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Folic Acid in Pregnancy and Childhood Asthma: A US Cohort

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Abstract

Prenatal folic acid exposure has been linked to higher risk of childhood asthma in countries that do not fortify the food supply with folic acid. This study seeks to examine this association in the United States, where the food supply is generally fortified with folic acid. Participants were 1279 mother-child pairs from Project Viva, an ongoing prospective birth cohort, with folic acid intake in pregnancy assessed through validated food frequency questionnaires. The primary outcome was physician-diagnosed asthma at mid-childhood. In an unadjusted logistic regression model, higher folic acid intake was associated with lower odds of asthma in mid-childhood (odds ratio [OR] 0.48; 95% CI 0.31–0.76). However, in the adjusted analysis this association was attenuated (adjusted OR [aOR] 0.80; 95% CI 0.49–1.33). Our results suggest that in the United States, where there is generalized folic acid fortification of food, maternal folic acid intake during pregnancy is not associated with asthma development in offspring.

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Authors' Note

The views expressed in this article do not necessarily represent the views of the US Government, the Department of Health and Human Services, or the National Institutes of Health.

Author Contributions

MKT, AAL made a substantial contribution to the concept and design, analysis and interpretation of data, drafted the article, revised it critically for important intellectual content, and approved the version to be published. SS, SLRS, CAC, STW, DLD, DRG: made a substantial contribution to the concept and design, analysis and interpretation of data, revised article critically for important intellectual content, and approved the version to be published. EO, MWG made a substantial contribution to the acquisition of data, revised article critically for important intellectual content, and approved the version to be published.

Declaration of Conflicting Interests

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Keywords

folic acid; maternal diet; pediatric; asthma; airway inflammation

Introduction

Nearly 7 million children in the United States are currently living with asthma and this condition remains the most common chronic disease of childhood with a prevalence that continues to increase.^{1–3}

In recent years, there has been concern that folic acid supplementation in pregnant women may be contributing to the increasing prevalence of childhood asthma.^{4,5} Prior longitudinal studies have found an increased asthma risk in children of mothers with higher folic acid exposure in pregnancy.^{4,6,7} However, these studies were conducted in countries that do not mandate the fortification of food products with folic acid and accordingly mean folic acid intake in these populations is much lower.

In 1992, the United States Public Health Service recommended that women of childbearing age should consume at least 400 µg of folic acid per day for the prevention of neural tube defects. In 1996, to support this recommendation, the Food and Drug Administration mandated folic acid fortification of enriched cereal grain products (140 µg/100 g) and permitted folic acid fortification in many other foods.⁸

There has been one prior longitudinal study in the United States examining the relationship between prenatal folic acid intake and the development of childhood asthma as a primary outcome. This study demonstrated no significant association. However, this study only assessed the exposure of folic acid through supplements and did not include dietary folic acid intake from nutrients, which is important in the United States, where there is mandated folic acid fortification of many foods.⁹ Hence, it is important to know whether mandated food fortification practices in the United States may be contributing to the asthma epidemic.

Here, we examine the extent to which maternal folic acid intake (from both foods and supplements) during pregnancy is associated with asthma risk in offspring in the United States.

Methods

Study subjects were pregnant women and their children enrolled in Project Viva, an ongoing prospective cohort study that was designed to investigate the effects of gestational diet and other factors on pregnancy outcomes and health of offspring. Recruitment occurred at 8 obstetric offices of Atrius Harvard Vanguard Medical Associates, a multispecialty group practice in eastern Massachusetts. Eligibility criteria included fluency in English, gestational age less than 22 weeks at the first prenatal visit, and singleton pregnancy. The detailed design of this cohort study, including recruitment and retention procedures, has been described previously.^{10–14}

Of the 2128 live born infants in the cohort, we excluded 849 with no mid-childhood follow-up data. Thus, our sample size for analysis was 1279 mother-child pairs. For our secondary spirometry outcome, we included 1116 of the 1279 who attended the mid-childhood visit in-person.

