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Maternal Folic Acid Supplementation during Pregnancy and Early Childhood Asthma

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Abstract

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Author contributions:

All authors made a significant contribution to one or more stages of the study. Dr. Carroll conceived the study. Drs. Carroll, Veeranki, Gebretsadik, Dupont, Hartert, Cooper, Dorris, Tylavsky, and Hartman participated in study design. Mr. Mitchel participated in acquisition of data. Drs. Gebretsadik led analyses with input from Drs. Dupont, Veeranki, and Carroll. All authors participated in interpretation of results. Dr. Veeranki drafted the initial manuscript and all authors contributed to critical revisions and approved the final version of the manuscript.

Conflict of interest statement:

The authors declare that they have no conflicts of interest related to this study.

Background—Asthma is one of the most common chronic childhood diseases. While folic acid supplementation around conception helps prevent neural tube defects, an animal model suggests it may be a risk factor for respiratory diseases; although epidemiologic studies have had conflicting results. We investigated the timing of folic acid-containing prescription filling during pregnancy and child asthma.

Methods—In a retrospective cohort study of 104,428 children, born 1996–2005, and their mothers enrolled in Tennessee Medicaid, we investigated the association of filling folic acid-containing prescriptions during pregnancy and childhood asthma at age 4.5–6 years. We categorized women into exposure groups based on prescription-filling centered around the first trimester: no folic acid prescription exposure, exposure in first trimester only, exposure after first trimester, and exposure in first trimester and beyond. We defined asthma using asthma-specific healthcare visits and medication fills. Using logistic regression models, we investigated the relationship adjusting for potential confounders.

Results—Overall 15% of children had asthma. Compared with children born to women with no folic acid prescription exposure, children born to women with exposures in the first trimester only or first trimester and later had increased relative odds of asthma [adjusted odds ratios (OR) 1.2, 95% confidence interval (CI) 1.1–1.3] and 1.2, 95% CI 1.2–1.3]; no association was seen in children born to women exposed after the first trimester.

Conclusion—Timing of folic acid-containing prescription filling during pregnancy was associated with childhood asthma. Our findings contribute to understanding of the role of prenatal nutritional supplements on child respiratory health.

Keywords

Childhood asthma; folic acid supplementation; pregnancy; prenatal vitamins; Tennessee Medicaid

INTRODUCTION

Asthma is a complex inflammatory disease of the airways associated with several risk factors including genetic predisposition and prenatal and early life exposures.^{1,2} A prenatal dietary exposure of interest is maternal folic acid supplementation. Adequate folate intake during the periconceptional period is important for the prevention of congenital anomalies such as neural tube defects (NTDs).³ However because of folate's vital role in several biological functions and findings from animal models that suggest high intake of methyl donors during pregnancy can influence an offspring's phenotype,⁴ an ongoing and important area of research is whether prenatal folic acid supplementation is associated with increased risk of childhood respiratory and atopic diseases potentially through effects on the developing fetal immune system.^{3,5}

Several epidemiologic studies have investigated the association of maternal folate status and asthma with inconsistent results.^{6–15} Some studies have found an increased risk of early childhood wheeze or asthma with self-reported prenatal folic acid supplementation or measured folate levels,^{8,10} while others have found an inverse association with folate levels during late pregnancy,¹³ or did not detect associations between self-reported folic acid supplementation during early pregnancy and child asthma.^{9,11,13} Few studies have studied

the association with higher folic acid intake, such as 1000 mcg, and child asthma outcomes. In a previous investigation, we assessed the relationship between maternal folic acid supplementation and viral bronchiolitis in the first year of life.¹² An estimated 30–40% of children with severe bronchiolitis during infancy subsequently develop asthma and epidemiologic and clinical investigations are addressing the question of whether severe viral infections during infancy may play a causal role in asthma development.^{16–18} In this current work we investigated the association between the filling of folic acid-containing prescriptions during pregnancy and child asthma at 4.5–6 years, a later respiratory phenotype, using a racially diverse, low-income retrospective cohort of 104,428 mother-child dyads, powered to detect clinically meaningful differences and examine multiple periods across pregnancy.

