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Folic acid supplementation in early pregnancy and asthma in children aged six

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Abstract

Objective—To assess whether folic acid intake during the first trimester of pregnancy is related to asthma in the offspring by the age of 6 years.

Study design—Prospective cohort study of 1,499 women who were followed from first trimester of pregnancy. Their children were followed until they were 6 years old.

Results—51% of the women used folic acid in the month before conception and 88% in the third month of pregnancy. The adjusted OR per 100 microgram increase in average daily intake of folic acid was 0.98 (95% CI:0.93-1.04). For categories of daily folate intake, there was no evidence of associations with childhood asthma nor evidence of any dose response relation for any time period (all $p_{trend}>0.05$)

Conclusion—Our results do not support any association of folic acid supplementation in pregnancy and asthma risk in offspring by age 6 years.

Keywords

childhood asthma; folic acid; pregnancy

Introduction

In 1991, an influential report published by the British Medical Council concluded that folic acid supplementation starting before pregnancy had a protective effect on the recurrence of

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The studies were conducted in New Haven, Connecticut, USA.

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neural tube defects (NTD) in the newborn infant.[1] The following year, a randomised controlled trial further demonstrated the protective effect of folic acid on first occurrence of NTDs.[2] To benefit from these studies, women of childbearing age were advised to use folic acid supplementation.[3] In the late 1990s several countries introduced mandatory folic acid supplementation of wheat flour, following which folate status in women of reproductive age has improved substantially.[4-6] The subsequent 50% decrease in neural tube defects has clearly demonstrated the positive effect of folic acid supplementation.[7-11]

It has been questioned whether *in utero* folic acid supplementation might also enhance development of adverse health outcomes. Folate, a source of methyl donors, regulates a complex network of biological pathways that are vital to growth.[12] A change in DNA methylation influences the degree of DNA accessibility for gene transcription and genomic stability.[13, 14] Increased methylation is usually associated with gene silencing or reduced gene expression which can bind the transient exposure of folic acid in early life to changes in gene expression. Immune development and differentiation are under epigenetic regulation,[15] and folate may have the capacity to promote an allergic phenotype by altering gene expression during early development. Animal studies have shown that the heritable risk of allergic airway disease was modified by *in utero* exposure to a diet rich in methyl donors[16] resulting in an increased risk of allergic airway disease in offspring.

In humans, results are conflicting whether folic acid intake before and/or during pregnancy is associated with increased risk of allergic disease in the offspring. Håberg et al. found that exposure to folic acid supplementation, particularly during the first trimester, was associated with a moderate increase in the risk of lower respiratory tract infections and wheezing up to 18 months of age.[17] Whitrow et al. reported that folic acid supplementation in late pregnancy was associated with an increased risk of asthma at 3.5 years of age.[18] Due to the uncertainty about any potential and unintended side effects of folic acid exposure *in utero*, these reported associations merit further study. Since prevention of neural tube defects through folate supplementation is one of the most important neonatal health advances to have been reported in recent years, it is important that supplementation does not gain distrust on unsubstantiated scientific grounds. In this cohort of nearly 1,500 US women with prospective information about folic acid intake, we assess the association of first trimester folic acid supplementation with asthma in the offspring at 6 years of age.

Materials and Methods

Between April 1997 and June 2000 a total of 3,413 women were invited from 56 private obstetric practices and 15 community-based clinics in Massachusetts and Connecticut to participate in the prospective Asthma in Pregnancy (AIP) study.[19] These women were interviewed in the first trimester, their hospital records from delivery were reviewed and the women were interviewed after delivery. Later, from September 2003 through January 2007 a subgroup of these subjects took part in a follow up study, Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM). In that study, women with a history of asthma diagnosis (n=872) or women who had symptoms or took asthma medications during pregnancy (n=449), and a simple random sample of pregnant women without asthma or asthma symptoms (n=550) were included. Details of study enrolment have been published elsewhere.[20] Non English speaking participants were excluded, as were three infant deaths which left 1,807 subjects eligible for interview. Of these, 302 mothers were excluded because of refusal, inability to locate, and missed interviews. Thus, 1505 women (83.3% of the 1807 eligible ones) were interviewed when the child was 6 years (+/− 3 months) old and included in our primary analyses. We excluded six individuals where information on confounding factors (marital status, family income and maternal asthma) was missing, leaving 1,499 participants in the final analyses.

