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Original Contribution

Effect of Supplemental Folic Acid in Pregnancy on Childhood Asthma: A Prospective Birth Cohort Study

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This study aimed to investigate the effect of the timing, dose, and source of folate during pregnancy on childhood asthma by using data from an Australian prospective birth cohort study ($n = 557$) from 1998 to 2005. At 3.5 years and 5.5 years, 490 and 423 mothers and children participated in the study, respectively. Maternal folate intake from diet and supplements was assessed by food frequency questionnaire in early (<16 weeks) and late (30–34 weeks) pregnancy. The primary outcome was physician-diagnosed asthma, obtained by maternal-completed questionnaire. Asthma was reported in 11.6% of children at 3.5 years ($n = 57$) and in 11.8% of children at 5.5 years ($n = 50$). Folic acid taken in supplement form in late pregnancy was associated with an increased risk of childhood asthma at 3.5 years (relative risk (RR) = 1.26, 95% confidence interval (CI): 1.08, 1.43) and with persistent asthma (RR = 1.32, 95% CI: 1.03, 1.69). The effect sizes did not change with adjustment for potential confounders. The association was similar at 5.5 years but did not reach statistical significance (RR = 1.17, 95% CI: 0.96, 1.42) in univariable models. These findings on childhood asthma support previous observations that supplementation with folate in pregnancy leads to an allergic asthma phenotype in mice via epigenetic mechanisms and is associated with poorer respiratory outcomes in young children.

asthma; child, preschool; folic acid; methylation; pregnancy

Abbreviations: CI, confidence interval; IgE, immunoglobulin E; RR, relative risk.

Current public health guidelines in the United States, the United Kingdom, and Australia recommend that women consume a supplemental dose of 400 μg of folic acid per day in the month preceding and during the first trimester of pregnancy (1–3) to reduce the risk of neural tube defects in children (4). However, the status of folate supplementation as unequivocally beneficial due to the preventive effect on neural tube defects has been challenged by recent studies in mice (5) and infants (6), demonstrating an adverse effect of supplemental folic acid intake during pregnancy on respiratory health in early life.

It is recognized that folic acid supplements are a potent source of methyl donors, which can induce epigenetic changes by altering the status of methylation-sensitive, DNA-binding proteins (7). This model has recently been applied in mice to demonstrate the impact of folate-induced DNA changes affecting the expression of T-helper type 2 (Th2) cytokines during fetal development, in turn altering the inflammatory response and thus risk of allergic airways disease in the offspring (5). Application of these findings to human studies has begun, with a large study of asthma symptoms in 32,077 children in Norway demonstrating that a history of folic acid supplementation in pregnancy was related to wheeze and lower respiratory tract infections (6). Håberg et al. (6) observed a small significant increase in wheeze at 6–18 months with folic acid supplementation dichotomized (yes/no) in early but not late pregnancy (relative risk (RR) = 1.06, 95% confidence interval (CI): 1.03, 1.10). A limitation of this study is that wheeze up to 18 months may be transient and is not as detrimental to long-term lung function as wheeze/asthma that persists up to 5 years (8).

To our knowledge, no previous study has reported the simultaneous effect of the *timing, dose, and source* of

maternal folic acid (synthetic supplement form) and folate (natural dietary form) during pregnancy on childhood asthma. The aim of this study is to examine data from a prospective pregnancy cohort study for any association between the dose and timing of maternal folic acid and folate intake during pregnancy and asthma status at the ages of 3.5 and 5.5 years.

MATERIALS AND METHODS

Sample and study design

The Generation 1 Cohort Study is a prospective longitudinal study of women and their children recruited in the first 16 weeks of pregnancy in 1998–2000 (prior to folic acid fortification of food in Australia) from 4 antenatal clinics in Adelaide, South Australia. The study was specifically designed to assess the role of maternal diet in pregnancy on growth to birth and postnatal development. Of the 605 women recruited, 557 (92%) completed the pregnancy phase of the study and had a live singleton baby. Participating women were similar to all women having children in South Australia in 1998–2000 for a range of social indicators (i.e., age, educational attainment, employment status, household income, relationship status, and family size) (9).