METHODS

Study cohort and population

To estimate the association of folic acid supplementation during pregnancy with early childhood asthma, we conducted a population-based retrospective cohort study of 104,428 mother-child dyads enrolled in Tennessee Medicaid (TennCare). Approximately 50% of infants born in Tennessee are enrolled into TennCare. Children born to mothers aged 15–44 years with a singleton pregnancy during 1996–2005 were eligible for inclusion to be followed up for ascertainment of asthma outcomes between ages 4.5 and 6 years. Study data were obtained from linked TennCare administrative data files and Tennessee state vital records, and included information on participant demographics, insurance enrollment, filled pharmacy prescriptions and health care encounters.^{12,16} The study population included mother-child dyads continuously enrolled in TennCare.^{12,16} For children, continuous enrollment included no more than 90 days of non-enrollment during the first year of life and no more than 60 days during 4.5–6 years. For women, continuous enrollment included no more than 60 days of non-enrollment six months prior to pregnancy through the date of delivery.¹²

To study the association of maternal folic acid supplementation and asthma in children without preexisting heart or lung disease, we included children who were born at term (gestational age ≥ 37 weeks), were non-low birth weight (birth weight ≥ 2500 grams) and did not have an *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis indicating congenital heart disease, chronic lung disease, or upper airway congenital anomaly.¹² Consistent with previous work, we calculated the estimated gestational age using the last menstrual period (LMP) date (83%) or estimated it using a previously described algorithm based on the median gestational period for the infant's race, birth weight, and birth year when LMP date was not available on the birth certificate (17%).^{16,19} Sensitivity analyses including complete case analysis and multiple imputations demonstrated highly consistent results in previous work.¹² The study protocol approval and waiver of informed consent was obtained from the Institutional Review Board of Vanderbilt University and study approval from representatives of the Bureau of TennCare.

Ascertainment of child asthma and atopic disease outcomes

The main outcome variable was early childhood asthma at age 4.5–6 years. An 18-month ascertainment period was used to include children who may receive treatment infrequently or only for routine annual preventive care.¹⁶ We ascertained outcomes after age 4 years in attempts to exclude children who may have wheezed only transiently in the first 3 years of life with viral infections.²⁰ Asthma diagnosis during 4.5–6 years was defined using a previously validated algorithm that uses asthma-specific healthcare visits (ICD-9 diagnosis) and asthma-specific medication fills, as previously described.^{16,21} We classified children as having a diagnosis of asthma at age 4.5–6 years versus none.

Maternal folic acid supplementation during pregnancy

The main predictor variable was filling of folic acid-containing prescriptions during pregnancy. We used prenatal vitamin prescriptions as a proxy measure for folic acid supplementation exposure, as prenatal vitamins constituted 99% of folic acid-containing prescriptions filled by women in the cohort during pregnancy. We obtained information on prenatal vitamins from the pharmacy files, including the filling date, days' supply and the folic acid dose. For those vitamins with no folic acid dose information in the pharmacy files, we conducted medication database and internet searches using the national drug code, a unique 10-digit, 3-segment numeric identifier assigned to each medication in the U.S., and were able to determine a specific dose for approximately 97% of prenatal vitamin prescriptions filled by women in the cohort.¹² Based on findings from work preparatory for research and the TennCare policy for medication filling, each vitamin prescription was assigned a maximum days' supply of 30 days. As folic acid supplementation during the periconceptional period helps prevent NTDs,^{12,22} we *a priori* characterized the women into four mutually exclusively categories using the filling date and days' supply of prenatal vitamin prescription, including no exposure (no prenatal vitamin prescription filled during pregnancy), folic acid prescription exposure in first trimester only (prescription fill that included at least one day in the first trimester, but none after the first trimester), exposure after first trimester (prescription fill that included at least one day after the first trimester only), and exposure in first trimester and beyond (prescription fill that included at least one day during and after the first trimester).¹²

Covariates

We selected specific maternal and child characteristics to include as covariates in the multivariate models based on the existing literature and plausible associations with both childhood asthma and maternal folic acid supplementation during pregnancy.^{12,21} Maternal characteristics included race (white, black, or other), age at delivery (years), education (years), smoking during pregnancy (yes/no), marital status (single/married), year of pregnancy, history of asthma (yes/no), region of residence (urban, suburban or rural based on standard metropolitan statistical areas) and adequacy of prenatal care. Adequacy of prenatal care was determined using the Adequacy of Prenatal Care Utilization (APNCU)/ Kotelchuck index and maternal asthma history was determined using a validated algorithm that includes asthma-specific healthcare visits and medication fills.^{23,24} Child characteristics included gender (male/female), birth weight (grams), estimated gestational age (weeks) and number

of siblings (none, 1, or 2 based on number of prior live births). We ascertained bronchiolitis outcomes during infancy using *ICD-9* diagnosis codes as previously described^{12,16,25} because bronchiolitis is associated with both maternal folic acid-containing prescription filling group and childhood asthma. To present the total effect of maternal folic acid supplementation on asthma without attenuation by infant bronchiolitis, main results were not adjusted for bronchiolitis. However, we adjusted for bronchiolitis along with other covariates in subsequent analysis.