Data collection in pregnancy (AIP study)

The pregnant women were interviewed, usually at home, before 24 weeks of gestational age. A standardized questionnaire included information on demographic and household characteristics including marital status, family income, health risk factors, medical conditions, and obstetric history. Pregnancy outcome data, which included prenatal, labour and delivery information including information of the newborn, was abstracted from medical records. A *post partum* interview was conducted in the hospital or by telephone within one month after delivery.

Information on folic acid, iron and vitamin use was obtained before 24 weeks of gestation from the following questions in the prenatal exposure questionnaire. “Have you used any of the following vitamin or mineral supplements: prenatal supplement vitamins, Multivitamin, Vitamin A, Vitamin C, Vitamin E, Iron/Ferrous Sulphate, Folic Acid/Folate, Calcium, or Other; specify.” If a respondent answered yes, she was specifically asked how often each item had been used (not at all, once a month, 2-3 times a month, twice a week, 3-4 times a week, 5-6 times a week, once a day or two or more times a day). This information was collected for the month before conception through the third month of pregnancy.

Folic Acid Exposure

We collected information on folic acid content (micrograms (mcg)) in each of the self-reported vitamin supplements. Using the detailed frequency information from the pregnancy questionnaire, we could calculate mean daily folic acid intake. Prenatal vitamins were estimated to contain 800 micrograms (mcg) folic acid per tablet, whereas vitamin supplements were estimated to contain 400 mcg folic acid[20] per tablet.

A dichotomous variable was created to characterize users from non-users. Mean daily intake was calculated for each month from the month before pregnancy through the third month and mean folic acid intake in the first trimester was defined as the average daily intake over these four months. For each month and for the total first trimester, daily folic acid intake was also divided into four categories (0, <400 mcg, 400-800 mcg, >800mcg). The majority of women (n=1,457) were enrolled in the study after starting of their third month of pregnancy and reported all three months of folic acid intake directly. Since 85% of the women with complete information reported the same intake in month two and three, women who were enrolled in the study and interviewed in their second month of pregnancy (n=42) were assumed to have the same folic acid intake in the third month as in the second.

Follow up of the children at 6 years of age (PRAM study)

Asthma in the 6 year old children was assessed by asking the mother the following questions “Has the child ever been diagnosed by a doctor or health professional as having asthma?” and “Has your child had wheezing or whistling in the chest in the last 12 months?” A positive answer to both these questions was considered a positive definition of current asthma.

Study ethics

The Human Investigation Committee of Yale University Medical School (New Haven, Connecticut) approved the study and all respondents provided written informed consent prior to participation.

Statistical analysis

Logistic regression was used to assess the association between folic acid supplementation in pregnancy and asthma in the children and expressed the effect estimates as odds ratios (ORs) with 95% confidence intervals (CIs). Information on potential confounding variables was obtained from the interviews conducted during early pregnancy and at 6 years (+/− 3 months) of age. They included maternal parity, ethnicity and marital status, household income, maternal asthma, smoking during pregnancy, use of other vitamins (C, D and E), iron use, and calcium use in first trimester.

Group differences in folic acid supplementation were initially identified using of unpaired t-tests if the variables were dichotomized and by analysis of variance (ANOVA) with Bonferroni and Scheffes Post Hoc tests when they were categorized in more than two groups. Covariables were identified as potential confounders and included in the analyses if they were associated with both the exposure of daily folic acid supplementation and outcome of asthma at six years of age, at a level of $p<0.10$ Adjusted models used a backward elimination procedure which retained only covariates that resulted in 10% or greater change in the effect estimate. The final model included maternal marital status, family income and maternal asthma.

The effect of folic acid supplementation was first assessed for the continuous variable per 100 mcg increase in daily intake, and successively for the four categories of intake (no use, <400mcg, 400-800 mcg and >800 mcg daily use). All analyses were done separately for four different time periods (the month before pregnancy and during 1st, 2nd and 3rd month). In these categorical analyses, no use of folic acid was used as the reference and two-sided P-values from linear trend tests were calculated by treating the folic acid dose categories as ordinal variables in the regression model.