Mothers were interviewed by a research nurse in early (<16 weeks) and late (30–34 weeks) pregnancy on their personal circumstances and health, including diet, using a structured food frequency questionnaire (9) and inventory of supplement use. Mothers and children had follow-up interviews with a structured protocol during the child's infancy (6, 9, 12 months), at 2 years, and at 3.5 years and by maternal-completed postal questionnaire at 5.5 years. Questionnaires requested detailed information on the child's and mother's health, family circumstances, and health behaviors. This study was conducted according to the principles expressed in the Declaration of Helsinki. Ethics approval from The University of Adelaide Human Research Ethics Committee was obtained.

Outcome measures

Mothers were asked 2 questions on their child's asthma status at 3.5 years (''Has your child been diagnosed with asthma?'' and ''Who made the diagnosis?'') and at 5.5 years (''Have you ever been told by a doctor that the child has asthma?'' and ''Does the child have asthma now?''). Asthma was affirmed at each age if it had been diagnosed by a physician and, at 5.5 years, the child currently had asthma. Persistent asthma was affirmed if the child had asthma at both 3.5 years and 5.5 years. In the absence of skin prick or blood test for atopy, asthma was defined as atopic if accompanied by one or more physician-diagnosed allergies (skin including eczema, food, drug, or hay fever) at 3.5 years only (atopy questions not asked at 5.5 years).

Exposure variables

Dietary folate. A maternal dietary food frequency questionnaire was administered in early and late pregnancy by a trained research nurse. The interviewer proceeded through a list of 197 foods, asking if the woman ate each food, and if so, how often and how much. Food models and photographs were used to assist in estimating serving sizes. Details of the development and validation of this instrument have been published elsewhere (9). Daily dietary intake of folate was calculated from the food frequency data by using a database of the nutritional content of common foods (NUTTAB91-92) (10).

Supplemental folic acid. Mothers reported retrospective consumption of folic acid supplements before pregnancy (yes/no). Mothers reported detailed (brand, dose, frequency) concurrent use of any supplements at both the early and late pregnancy interviews. Reported supplement intake (brand, dose, frequency) in early and late pregnancy was converted into daily intake (μg/day) of folic acid for early and late pregnancy by using dosage information provided on the package. When mothers did not report a specific brand of pregnancy supplement, they were assigned the average folic acid from the 3 available brands.

Confounder measurement

Potential confounders were included if there was evidence for an association between them and maternal folate intake or childhood asthma. This was often due to a shared association between the confounder, folate, and asthma and socioeconomic status. Information on potential confounding factors was taken from the pregnancy questionnaire, from the antenatal records, and from the 12-month interview. The potential confounders considered were maternal education; maternal smoking; maternal intake of vitamin E, vitamin A, vitamin D, and zinc (assessed as per method for dietary and supplemental folate above, supplement only for vitamin D); gestational age; parity; gravida; breastfeeding duration; and maternal asthma (mothers provided information on their own current asthma and medication during pregnancy and at all subsequent interviews. In addition, the experience of past asthma was explicitly obtained at 12 months).

Statistical analysis

Initial analyses examining differences in exposures in children included in the sample and those who did not provide information at 3.5 years or 5.5 years were assessed by using a t test (for normally distributed continuous variables), a Wilcoxon rank sum test (nonnormal continuous variables), and a chi-squared or Fisher's exact test (categorical data).

The association between maternal folic acid and folate intake (assessed as continuous variables) at each of the 4 time points (pre-, early, late, and early + late pregnancy) and each asthma outcome (3.5 years, 5.5 years, persistent) was investigated by using a Poisson regression model. In early and late pregnancy, folic acid and folate were initially included in the models as separate continuous variables because of their different bioavailability (11). Models were then rerun with the sum of folic acid and folate (continuous variable).

