures represent relationships for males with caregivers with a high school degree or less.

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TABLE I

Relationships between folate and allergic and symptom outcomes*

	Allergic inflammatory outcomes, predicted mean (95% CI)		
Folate quartile	**Total IgE (kU/L)**	**Feno (ppb)**	**No. of positive SPTs**
Q1 (n = 36)	113.5 (68.2–189.0)	26.9 (21.1–34.3)	5.3 (4.1–6.5)
Q2 (n = 36)	295.4 (174.8–499.2)†	36.6 (28.5–47.1)‡	7.0 (5.8–8.2)§
Q3 (n = 36)	149.7 (90.4–247.9)	33.5 (26.4–42.4)	5.7 (4.5–6.9)
Q4 (n = 36)	124.3 (74.2–208.3)	26.7 (20.8–34.2)	6.4 (5.2–7.7)

SPT, Skin prick test.

*Adjusted for age, sex, and educational attainment; symptoms expressed as days/2 weeks. Because Feno was measured at repeated clinic visits during a 1-year follow-up period, generalized estimating equations were used to account for the repeated measurements.

†$P < \leq .01$ vs Q1.

‡$P = .08$ vs Q2.

§$P = .05$ vs Q1.