Editorial
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Gene–Environment Interactions Should be Considered in Future Studies to Understand the Association Between Prenatal Folate Supplementation and Asthma Development

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Because the increasing prevalence of allergies within the last 20 to 30 years cannot be explained by genetic changes, most allergists have tried to find answers in environmental and lifestyle changes, as reflected by the hygiene hypothesis. Environmental exposures during pregnancy and early infancy during critical periods of immune development can have profound effects on allergy development. Food intake is a well-known environmental factor that influences allergy development and three specific nutrients—vitamin D, omega 3 polyunsaturated fatty acids and folate—have recently attracted attention.[1]

The methyl donor folate is a well-known nutrient supplement given during early pregnancy to prevent neutral tube defects in the developing fetus. A recent murine study has reported however that a maternal diet supplemented with folate increased the prevalence of allergic airway disease in offspring.[2] Of the 82 genes that were found in that mouse study to be differentially methylated after *in utero* supplementation with a methyl-rich diet, runt-related transcription factor 3, which regulates allergic airway disease, was shown to be excessively methylated. These results suggest that prenatal dietary factors can increase the risk of allergy development in offspring through epigenetic mechanisms. Other nutrients, including methionine, vitamin B12, choline, and betaine, are also known to induce methylation changes in genes.[3]

In contrast to the results in a mouse model, a number of human studies have tried to identify an association between an increased intake of folate during pregnancy and the risk of asthma in childhood but have not produced any solid evidence to support such an association. A previous meta-analysis of the effect of prenatal folate on the risk of postnatal asthma also found no evidence of this association, although only 14 articles were assessed in that analysis.[4] Likewise, in this current issue of *Allergy, Asthma & Immunology Research*, Wang *et al.*[5] did not find any association between prenatal folate and a risk of asthma, other than a risk of wheeze in early childhood. A previous large cohort study by Håberg *et al.*[6] reported that maternal folic acid supplementation during early pregnancy increased the risk of wheeze at 6-18 months postnatally. The weight of that study was calculated at 92% in the present meta-analysis of the relationship between maternal folic acid supplementation during pregnancy and the risk of wheeze in childhood, whereas the weights of the other 2 studies that found no relationship between these 2 factors were just 1.83% and 6.18%, respectively. However, 59.2% of children who developed a wheeze in the first 3 years after birth did not show this condition at the age of 6 years.[7] Indeed, although wheeze is the main symptom of childhood asthma, it is not diagnostic for asthma. Moreover, in another earlier meta-analysis,[4] when the data of Håberg *et al.* were removed, the association between prenatal folate and the risk of childhood wheeze became non-significant.

We conclude from the reported evidence to date that gene–environmental interactions affect the development of asthma and should therefore be considered when investigating the association between prenatal folate and asthma development. The data in many epidemiologic studies have been inconsistent in this regard. A single nucleotide polymorphism (C677T) in the methylenetetrahydrofolate reductase gene has been associated with folate metabolism, resulting in different blood concentrations of folate in individuals with different genotypes.[8] The risk

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of asthma should be evaluated in offspring with differing genotypes to determine how the genotype interacts with prenatal folate intake. Given that folate is a well-known methyl donor, epigenetic changes should also be evaluated in a future study. Prenatal folate intake may alter the methylation of genes involved in the development of the immune system, increasing the risk of asthma in humans, as found in mouse studies.

The limitations of previous epidemiologic studies should also be considered in any future study. Because most pregnant women take folate to prevent neural tube defects in their offspring, a randomized control trial of the relationship between prenatal folate intake and asthma development in children could not be conducted within ethical guidelines. Indeed, there has been no previous randomized control trial in this area, which is an obstacle to any meta-analysis conclusion supported by strong evidence. Previous studies of the association between prenatal folate and asthma development have varied in terms of the type, time, dose, duration, and method for measuring folate exposure, the definition of outcomes, and the child's age at the evaluation of outcomes. Given these factors, a detailed and well-considered study design is needed.

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