Models were built with the following: 1) prepregnancy folic acid as a binary exposure variable; 2) early pregnancy

folic acid and folate; 3) late pregnancy folic acid and folate; and 4) early and late pregnancy folic acid and folate. Each model was then repeated with adjustment for potential confounders as follows: all models (maternal age, maternal education, maternal asthma status, parity, gravida, gestational age, and breastfeeding duration); models 1 and 2 (early pregnancy maternal cigarette smoking and intakes of vitamins A, D, and E (all μg/day) and zinc (mg/day)); model 3 (late pregnancy maternal cigarette smoking and intakes of vitamins A, D, and E (all μg/day) and zinc (mg/day)); and model 4 (the confounders listed for models 2 and 3). Each model was then repeated as a multinomial logistic regression model with atopic asthma status at 3.5 years (no asthma, nonatopic asthma, atopic asthma) as the outcome variable.

Potential interactions between folate and maternal cigarette smoking, maternal asthma, parity, and the child's sex were identified in advance and tested in each model. Results are presented where significant at $P < 0.05$. Sensitivity analyses included rerunning the asthma at 3.5 years model by using the smaller 5.5-year sample size (i.e., excluding those children and women who did not complete the interview at 5.5 years). Analyses were also rerun assuming all maternal asthma missing at the 12-month interview ($n = 42$) was positive and then negative. As the latter analysis did not alter the association between folate and childhood asthma, a complete case analysis is presented here. All analyses were run in SAS statistical software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

At 3.5 years 490 (range, 3.4–3.8 years) and at 5.5 years 423 (range, 5.4–6.3 years) mothers and children (88% and 76% of the original sample, respectively) participated in the study and did not have missing data for maternal folate intake or confounder variables. Table 1 shows the maternal characteristics for children who met the inclusion criteria at the end of the pregnancy phase and when the child was aged 3.5 years and 5.5 years. Mothers of children not participating at 3.5 years were younger and less likely to have breastfed for ≥3 months than those who completed the pregnancy phase of the study ($P < 0.05$). Mothers of children not participating at 5.5 years were younger, less likely to take a prepregnancy folic acid supplement, less educated, more likely to smoke during early and late pregnancy, and more likely to report a history of asthma than those who completed the pregnancy phase of the study ($P < 0.05$). Doses of vitamins A, D, and E and zinc did not differ significantly by participation status (data not shown), with the exception of vitamin A in early pregnancy (1,180 (standard deviation, 627) μg/day in the pregnancy phase sample vs. 1,145 (standard deviation, 570) μg/day in the 5.5-year sample).

Asthma was reported in 11.6% of children at 3.5 years and in 11.8% of children at 5.5 years. Thirty children (7%) reported persistent asthma (at both 3.5 and 5.5 years). Maternal use of folic acid varied throughout pregnancy (Table 2), with one quarter of mothers not taking a supplement at any stage of pregnancy. The type of supplement and dosage also varied. In early pregnancy, mothers were more likely to take folic acid as a standalone supplement than in late pregnancy (31% vs. 9%). Standalone supplements contained a higher dose of folic acid than did multivitamins; that is, in early pregnancy, the median intake of folic acid from standalone supplement was 2,948 μg/day compared with 500 μg/day in a multivitamin. This is likely to have provided the higher early pregnancy daily intake of folic acid seen in Table 1.

Supplemental folic acid in late pregnancy was associated with an increased risk of both asthma at 3.5 years and persistent asthma (Table 3), which was robust to adjustment for potential confounders, including the addition of early pregnancy folate and folic acid to the model. The association was somewhat attenuated and not statistically significant at 5.5 years. Folic acid supplements taken in pre- or early pregnancy were not associated with asthma at any age. Dietary folate was not associated with asthma in either age group at any stage of pregnancy. When the sum of dietary folate and folic acid intake was included in the model, the results were the same as those for folic acid supplement alone (Table 3). This is likely to be due to the high contribution of supplemental folic acid to the total daily intake (84% in early and 63% in late pregnancy).

When the analysis was repeated with atopic and nonatopic asthma in separate categories (data not shown), the effect size for each was similar to that seen for overall asthma (Table 3). However, the association between maternal folic acid in late pregnancy and atopic asthma at 3.5 years was not significant (ratio of probabilities for late pregnancy supplement, 1.26; 95% CI: 0.99, 1.61).