P-values <0.05 and CIs that excluded the null value of 1 were considered statistically significant. Statistical analyses were performed with STATA/SE10 (College Station, TX, USA)

Results

Table 1 describes characteristics of the study population by daily intake of folic acid (mcg) in the month before conception and during the first trimester. Pregnant women who were above 25 years of age, of white ethnicity, had higher education, higher income, and were married, used higher doses of folic acid, as did women who did not smoke or had quit smoking before pregnancy. By study design, there was an over-sampling of women who had been diagnosed with asthma. These women had higher intake of folic acid compared to women without asthma in the month before and in the first trimester overall, with mean values (SD) of 323 (369) mcg vs. 279 (363) mcg ($p<0.01$) and 510 (299) vs. 481 (302) mcg ($p<0.05$) respectively (Table 1). Women who were giving birth for the first and second time used higher daily doses of folic acid than those who had given birth twice or more, but we found no association between parity and asthma in the children (P=0.30). Women who took other vitamins, iron and/or calcium used higher doses of folic acid supplementation than women who did not take these supplements. However, such supplementation was not associated with asthma development, (P=0.5).

A number of maternal characteristics were associated with asthma in the six year old child. In unadjusted analyses, asthma was significantly more often diagnosed in children whose mothers were younger, children of African-American or Hispanic mothers, mothers who had low education, low income, were single, who smoked, and who had themselves been diagnosed with asthma[21].

Table 2 presents mean daily folic acid dose in micrograms (mcg), and categories for daily folic acid intake for each of the four time periods under study. Mean intake of folic acid increased from 303 mcg the month before pregnancy, to 404 mcg in the first, 605 mcg in the second and 676 mcg in the third month of pregnancy. Mean supplementation in the first trimester as a whole was 497 mcg. Furthermore, the proportion of women who used folic acid supplementation increased from 51% before pregnancy to 61%, 81%, and 88% in the first, second and third months, respectively. Overall, 92 % of the pregnant women had used folic acid at some point during the first trimester.

Table 3 presents the crude and adjusted risk estimates for childhood asthma with folic acid use versus none. In unadjusted analyses, women who had taken folic acid in the month before and in the first month of pregnancy were less likely to have children with asthma. In adjusted analyses, there were no differences between users and non users.

Table 4 shows the crude and adjusted estimates of the logistic modeling of folic acid use per 100 mcg increase and daily intake with childhood asthma. Exposed women were compared with non exposed ones by time period. In the unadjusted analyses, we found a significant decreased risk of asthma from folic acid supplementation before conception, in the first month of pregnancy, and in the first trimester as a whole. In a final model that adjusted for potential confounders we found no significant increased risk of asthma from folic acid supplementation for any of the time periods studied (First trimester OR 0.98 CI (0.93-1.04).

Table 5 presents the crude and adjusted estimates of categories of folic acid supplementation for each time period with asthma among six year old children. In unadjusted analyses, daily doses from 400 to 800 mcg of folic acid in the month before and in the first month of pregnancy was significantly associated with a decreased risk of asthma. In the second month only doses >800 mcg was associated with a decreased risk, whereas in the third month as well as the whole first trimester, there was no association between folic acid supplementation and asthma. After adjustment for confounders, there was neither evidence of any associations between categories of folic acid intake and childhood asthma nor evidence of a dose response relationship for any time period (all p_{trend} >0.05).

Comment

In this prospective cohort study, supplementary folic acid in the month before and/or the first trimester of pregnancy was not associated with asthma in the offspring at 6 years of age.

A previous paper reported a slightly increased risk of wheezing and respiratory tract infections in children up to 18 months when mothers had used folic acid supplementation in early pregnancy.[17] However, no supplementation doses were recorded and the authors could not establish an adverse dose-response effect. In contrast to their findings, Whitrow et al. reported no association between folate intake or folic acid supplementation and asthma at 3.5 and 5.5 years of age.[18.]

The major strength of our study is its prospective design that enabled assessment of the association between prenatal exposures and childhood asthma. The study also included prospectively collected information on numerous potentially important confounding variables. Further, we were able to classify the quantity of folic acid supplementation and the time span of exposure. It is unlikely that misclassification of exposure was related to the outcome because folic acid supplementation was reported before birth. The sample size is robust (n=1499) and, given the hereditary risk of asthma, the sample was enriched with mothers who themselves had asthma. This allowed for examination of modifying effects by maternal asthma status.