There were differences between participants who were included in the study and those who were excluded due to loss to follow-up. In comparison with the 1279 participants, those who were lost to follow-up were more likely to be non-white (39% vs 35%), have lower educational attainment (58% were college graduates vs 69%), lower family income (55% with annual household income >\$70 000 vs 60%), higher rates of maternal asthma (15% vs 13%), and less likely to breastfeed at least 6 months (41% vs 55%).

The institutional review boards of Harvard Pilgrim Health Care, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center approved the study protocols, and all mothers provided written informed consent at enrollment and at follow-up.

Measurements

Folic Acid Intake—At each of the first and second-trimester in-person study visits, to assess the intake of folate from food, we administered a 130-item semiquantitative food frequency questionnaire (FFQ) modified from the well-validated instrument used in the Nurses' Health Study and further calibrated for use in pregnant women. For the FFQ used at the first-trimester visit (mean gestational age at visit = 11.7 weeks), the time referent was “during this pregnancy,” that is, from the date of the last menstrual period to the current dietary assessment. We also conducted a 33-item detailed interview about use (frequency, brand/type, dosage, and timing) of nutritional supplements in early pregnancy. We calculated total first-trimester maternal intake of the nutrients examined by summing food and supplement contributions. For the FFQ used at the second-trimester visit (mean gestational age at visit = 29.1 weeks), the time referent was “during the past 3 months.” The second-trimester FFQ itself also included questions about use of nutritional supplements, which we used to calculate total second-trimester intake. We adjusted micronutrient intake for total energy intake using the residuals method; details of our nutritional assessment have been previously reported.¹⁵ For this study, the term “folic acid” will be used to refer to the intake of this nutrient from both ingested foods and dietary supplements.

Outcome Assessment—Our primary study outcome was a diagnosis of current asthma in offspring at the mid-childhood visit. We assessed asthma with responses to questions based on the validated instruments from the International Study of Asthma and Allergies in Childhood (ISAAC).¹⁶ At the mid-childhood visit, we defined current asthma as present, if the mother answered “yes” to “Has your child ever been diagnosed with asthma by a physician?” plus the use of asthma medication or wheezing in the past 12 months. The reference group was children who had never been diagnosed with asthma. We excluded from analysis 60 participants (33 boys and 27 girls) who had ever been diagnosed with asthma, but who did not have current asthma. Our secondary study outcome was post-bronchodilator forced expiratory volume in 1 second (post-FEV₁) from spirometry assessed at mid-childhood visit. Pre- and post-bronchodilator spirometry measurements were performed

according to the American Thoracic Society standards.¹⁷ However, we chose to analyze post-FEV₁, because it is known to be the measure of “best lung function.”¹⁸

Covariate Assessment—At enrollment, mothers reported their age, history of asthma, educational attainment, and household income. We obtained child’s sex and date of birth from hospital records and determined gestational age at delivery. At the infant visit, mother’s reported the child’s race/ethnicity and breastfeeding duration. At the mid-childhood in-person visit, child age was recorded and we measured child height using a stadiometer.

Statistical Analysis

We performed unadjusted and multivariable adjusted logistic regression analyses to determine the association of maternal folic acid intake during pregnancy with the current asthma at mid-childhood (yes/no). We performed linear regression for the continuous spirometry outcome. FEV₁ was normally distributed.

In constructing our multivariable regression models, we included covariates that were possible confounders of the folic acid–asthma relationship, which we defined as a covariate that was significantly related to asthma ($P < .05$) in a model with folic acid and asthma alone *and* changed the effect estimate of folic acid (fourth quartile compared with first quartile) by $>10\%$. Based on these criteria, we included the following covariates in our regression models: maternal history of asthma, annual household income ($>\$70\,000$ or not), child’s race/ethnicity and gestational age (<34 weeks or not). We additionally adjusted for the following three variables, based on a priori decisions: maternal age, child’s age at the mid-childhood visit, and breastfeeding duration (>6 months or not). We included child age because of the range of ages between 7 and 10 years at the mid-childhood study visit. Maternal age was included for consistency with prior analyses.^{4,11} Breastfeeding duration was included to adjust for postnatal exposure to folic acid via breast milk, since prepared formula contains supplemented folic acid. This model was applied to all outcomes for consistency. Additionally, child’s height at the time of spirometry was included in the model for the spirometry outcome. We investigated for effect modification by child’s sex by including interaction P values in the multivariable adjusted models. We performed sex-stratified analyses using identical multivariable regression models separately among boys and girls. Quartiles of folic acid were included in the model as a categorical variable. All analyses were performed using SAS statistical software (version 9.3; SAS Institute Inc, Cary, NC).