With asthma at 3.5 years as the outcome, there was only one significant interaction. For every 100-μg increase in dietary folate in *early* pregnancy, the relative risk of asthma for the child at 3.5 years decreased by 43% if the mother had asthma ($RR_{interaction} = 0.57$; $P = 0.04$). For child asthma at 5.5 years, significant interactions were found. For a 100-μg unit increase in dietary folate in *early* pregnancy, the relative risk of the child's having asthma at 5.5 years increased by 77% if the mother smoked during early pregnancy ($RR_{interaction} = 1.77$; $P = 0.01$). For every 1,000-μg increase in folic acid in *late* pregnancy, the relative risk of the child's having asthma at 5.5 years more than doubled if the mother had a previous child ($RR_{interaction} = 2.20$; $P = 0.03$). For every 1,000-μg increase in folic acid in *late* pregnancy, the relative risk of the child's having asthma at 5.5 years decreased by 37% if the mother had asthma ($RR_{interaction} = 0.63$; $P = 0.03$).

The 3.5-year analysis was repeated by using the smaller 5.5-year sample size ($n = 423$). Effect sizes were slightly attenuated, and confidence intervals widened. There were no changes to the significance of results, other than the coefficients for folic acid in late pregnancy in the unadjusted models lost significance.

DISCUSSION

We believe that this is the first published study in humans to demonstrate that increasing consumption of folic acid, and specifically supplemental folate during late pregnancy,

Table 1. Maternal Characteristics of Children Included in the Sample at 3.5 Years and 5.5 Years in the Generation 1 Cohort Study, Adelaide, Australia, 1998–2005

Characteristic	Sample at Completion of Pregnancy Phase ($n = 557$)				Sample at 3.5 Years ($n = 490$)				Sample at 5.5 Years ($n = 423$)			
	No.	%	Mean (SD)	Median (Range)	No.	%	Mean (SD)	Median (Range)	No.	%	Mean (SD)	Median (Range)
Folate												
Prepregnancy supplement taken	237	42.6			216	44.1			199	47.0[a]		
Early pregnancy supplement taken	316	56.8			280	57.1			245	57.9		
Early pregnancy supplement, μg/day				658.3 (42.9–5,500.0)				700.0 (42.9–5,500.0)				666.6 (42.9–5,500.0)
Early pregnancy dietary, μg/day			224.7 (105.3)				224.9 (105.9)				224.3 (103.5)	
Late pregnancy supplement taken	211	38.0			187	38.2			164	38.8		
Late pregnancy supplement, μg/day				300.0 (27.4–5,895.4)				300.0 (27.4–5,895.4)				300.0 (27.4–5,895.4)
Late pregnancy dietary, μg/day			208.4 (88.4)				208.4 (88.0)				210.4 (85.3)	
Education												
Partial high school	188	33.8			162	33.1			120	28.4[a]		
Completed high school	98	17.6			86	17.6			76	18.0		
High school + technical college	86	15.4			78	15.9			74	17.5		
High school + university degree	99	17.8			90	18.4			86	20.3		
No high school + technical college or university	86	15.4			74	15.1			67	15.8		
Cigarette smoking												
Smoked early pregnancy	110	19.8			93	19.0			66	15.6[a]		
Smoked late pregnancy	110	19.8			92	18.8			62	14.7[a]		
Pregnancy												
Maternal age at child's birth, years			29.8 (5.0)				30.0 (5.0)[a]				30.5 (4.9)[a]	
Parity (≥1 previous child)	370	66.4			327	66.7			277	65.5		
Gravida (≥1 previous pregnancy)	415	74.5			366	74.7			310	73.3		
Gestational age, weeks			39.4 (1.6)				39.4 (1.6)				39.5 (1.5)	
Breastfeeding												
Partial or full for <12 weeks	259	46.7			221	45.1[a]			188	44.4		
Partial or full for ≥12 weeks	296	53.3			269	54.9			235	55.6		
Maternal asthma												
Any asthma during lifetime	144	27.5			133	27.1			106	25.1[a]		

Abbreviation: SD, standard deviation.

[a] The characteristic is significantly different ($P < 0.05$) between participants and those with missing data at 3.5 years or 5.5 years.