The folic acid and asthma hypothesis was most likely unknown to mothers, interviewers or physicians, making information bias unlikely. One strength of the study is that only cases with a physician verified diagnosis of asthma and with current symptoms at 6 years of age were included in the analyses. It is, however, a limitation that the doctor diagnosed asthma was ascertained through a renewed contact with the mother when the child was 6 years of age, at which time they were also asked about persistent symptoms. We are aware that some of the children might not have wheezing or whistling in the chest due to the effect of the prescribed asthma medications. In this category we found 38 infants. Re-analysis using this modification of our outcome did not materially affect the results.

The definition of asthma we used is common in epidemiologic research, and these same limitations affected the studies that previously reported increased risk of respiratory problems with folic acid supplementation.[17, 18]

It is a limitation that we had no information about folate intake from nutrients. Daily intake of folate from nutrients has been estimated to around 200 mcg without fortification[22] and around 400 mcg with fortification in flour.[6] If we assume that the nutrient intake of folic acid was evenly distributed among cases and controls, one should expect fortification had no influence on our results. Furthermore, the group of women that had intake above 800 mcg was small and too underpowered to demonstrate differences.

It is proposed that an increased risk of asthma may develop in the offspring due to an effect of folate on epigenic regulation of immune responses,[16] that silences the pathways for T1 helper cells. These cells normally inhibit T2 helper cells, which are allergy promoting. Mice have been tested to see whether *in utero* exposure to a diet rich in methyl donors enhances the allergy-promoting immunity. By reducing expression of key genes that regulate immunity, the severity of airway disease was enhanced.[16]

Whether the same allergy-promoting mechanism develops after folic acid supplementation in the human fetus is unknown. Given the extreme importance of folic acid supplementation in preventing congenital birth defects, it is paramount to establish whether exposures during the intrauterine period are truly causally related to development of asthma in later life. Given the clear relationship of maternal intake of folic acid and concentrations of folate in maternal serum and red blood cell folate, it is reasonable to think that maternal intake in pregnancy is a proxy for fetal exposure.[6] Studies in human embryos and fetuses are difficult to conduct. However, to support a causal relationship it may be required to study the association between maternal folic acid concentrations and immunologic and epigenetic characteristics of cord blood.[24] Methylation of DNA is an epigenetic regulator of gene-expression and is essential for normal embryonic development.[13]

Folic acid supplementation to women of childbearing age and fortification of nutrients has been greatly advantageous with rapidly decreasing NTD rates in several countries. [7-10] A dose-response of folic acid supplementation has been shown with a reduction in NTD of 23% from 200 mcg to 85% reduction with 5000 mcg daily intake.[25]

Large scale public health interventions, such as mandatory fortification of food, need to be carefully assessed for risks of harm. We were unable to find any effect of the recommended folic acid supplementation in early pregnancy on development of asthma in the offspring by the age of 6 years. However, further studies are needed to assess both the risk at doses higher than 800 mcg in early pregnancy as well as the risk, at all doses, of folic acid supplementation in the second and third trimesters.