To account for missing data, we performed multiple imputation for all 2128 mother-child pairs in Project Viva. We then limited the analysis to the 1279 included participants who completed any part of the mid-childhood assessment. For the secondary outcome of post-FEV₁, we limited the analysis to the 1116 participants who attended the mid-childhood assessment in person. Our primary analysis was based on imputed data. We used SAS (Proc MI) to impute 50 values for each missing observation and combined multivariable modeling estimates using Proc MI ANALYZE in SAS version 9.3 (SAS Institute, Cary, NC).

Results

Study Population Characteristics

The analytic cohort consisted of 1279 maternal-child pairs who had available data at the mid-childhood follow-up visit. The mean age of mothers at the time of study enrollment was 32.2 years, 69% were college graduates, and 9.5% smoked during pregnancy. Mean child age was 7.9 years and 226 of the children (18.5%) had current asthma at the mid-childhood follow-up visit, including 20.9% of boys and 16.2% of girls (Table 1).

Population Characteristics Based on Folic Acid Intake

Most women, even in the lowest quartile of folic acid intake, ingested more than the recommended 400 µg/day (Table 1). Ninety-four percent of participants took some form of folic acid supplement.

There were significant differences in the maternal and child characteristics according to quartile of folic acid intake in the first trimester. Mothers with higher folic acid intake (fourth quartile vs first quartile of intake) were older, had higher educational attainment, higher family incomes; their children were more likely to be breastfeed and white ethnicity.

Maternal Folic Acid Intake and Asthma in Offspring at Mid-childhood

In our analysis of the total cohort with imputed data, higher maternal folic acid intake in the first trimester (fourth vs first quartile) was associated with a lower risk of current asthma in mid-childhood: (unadjusted odds ratio [OR] 0.48; 95% CI 0.31–0.76). This association was attenuated after adjusting for several covariates (adjusted OR [aOR] 0.80; 95% CI 0.49–1.33) (Table 2).

We found statistical evidence of effect modification by child sex in both the first and second trimester in adjusted models. In the first trimester adjusted model, interaction $P = .04$.

Among the boys, higher maternal folic acid intake in the first trimester was significantly associated with lower odds of asthma (unadjusted OR 0.48; 95% CI 0.26–0.88); however, this association was substantially attenuated and no longer significant in the adjusted analysis (aOR 0.62; 95% CI 0.32–1.19). There was no relationship between maternal folic acid intake and current asthma in mid-childhood among girls in our multivariable adjusted analysis, for the imputed analysis (aOR 1.16; 95% CI 0.53–2.55).

Maternal Folic Acid and FEV₁ in Offspring at Mid-Childhood

There were 1116 mother-child participants available for the post-FEV₁ analysis. The mean post-FEV₁ was 1515 mL. There was no association between maternal folic acid intake and post-FEV₁ in the total cohort of children. Among the boys only, higher intake of maternal folic acid was associated with higher levels of post-FEV₁ (best lung function) in our multivariable adjusted analyses; however, the association was not statistically significant, $\beta = 44$ mL (95% CI –28 to 115) for Q4 versus Q1 (Table 3). Among the girls, we did not observe an association between maternal intake of folic acid and post-FEV₁ at mid-childhood.

Discussion

In our large prospective cohort study of pregnant women in Massachusetts and their offspring at 7 to 10 years of age, we found that higher maternal folic acid intake was not associated with increased odds for the development of asthma in offspring. This is an important finding that suggests that folic acid fortification practices in the United States may not be contributing to increased asthma prevalence, as it relates to maternal intake of folic acid. Our results are consistent with the prior US longitudinal study of maternal folic acid intake and childhood asthma, which showed no association, but only assessed folic acid exposure from supplements.⁹ Together, these results should help assuage the concern that folic acid fortification of foods is contributing to the US asthma epidemic.

