Periconceptional folic acid supplementation and child asthma: a Right From the Start follow-up study

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ABSTRACT
Objective: High maternal folic acid exposure has been studied as a risk factor for child asthma with inconclusive results. Folic acid supplementation that begins before pregnancy may propagate high exposures during pregnancy, particularly in regions with fortified food supplies. We investigated whether folic acid supplementation initiated periconceptionally is associated with childhood asthma in a US cohort.

Materials and methods: We re-contacted mother–child dyads previously enrolled in a prospective pregnancy cohort and included children age 4 to 8 years at follow-up (n = 540). Using first trimester interviews, we assessed whether initial folic acid-containing supplement (FACS) use occurred near/before estimated conception (“periconceptional”) or after (during the “first trimester”). Follow-up questionnaires were used to determine if a child ever had an asthma diagnosis (“ever asthma”) or asthma diagnosis with prevalent symptoms or medication use (“current asthma”). We examined associations between FACS initiation and asthma outcomes using logistic regression, excluding preterm births and adjusting for child age, sex, maternal race, maternal education, and parental asthma.

Results: Approximately half of women initiated FACS use periconceptionally (49%). Nine percent of children had “ever asthma” and 6% had “current asthma.” Periconceptional initiation was associated with elevated odds of ever asthma [adjusted odds ratio (95% Confidence Interval): 1.65 (0.87, 3.14)] and current asthma [1.87 (0.88, 4.01)], relative to first trimester initiation.

Conclusion: We observed positive, but imprecisely estimated associations between periconceptional FACS initiation and child asthma. Folic acid prevents birth defects and is recommended. However, larger studies of folic acid dosing and timing, with consideration for childhood asthma, are needed.

Introduction
Asthma is a common chronic disease affecting ~10% of children in the United States [1]. Asthma has a complex etiology that likely begins in utero and involves both genetic and environmental risk factors, including maternal nutritional factors that may be modifiable targets for asthma prevention [2]. High maternal folic acid intake, for example, has been widely studied as a possible risk factor for child asthma [3]. Acting as a potent carbon methyl donor, folic acid can induce epigenetic modification during development [4], potentially leading to adverse respiratory outcomes in offspring [5]. Several recent epidemiologic studies have suggested that prenatal folic acid supplement use or intake during pregnancy may be associated with childhood asthma [6–11] although overall findings have been inconsistent [12–17].

Folic acid supplementation in the month before conception through the first trimester of pregnancy is highly effective in preventing neural tube birth defects...
and women of childbearing age are advised to supplement with 0.4 to 0.8 mg/day to promote adequate exposure during critical windows of early pregnancy [18]. Certain populations, including the United States, are also exposed to folic acid through mandatory fortification of grains and cereals. Long-term folic acid supplement use increases levels of red blood cell folate, with some evidence suggesting this increase can occur steadily and without plateau for at least 24 weeks [19]. Combined exposure to daily periconceptional supplements and fortified foods may result in unintentionally excessive folate exposures during pregnancy [20,21]. Therefore, while folic acid is unequivocally important for birth defect prevention, there remains a need to understand how periconception supplementation may be associated with potentially adverse outcomes in offspring, such as asthma, particularly in fortified populations.

Most prior studies of maternal folic acid intake and childhood asthma characterize exposures during pregnancy. Few have characterized supplement use prior to pregnancy [8,13,16,22,23], and only one such study was conducted in the United States where subjects were also exposed to population-level grain and cereal folic acid fortification [14]. Here, we investigate the association between the timing of folic acid-containing supplement (FACS) initiation and child asthma in a US pregnancy cohort. We hypothesize that initiating FACS prior to pregnancy is associated with an increased risk of asthma, relative to initiation later in pregnancy, potentially due to higher accumulated dose associated with prolonged use. In characterizing risks associated with periconceptional folic acid supplementation, we aim to inform future studies that may more closely examine folic acid exposure and dosage recommendations.