Table 2. Maternal Use of Folic Acid Supplements at Each Stage of Pregnancy in the Generation 1 Cohort Study, Adelaide, Australia, 1998–2005

Timing of Folic Acid Supplementation	Total (n = 490)	
	No.	%
Prepregnancy only	35	7.1
Prepregnancy + early pregnancy	84	17.1
Prepregnancy + late pregnancy	21	4.3
Prepregnancy + early pregnancy + late pregnancy	76	15.6
Early pregnancy only	60	12.2
Early pregnancy + late pregnancy	60	12.2
Late pregnancy only	30	6.1
Supplement never taken	76	15.5

significantly increases the risk of physician-diagnosed asthma in the child at 3.5 years, persistent asthma (at 3.5 and 5.5 years), and possibly asthma at 5.5 years. This observed effect persists after adjustment for potential confounding factors (including early pregnancy intake) and was similar when looking at combined folate and folic acid intake, probably because of the small contribution of dietary folate to total daily intake. In this study, we observe the clinical outcomes suggested by Hollingsworth et al. (5), where they concluded that the increased prevalence of allergic asthma in humans may in part be related to increased perinatal dietary supplementation with methyl donors.

The only previous human study of asthma and folic acid in a cohort of infants found a small increase in risk of wheeze at 18 months associated with maternal folic acid supplementation commencing in early pregnancy (<12 weeks) (6). The overall effect was weaker when including those women who supplemented folate throughout pregnancy, rather than stopping after week 12. We found no increased risk associated with supplement use in early pregnancy. There are a number of potential reasons for this. The study by Håberg et al. (6) was limited by its short follow-up time (18 months), so it is possible that we are observing an overlapping but potentially different phenomenon across studies. Asthma presents as a number of different phenotypes (8) with potentially different etiologies. Early asthma and wheeze (<2 years) is often transient, subsiding later in childhood. Asthma that persists beyond 2 years is likely to result in the greatest detriment to lung function (8) and, hence, is of greater public health importance. A further limitation of the study by Håberg et al. (6) is their use of a relatively simple measure of folic acid supplement (yes/no, without dosage) that may not have been sensitive enough to detect a late pregnancy effect.

The timing of the effect of folic acid supplementation seen in our study may give insight into the biologic pathway involved. Our observation of an effect after the first trimester coincides with the development of the fetal immune system and the period during which there is a rise in fetal exposure to immunoglobulin E (IgE) and fetal IgE receptor activity (12). IgE is stimulated by Th2 cytokines. Although there are detectable levels of IgE in amniotic fluid during early gestation, the concentration increases during gestation to correlate significantly with maternal IgE concentrations during the second trimester, which is accompanied by the dramatic rise in IgE receptor activity in the fetus during weeks 16–20 (12). This raises the prospect that there is a potentially important window during which dosages may be manipulated to optimize the neuroprotective effects of supplemental folic acid while attempting not to increase the risk of asthma. Mothers' daily intake of folic acid was considerably greater in early compared with late pregnancy, mostly because of the greater tendency for mothers to take a standalone folic acid supplement in early pregnancy compared with late (when multivitamins were commonly taken). This is consistent with an important timing effect of exposure for the outcome of asthma. We did not find any correlation between folic acid and the other vitamins and minerals included in the models; however, we cannot exclude the possibility that the association we have seen in late pregnancy is due to another component of the multivitamins consumed.

We found an effect of folic acid when taken in supplement (synthetic) form but not when sourced from diet. A plausible explanation for this is the difference in bioavailability between folate forms; the polyglutamate form in foods has a lower bioavailability than the monoglutamate form in supplements (13). Furthermore, at levels of recommended supplementation (400 μg), the entire synthetic folic acid analog is converted into biologically active methyl-H_4 folate during absorption. Above this dose, synthetic polyglutamate appears in an unmodified form in the blood (13). Intake above the recommended level of folic acid would likely lead to repeated appearance of unmetabolized folic acid in fetal and maternal circulation, particularly in countries with fortification of food (14). The impact of this unmodified folate analog is uncertain. However, it would appear to indicate that there is a surfeit of folate to act as methyl donors for the regulation of gene expression.