In male offspring, we found a suggestion that higher intake of maternal folic acid in the first trimester of pregnancy may be associated with somewhat lower odds of childhood asthma and a higher post-bronchodilator FEV₁. However, given the smaller sample size in the stratified analysis, confidence intervals were wide and included both null and potentially harmful effects; this association would need to be studied further in other populations. If supported, this finding suggests that there may be differences in the way that carbon methyl donor intake influences males and female offspring asthma risk.

The proposed mechanism by which folic acid may alter the development of asthma in children is through variable DNA methylation in utero. Folic acid is a nutritional carbon source essential for the donation of methyl groups to DNA. Thus, intake of carbon methyl donors may lead to changes in genome expression. It was a murine model that initially demonstrated a link between dietary carbon methyl donors in pregnancy and offspring allergic airway disease.¹⁹

This initial study that sparked interest in the relationship, showed that pregnant mice with higher carbon methyl donors in the diet gave birth to offspring with increased allergic airway disease.¹⁹ This study has since been retracted due to issues with the airway hyperresponsiveness data, though other data were not affected.²⁰ We do recognize that the data connecting carbon methyl donor intake to asthma phenotype is limited.

However, there are reports of maternal carbon methyl donor intake differentially affecting other health outcomes of offspring, based on the child's sex.^{21–23} In a sheep model, a low folic acid diet during pregnancy resulted in offspring with hypomethylated DNA and adverse health phenotypes including high blood pressure and insulin resistance, with a stronger association observed in males.²¹ In a murine model, in utero methyl donor intake influenced glucose homeostasis in male offspring only.²²

It is also important to consider the known sex-specific lung maturation differences in utero. The fetal lung is less developed in boys from 16 to 26 weeks, measured by mouth movements that reflect fetal breathing, a critical determinant of lung development. In the last 4 weeks of gestation, airway resistance is higher in males.²⁴ In the first decade of life, both recurrent wheeze and doctor-diagnosed asthma are more common among males.²⁵ Boys up to 10 years old appear to have smaller airways in relation to lung size as compared with girls of the same age, height, and weight.²⁴ The post-FEV₁ measure is one that reflects both the

airway size as well as lung size.¹⁸ These known sex-specific distinctions in gestational and childhood lung maturation are important to consider when evaluating the results of our study as the suggestion of possible sex differences could be explained somewhat by these factors. Considering the aforementioned data and a finding from the Project Viva cohort that higher prenatal intake of carbon methyl donors was associated with a decrease in global blood methylation in male offspring only,²³ we were interested in performing a sex-stratified analysis. We hypothesized that higher maternal intake of folic acid would be associated with higher risk of asthma development and that this association would be stronger in boys. Our results did not support this hypothesis but we may not have had sufficient power to detect differences by sex.

Study Strengths

This study has several strengths. First, this was a large, prospective study wherein we collected maternal dietary data in the first and second trimesters, based on a nutritional assessment tool validated in pregnancy. Also, we followed children longitudinally up to 7 to 10 years of age, when the diagnosis of childhood asthma is more accurate than at younger ages. We used a well-validated asthma assessment tool for children older than 6 years (the ISAAC instrument) as well as the objective outcome of spirometry at an age when children can reliably perform this breathing test.²⁶ Additionally, to our knowledge, we are the first to perform a sex-stratified analysis to investigate the relationship between maternal folic acid intake in pregnancy and childhood asthma. Given the multiple comparisons we performed in our analysis, our null results are particularly notable, as false positives are more likely with multiple comparisons.