Materials and methods

Study design and data collection

Our analysis included a sample of mother–child dyads who participated in Right From the Start, a prospective community-based cohort study of pregnancy. Women were recruited from eight metropolitan areas in North Carolina, Tennessee and Texas between 2000 and 2012 using methods previously described [24,25]. In brief, these methods included efforts such as direct mail, paid advertising, distribution of materials in businesses and community groups, and partnerships with private and public health clinics. Eligible women were at least 18 years of age, had no plans to relocate for 18 months, were pregnant (<12 weeks’ gestation) or trying to become pregnant, did not use fertility treatment, and were fluent in English or Spanish with access to a telephone for interviews [24,25]. Women trying to become pregnant were formally enrolled upon conception.

Women provided basic demographic information at enrollment. Later within the first trimester [mean (standard deviation): 12.2 (3.1) gestational weeks], women completed extensive interviews related to medical and reproductive history, events during the current pregnancy, health behaviors and physical activity [25]. In these first trimester interviews, women were asked if they were currently using prenatal vitamins, and if so, whether they initiated use > or < 4 months ago. If initiation was <4 months ago, women were asked to estimate the date of initiation. Questions were repeated for other FACS (multivitamins and folic acid supplements). We restricted to women who completed this questionnaire ≤120 days after their last menstrual period (LMP). We defined FACS initiation as follows: “periconceptional” initiation included current use of FACS that began either “at least four months before interview” or on a date before LMP; “first trimester” initiation included current use of FACS that began after LMP. Women who completed first trimester interviews and reported never using FACS (2.8%) or previous (but not current) FACS use (2.6%) were rare and were therefore excluded, as were those with unknown use (<1%). LMP was based on self-report unless it differed by ultrasound-based estimates by >7 days, in which case the ultrasound-based estimate was used.

In 2013–2014, women were re-contacted by mail, telephone, and email and asked to complete an online questionnaire about the Right From the Start child. The questionnaire included topics related to the child’s demographics, current and previous respiratory health, family disease history, early life exposures, and current environment. Using the questionnaire data, we defined our outcome “ever asthma” as a mother’s report of whether a child ever had a diagnosis of asthma by a medical provider. We defined “current asthma” as “ever asthma” with additional reporting of either wheeze or use of asthma medication in the 12 months preceding the interview. Of 5013 live births, 1150 dyads responded to the follow-up questionnaire, with child ages ranging from 1.7 to 13.2 years (missing n = 2). Analysis was limited to those who were between 4 and 8 years (4.0 to < 9.0 years) at follow-up to optimally characterize childhood asthma. Age restrictions were applied because younger children may be more likely to have transient wheeze while
older children may experience changes in respiratory pathology due to onset of puberty [26–28]. Most dyads participating in follow-up were from a woman’s first pregnancy enrolled in Right From the Start; 2% (n = 18) were from a woman’s second enrolled pregnancy, where the first pregnancy resulted in either pregnancy loss (n = 11) or live birth (n = 7). In the event that a mother completed the follow-up questionnaire for her first and second Right From the Start live birth, only the older age-eligible sibling was included in analysis. All mothers provided informed consent. The study was approved by the Institutional Review Board of Vanderbilt University.

Of 4762 (95%) mothers with live births who completed first trimester interviews ≤120 days after LMP, we excluded preterm births (8%) to study the association between maternal FACS initiation and childhood asthma among children without early respiratory complications attributable to preterm delivery. Of 4399 term births, 1817 were 4 to 8 years at follow-up (defined as child’s age at questionnaire response or child’s age at attempted contact) and 1739 met our FACS initiation exposure definition. Of these, 540 mother–child dyads (31%) completed the follow-up survey and are included in this analysis.

**Statistical analysis**

We estimated the association between the timing of FACS initiation (assessed during pregnancy) and “ever asthma” and “current asthma” in children using logistic regression. We adjusted estimates for maternal race and education; child age and sex; and parental history of asthma. Additional variables considered *a priori* as covariates included maternal smoking, breast-feeding initiation, child daycare attendance, and infant RSV hospitalization. However, these variables were not included in multivariable modeling given low prevalence and limited variability (Table 1).