Statistical analysis

Descriptive analyses were conducted and presented as frequencies and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables. Bivariate analyses were conducted to assess the differences in maternal and child characteristics by prenatal vitamin prescription filling group using Chi-square contingency table statistics for categorical variables and Kruskal–Wallis test for continuous variables. We calculated the week that women filled their first prenatal vitamin prescription (time from their LMP) and reported the median (IQR) for each exposure group. The main exposure of interest was prenatal vitamin prescription filling group and the main outcome variable was child asthma diagnosis between ages 4.5–6 years. In our primary analysis, we conducted multivariable logistic regression to estimate the relative odds of early childhood asthma with prenatal vitamin prescription filling group, adjusting for child gender, estimated gestational age, birth weight, number of siblings, and maternal race, region of residence, year of pregnancy, marital status, age, education, asthma history, smoking, and adequacy of prenatal care. In subsequent analysis, we further assessed the relationship using multivariable logistic regression and the adjusted model also included bronchiolitis diagnosis during infancy. We tested *a priori*-specified interactions that included whether maternal asthma and infant gender as potential effect modifiers of the relationship between folic acid supplementation and early childhood asthma. In addition, as exploratory analyses, we tested the potential role of effect modification of maternal education, smoking during pregnancy, bronchiolitis diagnosis during infancy, and pre- and post-period of mandatory folic acid fortification programs (pre-1998 versus post-1998 time periods) on the relationship between folic acid supplementation and early childhood asthma. Each variable was included with maternal folic acid supplementation exposure as a cross-product in separate adjusted regression analysis. *P* value < 0.05 was used for all statistical inferences. We managed data using SAS version 9.1 (SAS Inc., Cary, NC, US) and conducted statistical analyses using R version 3.0.1 statistical software.

RESULTS

Table 1 presents the descriptive characteristics of the study cohort and the statistical differences in maternal and child characteristics by prenatal vitamin prescription filling group. A total of 104,428 mother-child dyads were included in the study. Overall, 44% of women were black, 46% had less than 12 years of education, 29% smoked during pregnancy, and 6% had a history of asthma. Among children, approximately 49% were females, 35% had two or more siblings, and the median estimated gestational age and birth weight were 39 weeks (IQR 39–40) and 3,260 grams (IQR 2982–3572), respectively. When

studying characteristics by the four prenatal vitamin prescription groups, approximately 44% and 58% of unexposed women (i.e. those who did not fill a folic acid containing prescription) or those exposed after the first trimester were black compared with 35% and 37% of women with folic acid prescription filling in the first trimester only or in the first trimester and beyond. Approximately one-fourth of women exposed after the first trimester were married (22%) or smoked during pregnancy (25%) while approximately one third of women in the other three groups were married or smoked during pregnancy. Approximately three-fourths of women exposed in the first trimester only or in the first trimester and beyond received at least adequate prenatal care (73% and 72% respectively) compared to approximately one-half of women unexposed or exposed after the first trimester.

Seventeen percent of women in the cohort did not fill a prenatal vitamin prescription and were categorized as unexposed. Overall, 10% of women were exposed (filled a folic acid containing prescription) in the first trimester only and 28% and 45% were exposed after the first trimester or in the first trimester and beyond, respectively. The median days of potential folic acid supplementation exposure was 30 (IQR 30–30) for women exposed in the first trimester only, 40 (IQR 30–84) for those exposed after the first trimester, and 90 (IQR 60–150) for those exposed in the first trimester and beyond. Approximately 84% of women in the cohort filled their first prenatal vitamin prescription after the 5th–6th week of pregnancy, and women exposed in the first trimester only or in the first trimester and beyond filled their first prescription at the median during the 6th (IQR 5–7) and 8th (IQR 6–10) week, respectively. Overall 99% of prenatal vitamin prescriptions filled contained 1,000 µg of folic acid.