Finally, and most important, our study examined not only prenatal intake of folic acid from supplements, but also from foods. This is essential because the United States fortifies food with folic acid. The other prior longitudinal study in the United States on folic acid in pregnancy and childhood asthma was limited in only looking at folic acid intake from supplements, with no assessment of intake from fortified foods.⁹

Study Limitations

Despite these strengths, there were study limitations, including the follow up rate of 60% at the 7-year old visit. A recent review showed that other prospective birth cohort studies on this topic had similar rates of loss to follow up after age 5 years.²⁷ However, as is often the case with longitudinal studies, our results may have been influenced by differential loss to follow-up. Subjects lost to follow-up had higher rates of maternal asthma, lower income, lower educational attainment, and higher rates of minority race. It is critical to note these differences, as they could introduce selection bias. To address the issue of missing data for covariates, we performed multiple imputation. There were not significant differences in the demographics of complete cases versus multiple imputation datasets and results from both analyses were similar. Also, our study cohort was relatively folic acid-replete with 94% of women taking a folic acid supplement and all women living in the United States, where fortification is ongoing. Thus, it is important to note that our results may only be relevant for a folic acid-replete population.

In summary, this longitudinal study in a US population, examined the relationship between folic acid intake (from both foods and supplements) during pregnancy and the development of asthma in offspring. Our data do not substantiate any association between prenatal folic acid intake and the development of childhood asthma in a country where folic acid fortification is ongoing. From our results, it appears that fortification practices in the United States are not likely contributing to increased asthma prevalence.

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Characteristics of 1279 Mothers and Children in the Project Viva Cohort With Information on Prenatal Folic Acid Intake and Asthma in Mid-childhood.

Table 1

Characteristic	Total (n = 1279)	First Trimester Folic Acid Quartile				Trend <i>P</i> Value
		Quartile 1 (n = 319)	Quartile 2 (n = 321)	Quartile 3 (n = 319)	Quartile 4 (n = 320)	
Maternal characteristics						
Age, years, mean (SD)	32.2 (5.2)	30.1 (6.3)	32.5 (5.1)	32.8 (4.4)	33.4 (4.1)	<.0001
College graduate, n (%)	885 (69.2)	143 (44.7)	225 (70.3)	248 (77.7)	268 (83.9)	<.0001
Annual household income >\$70 000, n (%)	771 (60.2)	128 (40.1)	183 (57.2)	219 (68.5)	241 (75.2)	<.0001
Maternal history of asthma, n (%)	161 (12.6)	55 (17.4)	38 (12.0)	29 (9.2)	38 (12.0)	0.04
Child characteristics						
Male, n (%)	645 (50.4)	165 (51.8)	167 (52.1)	157 (49.3)	155 (48.6)	0.35
Gestation 34 weeks, n (%)	1257 (98.3)	314 (98.5)	313 (97.7)	317 (99.1)	313 (97.8)	0.84
Race/ethnicity, n (%)						
Asian	43 (3.4)	15 (4.8)	8 (2.5)	11 (3.4)	9 (2.7)	
Black	202 (15.8)	99 (30.9)	57 (17.8)	21 (6.4)	26 (8.0)	
Hispanic	53 (4.2)	29 (9.1)	9 (2.8)	12 (3.7)	4 (1.1)	
White	831 (65.0)	126 (39.4)	219 (68.2)	243 (76.0)	244 (76.2)	
Other	150 (11.7)	51 (15.8)	28 (8.7)	34 (10.5)	38 (12.0)	
Breastfed 6 months, n (%)	700 (54.7)	129 (40.3)	163 (50.9)	189 (59.3)	218 (68.3)	<.0001
Age at mid-childhood visit, years, mean (SD)	7.9 (0.8)	8.1 (0.9)	7.9 (0.8)	7.8 (0.7)	7.9 (0.8)	0.0001
Maternal Folic Acid Intake						
	Mean	Quartile 1	Quartile 2	Quartile 3	Quartile 4	<i>P</i> Value
First trimester, µg/d	930	129–660	661–909	910–1175	1176–3497	<.0001
Second trimester, µg/d	1238	118–937	938–1357	1358–1502	1503–2601	<.0001

Table 2

Maternal Folic Acid Intake During Pregnancy and Asthma in Mid-childhood (n = 1279).^a