In sensitivity analyses, we applied stabilized inverse probability of censoring weights (IPCW) to assess the impact of loss to follow-up between first trimester interviews and child health follow-up questionnaire [29,30]. For eligible participants (children born at term, aged 4 to 8 years at time of follow-up with defined maternal FACS initiation), we used pooled logistic regression to determine the reciprocal of the predicted probability of remaining in the study at follow-up, conditional on exposure status (folic acid initiation), and on covariates available at baseline (maternal race, education, age, and parity) [30,31]. We included the IPCW in a weighted logistic regression model with robust variance to compare with unweighted (primary) results. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

**Results**

Of 1739 eligible dyads, 93% consumed FACS in the form of a prenatal vitamin or a prenatal vitamin combined with other FACS. Mothers of children who participated in follow-up (n = 540) were older, more likely to be white, more likely to be nulliparous at enrollment, and had higher educational attainment than mothers of eligible children who did not participate in follow-up (n = 1199, Table 1). Proportions of periconceptional and first trimester FACS initiation were similar between those who did and did not participate in follow-up (p = .32).

Among follow-up participants, approximately half initiated FACS use periconceptionally. Women with periconceptional FACS initiation were more likely to be white and more highly educated than those with first trimester initiation (Table 1). Most women (>90%) reported that their child was breastfed, attended daycare, and had no prenatal or household tobacco smoke exposure; these proportions did not differ by timing of FACS initiation. Distributions of other asthma risk factors, including maternal and parental history of asthma and RSV hospitalization in infancy, also did not differ by FACS initiation. Approximately 9% of children had “ever asthma” (n = 46) and 6% had “current asthma” (n = 33, Table 2).

After adjustment for covariates, we observed that children of women who initiated FACS use periconceptionally were ~65% more likely to have “ever asthma” [adjusted odds ratio (aOR): 1.65 (95% confidence interval {95%CI}; 0.87, 3.14)]; and 87% more likely to have “current asthma” [aOR: 1.87 (95%CI: 0.88, 4.01)], when compared with children of women who initiated supplementation in the first trimester (Table 2). Sensitivity analyses applying IPCW to logistic regression models did not substantially influence our results or conclusions [aOR for ever asthma: 1.59 (95% CI: 0.84, 2.99); aOR for current asthma: 1.82 (95%CI: 0.84, 3.89), (Supplementary Table S1)]. Descriptive characteristics for the follow-up sample weighted by IPCW are shown in Supplementary Table S2 for reference.

**Discussion**

In this prospective cohort study of US women and children, we observed elevated odds of childhood asthma following maternal periconceptional use of
FACS, after adjusting for multiple confounding factors. The estimates are imprecise given low prevalence of childhood asthma outcomes (9% and 6% for ever and current asthma, respectively) and loss to follow-up. However, loss to follow-up did not occur differentially by FACS exposure and our findings were robust to IPCW, suggesting minimal bias from selection.

We investigated whether initiating folic acid supplementation prior to pregnancy would be associated with the development of asthma in children relative to initiating supplementation later in order to better understand the timing of supplementation and potential associations with child asthma. Consistent with current recommendations, 50% of participants initiated FACS use prior to LMP. Almost all participants in Right From the Start reported FACS use in the first trimester, consistent with previous studies of US women [14,32]. We were not able to examine folic acid dose, however most women in our study reported FACS use in the form of prenatal vitamins which commonly contain 0.8–1.0 mg folic acid [9,21]. All women were exposed to a fortified US food supply which corresponds to an estimated average intake of 0.154 mg/day among women aged 19–30 years [33].