Overall, 15% of children were classified as having asthma during 4.5–6 years of age. The proportion of children diagnosed with early childhood asthma differed by prenatal vitamin prescription exposure groups. Approximately 13% of children born to women who did not fill a folic acid-containing prescription were diagnosed with asthma. Asthma was diagnosed in 17% of children born to women who filled a prescription in the first trimester, in 13% of those born to women who filled a prescription after the first trimester, and in 17% of those born to women who filled prescriptions in the first trimester and beyond.

Table 2 presents the unadjusted and adjusted estimates, all compared to children born to women who did not fill a folic acid prescription, of the association of maternal folic acid-containing prescription filling group with child asthma. Children born to women who filled a folic acid prescription in the first trimester only group had increased relative odds of asthma (adjusted Odds Ratios [OR] 1.2, 95% Confidence Interval [CI] 1.1–1.3), and children born to those who filled prescriptions in the first trimester and beyond had adjusted OR for diagnosis of asthma of 1.2 (95% CI 1.2–1.3). When infant bronchiolitis was added to the model, we found that exposure during the first trimester only or in the first trimester and beyond were associated with increased relative odds of child asthma [First trimester only: adjusted OR 1.2, 95% CI 1.1–1.2; first trimester and beyond: adjusted OR 1.2, 95% CI 1.2–1.3]. Overall, 29% of children had mothers who smoked during pregnancy. We detected marginal interaction of maternal smoking during pregnancy and maternal folic acid supplementation on child asthma diagnoses ($P=0.05$). However, when we compared the pre-specified groups of prenatal vitamin prescription filling for association with childhood

asthma in the two strata of maternal smoking status, there were no differences. We did not detect an interaction with maternal education, early diagnosis of bronchiolitis, or period of time of pregnancy related to folic acid fortification in the U.S. (all P value >0.15). Overall, 17% and 13% of male and female children were classified as having asthma during 4.5–6 years age, respectively. In a separate model testing the interaction of child gender with maternal folic acid supplementation on childhood asthma, the P -value for interaction was 0.09 and gender stratified analyses are presented in Table 2.

DISCUSSION

In a retrospective cohort of 104,428 racially diverse low-income mother-child dyads, we found that children born to women who filled folic acid-containing prescriptions during the first trimester only and women with potential exposure from filled prescriptions in the first trimester and beyond had increased relative odds of asthma at age 4.5–6 years compared with children born to women who did not fill a folic acid-containing prescription during pregnancy.

Overall, 15% of children in the study had an asthma diagnosis. The pulmonary and immune systems develop at discrete time periods of fetal development, and folic acid supplementation prevents neural tube defects when administered during the periconceptional period; thus we *a priori* categorized prenatal filling of folic acid-containing prescriptions in relation to the first trimester into four exposure groups.¹² Previous work in this cohort focused on bronchiolitis during infancy, a common viral lower respiratory infection with associated acute morbidity and an increased risk of asthma in later childhood, while the current effort was designed to focus on early childhood asthma, a chronic inflammatory disease of the lower airways and distinct from viral bronchiolitis.²⁶ We found approximately 20% higher relative odds of asthma in children born to women exposed in the first trimester only or the first trimester and beyond than children born to women with no folic acid prescription fills during pregnancy. Although the effect sizes were modest, they were similar to point estimates found in some studies for other maternal factors such as maternal smoking.²⁷ Similarly, in a smaller study with maternal folic acid supplementation during late pregnancy, Whitrow *et al.*¹⁰ demonstrated a 26% and 17% increased relative risk of asthma in children at 3.5 and 5.5 years, respectively; however adjusted estimates likely lacked sufficient power to conclude that asthma risk was elevated at 5.5 years age. Studies by Martinussen *et al.*⁹ and Magdeljins *et al.*¹³ revealed similarly powered increased relative odds (23% and 27%, respectively) of asthma at 6 to 7 years of age with folic acid supplementation during early pregnancy, while Bekkers *et al.*¹¹ and Nwaru *et al.*¹⁴ identified smaller associations. Other studies have investigated the association of maternal folate levels and child respiratory and atopic disease outcomes. In a nested case-control study, Haberg *et al.*⁸ found a dose-response relationship between second trimester folate levels and asthma in children at age 3 years, with children born to mothers in the highest quintile having a 66% increased relative odds of asthma compared with children born to mothers in the lowest quintile. Magdeljins *et al.*¹³, however, identified an inverse relationship between third trimester maternal red blood cell folate levels and asthma in children at 6–7 years. In addition, in a cohort of children at high risk for asthma, higher folate levels during early childhood was associated with allergic sensitization.²⁸ In our earlier study that included the