Folic acid Intake	Quartile ^b	Total (n = 1279)		Boys (n = 645)		Girls (n = 634)	
		Unadjusted	Adjusted ^c	Unadjusted	Adjusted ^c	Unadjusted	Adjusted ^c
First trimester	Q1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Q2	0.76 (0.49, 1.16)	1.05 (0.66, 1.67)	0.77 (0.44, 1.35)	0.87 (0.49, 1.58)	0.73 (0.38, 1.42)	1.39 (0.65, 2.97)
	Q3	0.58 (0.38, 0.89)	0.98 (0.61, 1.57)	0.61 (0.34, 1.09)	0.82 (0.44, 1.51)	0.55 (0.29, 1.05)	1.31 (0.61, 2.82)
	Q4	0.48 (0.31, 0.76)	0.80 (0.49, 1.33)	0.48 (0.26, 0.88)	0.62 (0.32, 1.19)	0.50 (0.26, 0.96)	1.16 (0.53, 2.55)
Second trimester	Q1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Q2	0.89 (0.56, 1.41)	1.02 (0.63, 1.65)	0.88 (0.49, 1.58)	0.96 (0.52, 1.77)	0.90 (0.45, 1.80)	1.04 (0.50, 2.17)
	Q3	0.74 (0.48, 1.14)	0.97 (0.61, 1.53)	0.75 (0.42, 1.34)	0.92 (0.50, 1.69)	0.72 (0.37, 1.40)	0.96 (0.46, 1.97)
	Q4	0.78 (0.49, 1.25)	0.95 (0.59, 1.54)	0.77 (0.41, 1.45)	0.87 (0.46, 1.66)	0.81 (0.40, 1.62)	1.08 (0.51, 2.29)

^aValues are presented as odds ratio (95% confidence interval).^bQuartiles of energy-adjusted folic acid, with the first quartile being the lowest and the fourth quartile being the highest (see Table 1 for details on distribution of folic acid intake).^cAdjusted for maternal age, maternal history of asthma, household income, child race/ethnicity, gestational age, breastfeeding duration, and age at mid-childhood visit. The bold faced values represent odds ratios with a p-value <0.05.

Table 3

Maternal Folic Acid Intake During Pregnancy and Post-bronchodilator FEV₁ (mL) in Mid-childhood (n = 1116).^a

Folic Acid Intake	Quartile ^b	Total (n = 1116)		Boys (n = 559)		Girls (n = 557)	
		Unadjusted	Adjusted ^c	Unadjusted	Adjusted ^c	Unadjusted	Adjusted ^c
First trimester	Q1	0.0 (ref)	0.0 (ref)	0.0 (ref)	0.0 (ref)	0.0 (ref)	0.0 (ref)
	Q2	48 (-10, 107)	7 (-41, 55)	68 (-12, 148)	21 (-43, 86)	27 (-57, 111)	-8 (-78, 62)
	Q3	27 (-30, 84)	9 (-42, 61)	104 (23, 186)	52 (-18, 122)	-49 (-130, 32)	-35 (-105, 35)
	Q4	38 (-20, 96)	10 (-45, 65)	82 (0, 164)	44 (-28, 115)	-4 (-83, 76)	-22 (-96, 53)
Second trimester	Q1	0.0 (ref)	0.0 (ref)	0.0 (ref)	0.0 (ref)	0.0 (ref)	0.0 (ref)
	Q2	28 (-35, 90)	4 (-44, 53)	68 (-18, 153)	18 (-48, 85)	-12 (-95, 71)	-10 (-75, 55)
	Q3	23 (-35, 81)	6 (-41, 53)	68 (-16, 152)	25 (-43, 94)	-24 (-102, 55)	-15 (-78, 47)
	Q4	10 (-55, 75)	16 (-35, 68)	52 (-36, 141)	44 (-22, 111)	-32 (-119, 56)	-10 (-79, 60)

Abbreviation: FEV₁, forced expiratory volume in 1 second.^a Values are presented as coefficient β (95% confidence interval).^b Quartiles of energy-adjusted folic acid, with the first quartile being the lowest and the fourth quartile being the highest (see Table 1 for details on distribution of folic acid intake).^c Adjusted for maternal age, maternal history of asthma, household income, child race/ethnicity, gestational age, breastfeeding duration, child age, and height at mid-childhood visit.

The bold faced values represent a beta estimate with p-value <0.05.