applicable to adult-onset asthma, as these differ in phenotypes and lifestyle and environmental exposures that are related to the risk of asthma.[8] For example, it has been reported that early-onset (before the age of 12 years) and late-onset (after the age of 12 years) severe asthma differ by presence of allergies, eosinophilia, and other inflammatory processes.[9]

Our systematic review revealed only 1 previous study on heredity and adult-onset asthma. Lee et al[1] studied 24,784 Taiwanese adults, of which 286 had new-onset asthma (symptoms within the preceding 5 years) based on questionnaire. The risk of adult-onset asthma associated with paternal asthma in their study (adjusted OR, 2.63, 95% CI, 1.55-4.24) was similar to that found in our study (2.53, 95% CI, 1.62-3.89). They found maternal asthma to be a stronger risk factor with the effect estimate of 11.61 (95% CI, 8.07-16.42), which is higher than our effect estimate (1.94, 95% CI, 1.31-2.88). Several differences between the studies including the definition of asthma (symptom-based vs clinical lung function–based), categorization of parental asthma, and factors that were adjusted for in the analyses may explain the detected differences. In addition, the genetic composition of the Taiwanese and Finnish populations is expected to be quite different.

No previous study has addressed the role of other first-degree relatives in characterizing the risk of adult-onset asthma. The highest risk in our study was seen among those who had asthma present in several categories of first-degree family members (parents, siblings, and/or children), thus indicating that in such families the asthma susceptibility is strongly present.

In our study, the possibility of selection bias is small due to the high response rates. Thorough recruitment of patients and controls, the high quality of asthma diagnosis based on clinical and lung function investigations, and the utilization of the inclusive medical and medication reimbursement records available in Finland ensure that we were able to identify and include a high proportion of new cases of adult-onset asthma and that all the asthma cases in our study were genuinely new and adult onset. The statistical analyses were adjusted for several environmental factors and other potential confounders. Our study is so far the largest one (477 cases and 842 controls) investigating the influence of parental asthma on adult-onset asthma and the only one using clinically defined asthma and considering the role of siblings' and children's asthma in this setting.

Our results strengthen the evidence that parental asthma is a strong determinant of adult-onset asthma and provide new evidence that the risk of adult-onset asthma is associated with the presence of asthma among siblings and the person's children. Our results also provide new evidence that the highest risk of adult-onset asthma is present among those with several categories of first-degree family members having asthma. From the clinical perspective, this means that asking the patient about the asthma of his or her siblings and children, in addition to parents, provides useful information on the probability of asthma.

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Relationships between folate and inflammatory features of asthma

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.

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

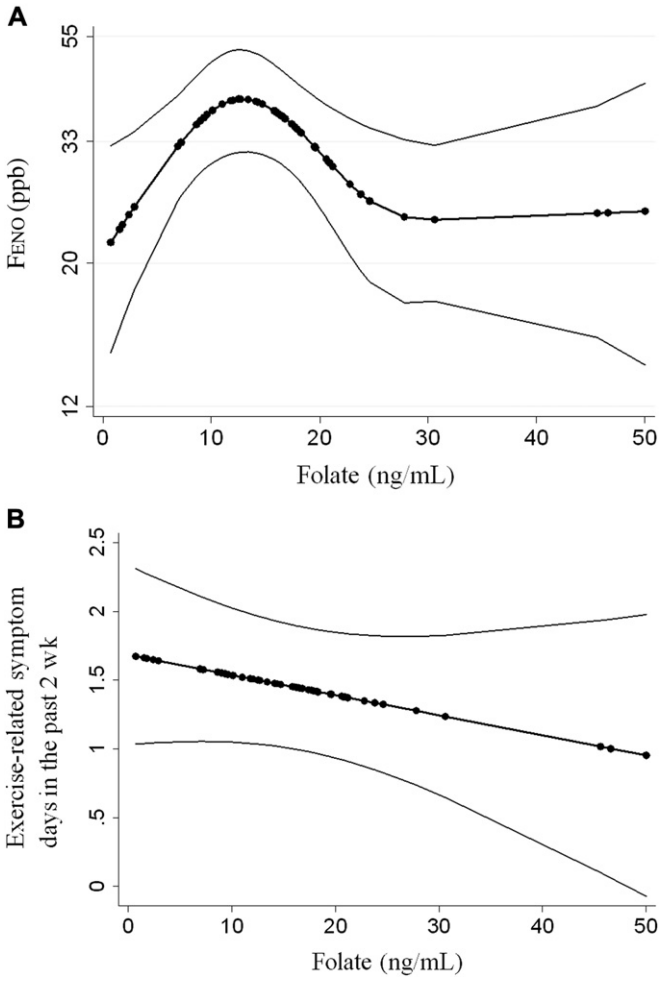

FIG 1. Predicted FENO **(A)** and exercise-related days of symptoms **(B)** are depicted on the *y-axes*, respectively. Serum folate levels are depicted on the *x-axes*. 95% CIs are indicated by *shaded areas*. Figures represent relationships for males with caregivers with a high school degree or less.

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

TABLE I. Relationships between folate and allergic and symptom outcomes*

Folate quartile	Allergic inflammatory outcomes, predicted mean (95% CI)		
	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.

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 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.