outcome of bronchiolitis, there was marginal effect modification of maternal prenatal vitamin filling group on bronchiolitis by maternal asthma history,¹² however the current work did not detect a similar interaction between maternal folic acid supplementation and maternal asthma history on childhood asthma outcome.

Due to folate's role in important biologic mechanisms, biologic plausibility due to potential effects on the fetal immune response, and findings from animal models, investigations have focused on whether maternal prenatal folic acid intake or folate levels are associated with the development of child respiratory and atopic diseases. The folate derived tetrahydrofolate (5-methyl-THF) serves as a methyl donor in the synthesis of *S-adenosylmethionine*, the universal methyl donor, which is the key source of methyl groups for DNA methylation.²⁹ DNA methylation in conjunction with other epigenetic mechanisms influences T-helper (Th) cell development and regulation and may skew towards increased susceptibility to development of asthma and allergy diseases.³⁰ Experiments by Hollingsworth *et al.* conducted in a murine model demonstrated that a maternal diet high in methyl donors and co-factors, supplemented with folic acid vitamin B12, choline, L-methionine, zinc, and betaine, during pregnancy was associated with lung tissue methylation changes in key regulatory genes and an enhanced allergic response in the offspring compared with offspring of mothers fed a low methyl donor diet.⁴ Although not demonstrated in humans, it is plausible that maternal folic acid supplementation may be associated with risk of allergic airway disease in children. In an animal model, Sinclair *et al.* found that experimentally decreased periconceptional methyl donor intake was associated with epigenetic changes and phenotypic differences in the offspring, including measures of immune functioning, insulin resistance, and cardiovascular effects, which were most pronounced in males.³¹ In our study, gender differences in the relationship between maternal prenatal vitamin supplementation and child asthma were not substantial, based on the odds ratios and 95% CIs observed (Table 2), however these should be further delineated in future studies. In our study, 84% of women in the study cohort filled prenatal vitamin prescriptions after the 5th–6th week of pregnancy, the time period about which the anterior and posterior neuropores of the neural tube have closed,³² which highlights the need for further studies around the timing of folic acid supplementation and early childhood asthma.

The study has limitations to consider. We captured folic acid in prescribed supplements and it is likely that women in the study cohort also consumed folic acid in fortified foods.¹² However, previous studies using low-income populations demonstrated that consumption of dietary folic acid would be unlikely to result in intake equivalent to the 1000 µg of folic acid found in most prescriptions filled in the study.³³ In addition, Yang *et al.* demonstrated that women who consumed folic acid supplements (> 400 µg folic acid/day) had higher serum folate levels and intakes that were more likely to exceed the upper tolerable intake level.³⁴ It is also possible that women obtained folic acid supplements from over-the-counter or other sources that might have led to misclassification. In addition, women who filled prenatal vitamin prescriptions might not have taken them as prescribed. Prenatal vitamins contain other micronutrients that are under investigation for their potential influence on child respiratory health; however, most have been associated with potential protective effects.^{35,36} There were differences in the adequacy of prenatal care by maternal prenatal vitamin prescription filling groups, which may be related to maternal healthcare-seeking behavior