### Table 1. Characteristics of Right From the Start dyads by folic acid-containing supplement initiation and inclusion status.

| Characteristics at baseline | Periconception initiation | First trimester initiation* | Total included | Non-respondent/excludedb,c |
|----------------------------|---------------------------|-----------------------------|---------------|----------------------------|
| Maternal age (years), mean (SD) | 30.4 (3.9) | 30.1 (4.7) | 30.2 (4.3) | 29.3 (4.7)** |
| Maternal race, n (%) | 25 (9) | 60 (22)** | 85 (16) | 293 (24)** |
| White | 242 (91) | 213 (78) | 455 (84) | 905 (76) |
| Education, n (%) | 30 (11) | 49 (18)* | 79 (15) | 338 (28)** |
| Some college or less | 237 (89) | 224 (82) | 461 (85) | 861 (72) |
| College or more | 146 (55) | 150 (55) | 296 (55) | 578 (48)* |
| Parity, n (%) | 121 (45) | 123 (45) | 244 (45) | 618 (52) |
| 0 | 215 (81) | 249 (91)** | 464 (86) | 1020 (85) |
| 1+ | 28 (10) | 9 (3) | 37 (7) | 88 (7) |
| Other FACS | 24 (9) | 15 (6) | 39 (7) | 91 (8) |
| Characteristics at follow-upd | 63 (1.3) | 6.4 (1.2) | 6.3 (1.2) | – |
| Child age (years), mean (SD) | 6.3 (1.3) | 6.4 (1.2) | 6.3 (1.2) | – |
| Child sex, n (%) | 143 (54) | 130 (48) | 273 (51) | – |
| Male | 124 (46) | 143 (52) | 267 (49) | – |
| Female | 188 (71) | 201 (74) | 389 (72) | – |
| Parental asthma, n (%) | 77 (29) | 71 (26) | 148 (28) | – |
| No | 218 (82) | 231 (85) | 449 (84) | – |
| Yes | 47 (18) | 41 (15) | 88 (16) | – |
| Maternal asthma, n (%) | 8 (3) | 12 (4) | 20 (4) | – |
| No | 257 (97) | 260 (96) | 517 (96) | – |
| Yes | 260 (98) | 268 (99) | 528 (98) | – |
| Ever breast fed, n (%) | 5 (2) | 4 (1) | 9 (2) | – |
| No | 254 (96) | 252 (93) | 506 (94) | – |
| Yes | 11 (4) | 20 (7) | 31 (6) | – |
| Prenatal smoking, n (%) | 17 (6) | 22 (8) | 39 (7) | – |
| No | 248 (94) | 250 (92) | 498 (93) | – |
| Yes | 263 (98) | 270 (99) | 533 (99) | – |
| Current smoking in home, n (%) | 4 (2) | 3 (1) | 7 (1) | – |

**p < .05; *p < .01, corresponding to χ² tests and t-tests for categorical and continuous variables, respectively, comparing periconception initiation with first trimester initiation.**

**b**p < .05; **c**p < .01, corresponding to χ² tests and t-tests for categorical and continuous variables, respectively, comparing total included (n = 540) with excluded (n = 1,199).

“Non-respondent/excluded” participants are term births who were between 4.0 and <9.0 years old at time of follow-up who did not complete the follow-up questionnaire; missing from non-respondent/exclude participants: maternal race, n = 1; parity, n = 3.

“Non-respondent/exclude participants: ever breast fed, n = 3; maternal prenatal smoking, n = 3; current household smoking, n = 3; daycare attendance, n = 3.

FACS: folic acid-containing supplement; PNV: prenatal vitamin; RSV: respiratory syncytial virus.
Potential concerns about folic acid exposure during pregnancy stem from the capacity for folic acid to promote DNA methylation in early development [4]. This phenomenon may be sensitive to timing and duration of folic acid exposure. A recent study of cord blood methylation suggests that FACS use >6 months prior to conception results in higher methylation at certain genetic loci than FACS use after conception [34]. While adverse health outcomes driven by altered DNA methylation are not well characterized, methylation is typically associated with decreased gene expression, and can interfere with immune system development and function, including regulation of Th1 genes that may be important in respiratory diseases such as asthma [35].