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References

1. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet. 1991; 338:131–7. [PubMed: 1677062]
2. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992; 327:1832–5. [PubMed: 1307234]
3. Centers for Disease Control and Prevention. Knowledge and use of folic acid by women of childbearing age--United States, 1997. MMWR Morb Mortal Wkly Rep. 1997; 46:721–3. [PubMed: 9262072]
4. Jacques PF, Selhub J, Bostom AG, Wilson PW, Rosenberg IH. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. N Engl J Med. 1999; 340:1449–54. [PubMed: 10320382]
5. Lawrence JM, Petitti DB, Watkins M, Umekubo MA. Trends in serum folate after food fortification. Lancet. 1999; 354:915–6. [PubMed: 10489953]
6. Hertrampf E, Cortes F, Erickson JD, et al. Consumption of folic acid-fortified bread improves folate status in women of reproductive age in Chile. J Nutr. 2003; 133:3166–9. [PubMed: 14519804]
7. Williams LJ, Mai CT, Edmonds LD, et al. Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. Teratology. 2002; 66:33–9. [PubMed: 12115778]
8. De Wals P, Tairou F, Van Allen MI, et al. Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med. 2007; 357:135–42. [PubMed: 17625125]
9. Lopez-Camelo JS, Orioli IM, da Graca Dutra M, et al. Reduction of birth prevalence rates of neural tube defects after folic acid fortification in Chile. Am J Med Genet A. 2005; 135:120–5. [PubMed: 15846825]
10. Berry RJ, Li Z, Erickson JD, et al. Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. N Engl J Med. 1999; 341:1485–90. [PubMed: 10559448]
11. Bower C, D'Antoine H, Stanley FJ. Neural tube defects in Australia: trends in encephaloceles and other neural tube defects before and after promotion of folic acid supplementation and voluntary food fortification. Birth Defects Res A Clin Mol Teratol. 2009; 85:269–73. [PubMed: 19180646]
12. Beaudin AE, Stover PJ. Insights into metabolic mechanisms underlying folate-responsive neural tube defects: a minireview. Birth Defects Res A Clin Mol Teratol. 2009; 85:274–84. [PubMed: 19180567]
13. Burdge GC, Lillycrop KA. Nutrition, epigenetics, and developmental plasticity: implications for understanding human disease. Annu Rev Nutr. 2010; 30:315–39. [PubMed: 20415585]
14. Lillycrop KA, Phillips ES, Torrens C, Hanson MA, Jackson AA, BURDGE GC. Feeding pregnant rats a protein-restricted diet persistently alters the methylation of specific cytosines in the hepatic PPAR alpha promoter of the offspring. Br J Nutr. 2008; 100:278–82. [PubMed: 18186951]
15. Shin HJ, Park HY, Jeong SJ, et al. STAT4 expression in human T cells is regulated by DNA methylation but not by promoter polymorphism. J Immunol. 2005; 175:7143–50. [PubMed: 16301617]
16. Hollingsworth JW, Maruoka S, Boon K, et al. In utero supplementation with methyl donors enhances allergic airway disease in mice. J Clin Invest. 2008; 118:3462–9. [PubMed: 18802477]
17. Haberg SE, London SJ, Stigum H, Nafstad P, Nystad W. Folic acid supplements in pregnancy and early childhood respiratory health. Arch Dis Child. 2009; 94:180–4. [PubMed: 19052032]
18. Whitrow MJ, Moore VM, Rumbold AR, Davies MJ. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. Am J Epidemiol. 2009; 170:1486–93. [PubMed: 19880541]

19. Bracken MB, Triche EW, Belanger K, Saftlas A, Beckett WS, Leaderer BP. Asthma symptoms, severity, and drug therapy: a prospective study of effects on 2205 pregnancies. Obstet Gynecol. 2003; 102:739–52. [PubMed: 14551004]

20. Hoag SW, Ramachandruni H, Shangraw RF. Failure of prescription prenatal vitamin products to meet USP standards for folic acid dissolution. J Am Pharm Assoc (Wash). 1997; NS37:397–400. [PubMed: 9519649]

21. Risnes KR, Belanger K, Murk W, Bracken MB. Antibiotic exposure by 6 months and asthma and allergy at 6 years: findings in a cohort of 1,401 US children. Am J Epidemiol. 2011; 173:310–318. [PubMed: 21190986]

22. Wilcox AJ, Lie RT, Solvoll K, et al. Folic acid supplements and risk of facial clefts: national population based case-control study. BMJ. 2007; 334:464. [PubMed: 17259187]

23. Geha RS, Jabara HH, Brodeur SR. The regulation of immunoglobulin E class-switch recombination. Nat Rev Immunol. 2003; 3:721–32. [PubMed: 12949496]

24. Shaw GM, Zhu H, Lammer EJ, Yang W, Finnell RH. Genetic variation of infant reduced folate carrier (A80G) and risk of orofacial and conotruncal heart defects. Am J Epidemiol. 2003; 158:747–52. [PubMed: 14561664]

25. Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. Lancet. 2001; 358:2069–73. [PubMed: 11755633]

Table 1

Folic acid supplementation use during first trimester of pregnancy in the PRAM study, Connecticut, USA by characteristics of study population (n=1499).