and we included this factor in our adjusted models.¹² Our study population was assembled using Medicaid administrative data, thus there is the potential for differences in exposure and outcome among dyads continuously enrolled versus those who were not. However, in earlier work using TennCare claims by Cooper *et al.*,³⁷ it was found that approximately 10% of children had an enrollment gap and that there were no differences in asthma related healthcare visits when comparing children with an enrollment gap to children without a gap (adjusted incidence rate ratios, 95% CI of 1.06, 95% CI 0.70–1.61 for hospitalizations and 1.08, 95% CI 0.89–1.32, for emergency department visits).³⁷ We defined child asthma using asthma-specific healthcare visits and medication use, and it is possible that there were individuals with asthma who were not identified, although this would likely bias the results to the null. In addition, we determined asthma outcomes using a validated algorithm that represents an objective measurement of outcome and would serve to minimize information bias.^{16,21} As the study was hypothesized to estimate the relationship among children born at term, infants born preterm were not included in the cohort. It is possible that maternal folic acid supplementation is related to both gestational age and asthma,^{38,39} and this could have induced collider stratification that might have resulted in biased estimates of the association.⁴⁰ Future studies assessing the relationship should include infants born preterm and will give insight on the extent of potential collider stratification bias. This epidemiologic investigation may be influenced by unmeasured confounding.⁴¹ Despite these limitations, animal models and epigenetic studies lend biologic plausibility to the hypothesis that prenatal folic acid intake influences development during a critical period with potential influence on subsequent asthma, associations were seen in this study even after adjusting for numerous important maternal and child demographic and health-related factors, and this study provides insight into the potential direction and effect size.^{4,8,10,27,42}

Using objective measures of asthma outcomes in children and folic acid-containing prescription filling during pregnancy, we found that maternal filling patterns of folic acid-containing prescription during the first trimester, and during and after the first trimester of pregnancy were associated with increased relative odds of early childhood asthma in a large retrospective cohort of 104,428 racially diverse low-income mother-child dyads. The study findings contribute to ongoing efforts in understanding the role and timing of prenatal nutritional supplements in the development of childhood respiratory diseases.

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Table 1

Maternal and child characteristics by folic acid supplementation during pregnancy in a cohort of term children, born during 1996–2005, and their mothers enrolled in Tennessee Medicaid.

Characteristics	Prenatal vitamin prescription filling category during pregnancy					Total cohort 104,428
	No prescriptions filled; % (n)	First trimester only; % (n)	After first trimester; % (n)	First trimester and beyond ^a ; % (n)		
Child gender	17 (18,057)	10 (9,976)	28 (29,159)	45 (47,236)		
Male	52 (9,311)	51 (5,056)	51 (14,961)	51 (24,256)		51 (53,584)
Female	48 (8,746)	49 (4,920)	49 (14,197)	49 (22,979)		49 (50,842)
Birth weight, grams, Median (IQR)	3,260 (2,977–3,544)	3,260 (2,977–3,572)	3,247 (2,977–3,544)	3,289 (3,005–3,600)		3,260 (2,982–3,572)
Infant EGA, weeks, Median (IQR)	39 (38–40)	39 (38–40)	39 (39–40)	39 (39–40)		39 (39–40)
Maternal race						
White	53 (9,579)	62 (6,212)	40 (11,715)	60 (28,255)		53 (55,761)
Black	44 (7,984)	35 (3,541)	58 (16,773)	37 (17,705)		44 (46,003)
Other	3 (494)	2 (223)	2 (671)	2 (1,276)		3 (2,664)
Maternal age, years, Median (IQR) ^b	22 (20–26)	22 (19–25)	21 (19–25)	22 (19–26)		22 (19–26)
Maternal education, years						
< 12	46 (8,188)	46 (4,602)	50 (14,457)	43 (20,245)		46 (47,492)
12	42 (7,620)	44 (4,355)	41 (11,827)	45 (21,043)		43 (44,845)
> 12	12 (2,212)	10 (1,007)	10 (2,797)	12 (5,854)		11 (11,870)
Maternal smoking ^c						
Yes	30 (5,483)	32 (3,237)	25 (7,252)	30 (14,037)		29 (30,009)
No	70 (12,538)	68 (6,723)	75 (21,865)	70 (33,134)		71 (74,260)
Marital status						
Single	67 (12,154)	62 (6,223)	78 (22,656)	64 (30,384)		68 (71,417)
Married	33 (5,896)	38 (3,750)	22 (6,492)	36 (16,844)		32 (32,982)
Adequacy of prenatal care ^d						
Adequate plus	18 (3,184)	29 (2,917)	16 (4,598)	27 (12,669)		22 (23,368)
Adequate	34 (6,200)	44 (4,437)	32 (9,304)	45 (21,378)		40 (41,319)
Intermediate	13 (2,283)	14 (1,368)	14 (4,162)	15 (7,092)		14 (14,905)
Inadequate	31 (5,575)	8 (793)	33 (9,693)	9 (4,073)		19 (20,134)