The strengths of this study are its rigorous prospective exposure measurement and its timing; mothers were recruited prior to the introduction of voluntary folic acid fortification of food in Australia. Our study has the limitation that 76% of the original sample provided complete information at the 5.5-year assessment, when we found that the effect of late pregnancy folic acid supplements on asthma was associated with a modest and statistically insignificant increase in risk. However, we observed a similar attenuation of the effect size and widening of confidence intervals when the 3.5-year analyses were restricted to data available only in the smaller 5.5-year sample. Our observed effects may therefore be conservative estimates. It is unclear why we observed significant interactions between folic acid and maternal smoking, parity, and maternal asthma status and childhood asthma at 5.5 years but only for maternal asthma status at 3.5 years. It is possible that our assessment of asthma measured by postal questionnaire at 5.5 years was not as reliable as it was when measured by a structured interview. It may, however, also indicate the importance of both prenatal and prolonged postnatal exposures on asthma risk. We did not collect information on current child supplement use. It is unlikely that Generation 1 children consumed high levels of supplements, as a previous study

Table 3. Association of Maternal Folate Intake During Pregnancy and Asthma in Children Aged 3.5 Years or 5.5 Years in the Generation 1 Cohort Study, Adelaide, Australia, 1998–2005

	Asthma at 3.5 Years (n = 490)				Asthma at 5.5 Years (n = 423)				Persistent Asthma (at 3.5 Years and 5.5 Years) Versus No Asthma (n = 412)			
	Relative Risk	95% Confidence Interval	Adjusted Relative Risk[a]	95% Confidence Interval	Relative Risk	95% Confidence Interval	Adjusted Relative Risk[a]	95% Confidence Interval	Relative Risk	95% Confidence Interval	Adjusted Relative Risk[a]	95% Confidence Interval
Prepregnancy												
Supplement (no = 1.00)	0.92	0.56, 1.51	1.22	0.70, 2.15	0.96	0.57, 1.62	1.00	0.59, 1.72	1.10	0.55, 2.20	1.16	0.55, 2.46
Early pregnancy[b]												
Diet (100 μg/day)	1.14	0.93, 1.41	1.09	0.78, 1.51	1.03	0.74, 1.44	0.97	0.63, 1.50	1.10	0.70, 1.71	1.00	0.56, 1.79
Supplement, mg/day	0.92	0.78, 1.07	0.92	0.79, 1.08	0.90	0.74, 1.08	0.92	0.77, 1.10	0.86	0.67, 1.11	0.88	0.67, 1.14
Diet + supplement, mg/day	0.92	0.79, 1.08	0.93	0.97, 1.08	0.90	0.75, 1.08	0.92	0.77, 1.11	0.87	0.68, 1.12	0.88	0.67, 1.15
Late pregnancy[b]												
Diet (100 μg/day)	0.97	0.71, 1.32	1.03	0.66, 1.60	0.85	0.62, 1.18	0.86	0.57, 1.28	0.87	0.55, 1.37	0.83	0.46, 1.49
Supplement, mg/day	1.23*	1.07, 1.43	1.26*	1.09, 1.47	1.15	0.95, 1.40	1.16	0.94, 1.43	1.22	0.96, 1.56	1.32*	1.03, 1.69
Diet + supplement, mg/day	1.23*	1.06, 1.42	1.26*	1.09, 1.47	1.14	0.84, 1.40	1.16	0.94, 1.43	1.21	0.95, 1.55	1.32*	1.02, 1.69
Early and late pregnancy, combined model[c]												
Early diet (100 μg/day)	1.23	0.99, 1.54	1.15	0.82, 1.61	1.18	0.85, 1.63	1.08	0.72, 1.60	1.27	0.83, 1.93	1.19	0.73, 1.94
Early supplement, mg/day	0.87	0.74, 1.03	0.88	0.74, 1.05	0.88	0.73, 1.06	0.90	0.74, 1.10	0.84	0.65, 1.07	0.83	0.61, 1.14
Late diet (100 μg/day)	0.80	0.55, 1.15	0.94	0.63, 1.40	0.75	0.52, 1.09	0.80	0.51, 1.24	0.70	0.43, 1.15	0.71	0.38, 1.35
Late supplement, mg/day	1.27*	1.10, 1.47	1.32*	1.14, 1.53	1.18	0.97, 1.43	1.18	0.96, 1.45	1.25	0.99, 1.58	1.38*	1.06, 1.79

* $P < 0.05$.