We previously reported children born to Medicaid-enrolled women who filled first trimester prenatal vitamin prescriptions had increased odds of asthma, relative to those who did not [9]. Here, we further examine the timing of folic acid exposure by contrasting periconceptional and first trimester FACS initiation among FACS users. Few studies have examined periconceptional folic acid supplement use in subjects exposed to population-level dietary folic acid fortification, as ours did [14]. Martinussen and colleagues reported that folic acid supplementation in the month before conception was not associated with childhood asthma when compared with no pre-conception supplementation. Similar to our study, investigators assessed folic acid exposure during pregnancy, thus eliminating the potential for recall bias at follow-up, and also included lengthy prospective follow-up for asthma ascertainment. However, this study oversampled women with asthma and, consequently, many children had familial predisposition for asthma. While our study is smaller in comparison (n = 540 vs. n = 1499), it has the strength of reflecting asthma risks in a population less heavily influenced by hereditary factors.

A limitation of our study is that supplement use was only characterized in the first trimester. We do not know how long women continued using FACS throughout the duration of pregnancy. Thus we were not able to examine associations between late pregnancy FACS use and child asthma, as described by Whitrow et al. [8], or determine whether the association between periconceptional FACS use is modified by continued use beyond the first trimester. Additionally, we were not able to assess genetic factors related to folate metabolism which have previously been shown to modify the association between periconceptional folic acid use and child lung function [16]. Finally, we acknowledge the potential for unmeasured confounding. Women who initiate FACS use prior to pregnancy likely have other characteristics that differ from women who initiated FACS later. While many of these factors are likely beneficial health behaviors (e.g. other health-conscious behaviors, health care utilization, etc.), it is possible that some unmeasured factors may be contributing to the elevated, but not significant, observed findings of our study.

The importance of folic acid in the prevention of birth defects is established [18] and promotion of folic acid supplements is necessary: ~25% of reproductive-aged women in the United States have suboptimal folate levels, despite fortification [36]. However, unintended adverse effects of high folic acid intake must also be considered. While noting the unequivocal importance of achieving adequate folate levels in early pregnancy, we suggest a need for larger studies in which our findings can be replicated and where optimal folic acid supplement dosing and timing can be assessed in relation to adverse outcomes such as childhood asthma, particularly among reproductive-aged women who are exposed to a fortified food supply.

**Authors’ contribution**

M.A.A. led the analysis, contributed to the conception and design of this work, interpretation of the data, and drafted and revised the manuscript. S.V. and A.M. contributed to the acquisition of the data and critically revised the manuscript. D.R.V.E., S.H.J., and E.T. contributed to the acquisition and interpretation of data and

|                | Yes     | No     | Crude odds ratio (95% CI) | Adjusted odds ratio (95% CI)* |
|----------------|---------|--------|---------------------------|-------------------------------|
|                | n (%)   | n (%)  |                          |                               |
| Ever asthma    |         |        |                          |                               |
| First trimester| 20 (7)  | 253 (93)| 1.00 (Reference)         | 1.00 (Reference)              |
| Periconception | 26 (10)| 241 (90)| 1.36 (0.74–2.51)         | 1.65 (0.87–3.14)              |
| Current asthma |         |        |                          |                               |
| First trimester| 14 (5)  | 259 (95)| 1.00 (Reference)         | 1.00 (Reference)              |
| Periconception | 19 (7)  | 248 (93)| 1.42 (0.70–2.89)         | 1.87 (0.88–4.01)              |

*Adjusted for maternal race, maternal education, parental asthma, child sex, and child age.
critically revised the manuscript. K.E.H. and K.N.C. contributed to the conception and design of this work, the acquisition and interpretation of data, and critically revised the manuscript. All authors approve the final version of the manuscript and agree to be accountable for all aspects of the work.

**Disclosure statement**

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**Data availability statement**

The data that support the findings of this study are available by request (DRVE), subject to application and review.

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