Characteristics	Prenatal vitamin prescription filling category during pregnancy				Total cohort
	No prescriptions filled; % (n)	First trimester only; % (n)	After first trimester ; % (n)	First trimester and beyond ^d ; % (n)	
Unknown	17(18,057)	10 (9,976)	28 (29,159)	45 (47,236)	104,428
Maternal asthma					
Yes	5 (815)	5 (461)	5 (1,402)	4 (2,024)	5 (4,702)
No	4 (767)	7 (654)	5 (1,470)	8 (3,641)	6 (6,532)
Siblings ^e					
None	96 (16,869)	93 (9,180)	95 (27,098)	92 (42,962)	94 (96,109)
1					
None	18 (3,316)	27 (2,659)	28 (8,130)	35 (16,592)	29 (30,697)
2	35 (6,348)	40 (3,965)	33 (9,497)	36 (16,848)	35 (36,658)
2	46 (8,359)	33 (3,330)	39 (11,475)	29 (13,689)	35 (36,853)
Region of residence					
Urban	30 (5,453)	41 (4,047)	23 (6,826)	36 (16,941)	32 (33,267)
Suburban	24 (4,326)	23 (2,291)	17 (5,035)	22 (10,477)	21 (22,129)
Rural	46 (8,234)	36 (3,631)	59 (17,279)	42 (19,779)	47 (48,923)
Asthma at 4.5–6 years					
Yes	13 (2,305)	17 (1,652)	13 (3,738)	17 (8,081)	15 (15,776)
No	87 (15,752)	83 (8,324)	87 (25,421)	83 (39,155)	85 (88,652)
Bronchiolitis during infancy					
Yes	24 (4,304)	29 (2,881)	22 (6,427)	26 (12,216)	25 (25,828)
No	76 (13,753)	71 (7,095)	78 (22,732)	74 (35,020)	75 (78,600)

EGA=Estimated Gestational Age

IQR=InterQuartile Range

^a Prenatal vitamin prescriptions filled during and after the first trimester^b Maternal age at delivery^c Maternal smoking during pregnancy^d Kotelchuk index^e Siblings based on prior live births

Table 2

Relative odds of asthma diagnosis^a by maternal folic acid-containing prescription filling during pregnancy among term children, born during 1996–2005, and their mothers enrolled in Tennessee Medicaid in all dyads and by child gender

Maternal prenatal vitamin prescription filling category; % (n)	Asthma diagnosis ^a in children at age 4.5–6 years		
	% (n)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
All dyads, N= 104,428			
None filled; 17 (18,057)	13 (2,305)	1.0	1.0
First trimester only; 10 (9,976)	17 (1,652)	1.4 (1.3, 1.5)	1.2 (1.1, 1.3)
After first trimester ; 28 (29,159)	13 (3,738)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)
First trimester and beyond ^b ; 45 (47,236)	17 (8,081)	1.4 (1.3, 1.5)	1.2 (1.2, 1.3)
Maternal prenatal vitamin prescription filling category by child gender; % (n)			
Males, N=53,584	% (n)		
None filled; 17 (9,311)	15 (1,382)	1.0	1.0
First trimester only; 9 (5,056)	19 (937)	1.3 (1.2, 1.4)	1.1 (1.0, 1.2)
After first trimester ; 28 (14,961)	15 (2,245)	1.0 (0.9, 1.1)	1.0 (1.0, 1.1)
First trimester and beyond ^b ; 46 (24,256)	19 (4,713)	1.4 (1.3, 1.5)	1.2 (1.1, 1.3)
Females, N=50,842	% (n)		
None filled; 17 (8,746)	11 (923)	1.0	1.0
First trimester only; 10 (4,920)	15 (715)	1.4 (1.3, 1.6)	1.3 (1.1, 1.4)
After first trimester ; 28 (14,197)	11 (1,493)	1.0 (0.9, 1.1)	1.0 (1.0, 1.1)
First trimester and beyond ^b ; 45 (22,979)	15 (3,367)	1.5 (1.4, 1.6)	1.3 (1.2, 1.4)

Abbreviations: OR means Odds Ratio, CI means Confidence Interval

OR adjusted for infant gender, estimated gestational age (weeks), birth weight, other living siblings, maternal race, region of residence, pregnancy year, marital status, age at delivery, level of education, smoking during pregnancy, asthma, and adequacy of prenatal care

^a asthma-specific healthcare visits or medication use

^b Prenatal vitamin prescriptions filled during and after the first trimester