[a] All models adjusted for "a" (maternal education, maternal age, parity, gravida, gestational age, maternal asthma status, and breastfeeding (partial or full for <3 months)). Pre- and early pregnancy models adjusted for "a" and vitamin A, vitamin E, vitamin D, zinc from diet and supplements in early pregnancy, and maternal smoking during early pregnancy. Late pregnancy model adjusted for "a" and vitamin A, vitamin E, vitamin D, zinc from diet and supplements in late pregnancy, and maternal smoking during late pregnancy. Early and late pregnancy combined model adjusted for all the potential confounders listed above.

[b] Diet and supplement folate included in the same model as continuous variables.

[c] Diet and supplement folate intake in early and late pregnancy included in the same model as continuous variables.

within this sample found that the majority (76.4%) of parents did not believe children under 12 months needed supplements (15), and data from the Australian Bureau of Statistics indicate that a low proportion of Australian children consumed a supplement in 2006 (9.6% of children aged 2–3 years and 9.8% of children aged 4–8 years) (16).

Because of time constraints during the study interviews, it was not feasible to ask parents the suite of questions on asthma symptom occurrence and timing as recommended by the International Asthma and Allergy in Childhood (ISAAC) Study (17). In our study, asthma was determined by parental report of a diagnosis that was made by a physician, similar to the approach taken in other research studies (18) and national health surveys (19). The objective measurement of asthma and its severity is an important matter for subsequent studies. Our prevalence estimates for the sample are similar to those reported in the Australian National Health Survey undertaken in a similar time period (0–4 years, 12.3% boys, 10.1% girls) (19). We urge caution on the interpretation of the findings in relation to atopy, which was not assessed at 5.5 years and was measured at 3.5 years by using indicators of allergy rather than by an objective measure, such as a skin prick or blood test. It would have been advantageous to investigate other asthma phenotypes (e.g., early and late onset wheeze); however, that was beyond the scope of this study.

Our findings related to timing and sources of folate in pregnancy have important implications for recommendations about optimal folate intake in pregnancy. Current recommendations worldwide advocate a daily intake of around 400 μg of folic acid prior to pregnancy and in the first trimester for the prevention of neural tube defects (4). Nearly half (48.5%) of mothers in this study took a supplement prepregnancy, and 56% met the required 400 μg/day in early pregnancy. Broadly, dietary and supplemental intakes in our study were comparable with intakes seen in other Caucasian pregnant populations (20–22). As would be expected, dietary intakes in our study appear to be less than dietary intakes reported in women of reproductive age in countries where food fortification is present (23, 24). Our findings are in agreement with current recommendations pre- and in early pregnancy. However, they highlight the need to consider current supplementation strategies so as to maximize the neuroprotective effects of folic acid while minimizing potential adverse postnatal respiratory effects. We acknowledge the need for further studies replicating our findings before any specific recommendations against folic acid supplementation in late pregnancy can be made.

In summary, we have shown that folic acid supplementation in late pregnancy significantly increases the risk of asthma in the child at 3.5 years and of persistent asthma at 3.5 and 5.5 years in a prospective cohort of Australian families. The findings have significant implications for our understanding of the transmission of asthma risk, and they support a possible role of folate-impaired methylation in pregnancy in alteration of the fetal immune phenotype, resulting in adverse respiratory health in childhood. They raise the prospect that there is a potentially important critical period during which supplement dosages may be manipulated to optimize the neuroprotective effects of supplemental folic acid while attempting not to increase the risk of asthma. They also provide testable theories to explain the rise in asthma prevalence noted internationally (25). We now call for the expansion of previous molecular research to help identify specific underlying etiologic pathways. Such further research is vital in order to determine whether restricting folic acid intake in late pregnancy will have a beneficial impact on asthma prevention and thus the respiratory health of children.

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