Characteristics	*n*	*Proportion (%)*	*Folic acid Intake per day, month before pregnancy Mean (mcg) (SD)*	*Folic acid Intake per day in first trimester Mean(mcg) (SD)*
All Participants	1499	100	304 (367)	497 (301)
Maternal age (years)				
<25	341	22.75	66 (200)	280 (257)
25-35	884	58.97	364 (365)[a]	548 (272)[a]
>35	274	18.28	405 (407)[a]	603 (311)[a, b]
Maternal ethnicity				
White	1086	72.45	375 (373)[a]	565 (277)[a]
African American	144	9.61	105 (286)	318 (299)
Hispanic	209	13.94	90 (222)	294 (260)
Asian/other	60	4.00	222 (363)	394 (333)
Maternal education				
Less than or equal 12 years	418	27.89	111 (246)	317 (267)
At least some College	735	49.03	338 (368)[a]	542 (283)[a]
At least some graduate school	346	23.08	463 (388)[a, b]	619 (279)[a, b]
Household income ($)				
> 40 000	1061	70.78	368 (365)[a]	558 (273)[a]
<= 40 000	390	26.02	107 (281)	317 (229)
Do not know	48	3.20	467 (440)[a]	604 (344)[a]
Maternal marital status				
Married	1093	72.92	388 (375)[a]	572 (279)[a]
Single/divorced	406	28.08	76 (220)	294 (262)
Smoking				
Never	917	61.17	345 (375)[a]	523 (297)[a]
Quit before becoming pregnant	315	21.01	351 (386)[a]	543 (322)[a]
1st trimester	173	11.54	104 (227)	353 (241)
Throughout pregnancy	94	6.27	107 (223)	346 (236)
Mothers diagnosed with asthma				
Yes	828	55.24	323 (369)[a]	510 (299)[a]
No	671	44.76	279 (363)	481 (302)
Parity				
0	670	44.70	324 (376)[a]	518 (299)[a]
1	516	34.42	317 (367)[a]	500 (295)[a]
≥2	313	20.88	238 (341)	445 (308)
Also vitamins C, D, E				

Characteristics	***n***	***Proportion (%)***	***Folic acid Intake per day, month before pregnancy Mean (mcg) (SD)***	***Folic acid Intake per day in first trimester Mean(mcg) (SD)***
No	1316	87.79	286 (363)	480 (299)
Yes	183	12.21	431 (371)[a]	618 (284)[a]
Iron use				
No	1374	91.66	299 (357)	491 (290)
Yes	125	8.34	348 (459)	559 (399)
Calcium use				
No	1334	88.99	278 (352)	475 (294)
Yes	165	11.01	509 (417)[a]	674 (298)[a]

[a] P<0.05 vs. the lower number within each category,

[b] P<0.05 vs. the second lowest number within each category

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Table 2

Daily Supplementation of Folic acid in the PRAM study (Connecticut, USA): month before conception through 3rd month of pregnancy.

	Folic acid **Mean (SD)**	***N***	***% of total group***	***Asthma at 6 years***	
				(n=223)	**(14.9%)**
Month before conception					
Folic acid (mcg)	303 (367)	768	51.2	92	6.1
No use		731	48.8	131	8.7
<400		89	5.9	15	1
400-800		625	41.7	70	4.7
>800		54	3.6	7	0.5
First month of pregnancy					
Folic acid (mcg)	402 (402)	913	60.9	112	7.5
No use		586	39.1	111	7.4
<400		87	5.8	16	1.1
400-800		746	49.8	86	5.7
>800		80	5.3	10	0.7
Second month of pregnancy					
Folic acid (mcg)	605 (390)	1218	81.3	174	11.6
No use		281	18.8	49	3.3
<400		92	6.1	11	0.7
400-800		1009	67.3	152	10.1
>800		117	7.8	11	0.7
Third month of pregnancy					
Folic acid (mcg)	676 (349)	1288	88.4	187	12.5
No use		191	12.7	36	2.4
<400		69	4.6	11	0.7
400-800		1144	76.3	165	11
>800		95	6.3	11	0.7
First trimester					

	Folic acid **Mean (SD)**	*N*	*% of total group*	*Asthma at 6 years*	
				(n=223)	**(14.9%)**
Folic acid (mcg)	497 (301)	1381	92.1	202	13.5
No		118	7.9	21	1.4
<400		342	22.8	65	4.3
400-800		953	63.6	130	8.7
>800		86	5.7	7	0.1

Table 3

Association between Folic Acid supplementation one to three months before conception, during first trimester of pregnancy and asthma in offspring at six years of age (n = 1499).

Folic Acid Supplementation	Unadjusted		Adjusted[a]	
(OR associated with use versus non-use)	OR	95% CI	OR	95% CI
Month before conception	0.62	0.47-0.83	0.95	0.68-1.32
First Month	0.60	0.45-0.80	0.89	0.69-1.23
Second month	0.79	0.56-1.11	1.31	0.89-1.93
Third month	0.72	0.48-1.07	0.94	0.62-1.43
First trimester	0.79	0.48-1.30	1.23	0.73-2.07

[a]Adjusted for household annual income (40 000 USD <vs.>40 000 USD), maternal marital status (married vs not married) and physician diagnosed maternal asthma (yes/no).

Table 4

Association between Folic Acid supplementation (per 100 mcg increase in average daily intake) one month before conception, during first trimester of pregnancy and asthma in the offspring at six years of age (n = 1499).

Folic Acid Supplementation	Unadjusted		Adjusted[a]	
(per 100mcg increase in daily intake)	OR	95% CI	OR	95% CI
Month before conception	0.93	0.89-.097	0.98	0.94-1.03
First Month	0.94	0.90-0.97	0.98	0.94-1.02
Second month	0.96	0.92-1.00	0.99	0.95-1.03
Third month	0.96	0.92-1.00	0.99	0.95-1.03
First trimester	0.92	0.87-0.97	0.98	0.93-1.04

[a] Adjusted for household annual income (40 000 USD <vs.>40 000 USD), maternal marital status (married vs not married) and physician diagnosed maternal asthma (yes/no).

Table 5

Association between Amount of Folic Acid Supplementation One Month Before Conception and During First Trimester of Pregnancy, and Asthma in the Offspring at Six Years of Age. Results are presented as Odds Ratio (OR) with 95% Confidence Intervals (95% CI) and p for trend

		Unadjusted			Adjusted[a]		
Folic Acid Use	**n**	**OR**	**95% CI**	**P trend**	**OR**	**95% CI**	**P trend**
Month before Conception							
No use	731	Ref			Ref		
<400 mcg	89	0.93	0.52-1.67		1.29	0.70-2.40	
400-800 mcg	625	0.58	0.42-0.79		0.89	0.62-1.27	
>800 mcg	54	0.68	0.30-1.54	0.001	1.02	0.44-2.40	0.70
Month 1 of pregnancy							
No use	586	Ref			Ref		
<400 mcg	87	0.96	0.54-1.72		1.31	0.71-2.41	
400-800 mcg	746	0.56	0.41-0.76		0.82	0.58-1.17	
>800 mcg	80	0.61	0.31-1.22	<0.001	0.94	0.46-1.97	0.33
Month 2 of pregnancy							
No use	281	Ref			Ref		
<400 mcg	92	0.64	0.32-1.30		1.03	0.49-2.14	
400-800 mcg	1009	0.84	0.59-1.20		1.45	0.97-2.16	
>800 mcg	117	0.49	0.25-0.98	0.13	0.88	0.42-1.82	0.30
Month 3 of pregnancy							
No use	191	Ref			Ref		
<400 mcg	69	0.82	0.39-1.71		0.80	0.37-1.72	
400-800 mcg	1144	0.73	0.49-1.08		0.96	0.63-1.47	
>800 mcg	95	0.56	0.27-1.16	0.07	0.79	0.37-1.68	0.77
First trimester overall							
No use	118	Ref			Ref		
<400	342	1.08	0.63-1.87		1.34	0.76-2.35	
400-800	953	0.73	0.44-1.21		1.18	0.68-2.04	
>800	86	0.41	0.17-1.01	0.006	0.73	0.28-1.87	0.70

[a] Adjusted for household annual income (40 000 USD <vs.>=40 000 USD), maternal marital status (married vs not married) and physician diagnosed maternal asthma (yes/no).

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