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Maternal periconceptional folate status and infant atopic dermatitis: A prospective cohort study

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Abstract

Background: Maternal folate status is linked with the risk of allergic disorders including atopic dermatitis (AD) in children, but findings remain inconclusive. We aim to assess the relationship between maternal folate status in early gestation and early-onset infant AD, based on a prospective mother-child cohort study.

Methods: Pregnant women were recruited at 12-14 weeks of gestation. Red blood cell folate (RBC folate) and serum folate concentrations were examined at enrollment. Periconceptional folic acid supplementation was investigated through a self-administered questionnaire. The primary outcome was AD incidence before 6 months of age, diagnosed according to Williams' criteria. Multivariate logistic regression was used to evaluate associations of maternal folate status with infant AD by adjusting parental and child covariates.

Results: In total, 107 (23.4%) of 458 infants developed AD before 6 months, with more male infants affected ($P = .002$). Higher maternal RBC folate levels (per 100 ng/mL) were associated with an increased risk of AD (adjusted odds ratio [aOR] 1.16, 95% confidence interval [CI] 1.04-1.31). An RBC folate level ≥ 620 ng/mL was associated with increased infant AD by 91% (aOR 1.91, 95% CI 1.09-3.36). However, associations were not observed for maternal serum folate at early gestation or periconceptional folic acid supplement intakes.

Conclusions: We provide the first evidence that higher maternal RBC folate concentrations during early gestation are associated with increased early-onset infant AD. Our findings support the importance of maintaining appropriate folate levels during the periconceptional period to reduce the risk of AD in infants.

KEYWORDS

allergy, atopic dermatitis, birth cohort, folic acid supplement, infant, maternal folate status, pregnancy

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1 | INTRODUCTION

Atopic dermatitis (AD) is a common and recurrent chronic inflammatory skin disease in children, affecting about 5%-25% of children globally,^{1,2} and up to 30% of infants below 1 year of age in China.³ Maternal exposure to certain nutritional factors during the periconceptual period, such as folate, has been reported as risk factors.⁴⁻⁶

Past studies suggested that maternal inadequate folate intake or folate deficiency was associated with increased risks of neural tube defects (NTD) in infants.^{7,8} However, higher folic acid intake or higher folate levels may increase the risk of allergic diseases.^{9,10} Infants exposed to maternal intakes of more than 500 µg folic acid supplements per day were more likely to develop eczema at 1 year compared with those exposed to <200 µg.¹¹ Maternal serum folate concentrations over 16.2 nmol/L in early pregnancy were positively associated with AD in 4-year-old children.¹² However, cohort studies from America, Japan, and Korea did not find such an association.¹³⁻¹⁵ In most previous studies, maternal folate status was measured by dietary intake, folic acid supplements, or serum folate concentrations, which may fluctuate after food ingestion and provide a less reliable indication of long-term folate status compared with red blood cell (RBC) folate levels.¹⁶ Only one study by Fabienne et al in which RBC folate at late gestation was investigated did not find significant association with infant AD.¹⁷ In the current prospective birth cohort, we measured RBC folate concentrations during early gestation to investigate its association with AD occurring in infants within 6 months of age.

2 | METHODS

2.1 | Study design and recruitment

This was a prospective mother-child cohort study. Pregnant women were recruited at a primary maternity clinics in Shanghai, China, if they were receiving first antenatal care at 12-14 weeks of gestation, planning to attend antenatal care, deliver baby, and continue routine postnatal child care at the very hospital. Multiple pregnancies, perinatal death, or a fetus with congenital skin or appendages disorders were excluded. Infants of the cohort were enrolled at birth and received routine child care visits for monitoring growth on the 42nd day, 6th month, and 12th month after birth. Skin status was examined via onsite interview by pediatric dermatologists. Parents consulted or visited a dermatologist once their baby developed any skin symptoms during the year.

The study protocol was approved by the Ethics Committee of Children's Hospital of Fudan University (CHFUF; Approval Number: 2016-34) and registered at www.clinicaltrials.org (NCT02889081) prior to the recruitment.

Key message

We provide the first evidence of the association between higher maternal RBC folate concentrations during early gestation and increased risk of early-onset infant AD. This finding suggests the importance of keeping appropriate maternal folate levels for the prevention of different infant outcomes.

2.2 | Assessment of periconceptual folic acid supplement intake

At enrollment, folic acid supplement use in the 3 months before pregnancy or in the first trimester of gestation was investigated via a self-administered questionnaire. To calculate the amount of supplements, participants were asked to provide an image of the brand and content of the supplement product.

2.3 | RBC folate and serum folate concentrations

Fasting serum and blood samples (EDTA anticoagulation) from peripheral venous blood were collected at enrollment and processed within 6 hours under protection from light. The samples were stored at -20°C within 2 weeks before transporting to -80°C. The RBC folate and serum folate were analyzed using a chemiluminescent microparticle immunoassay on an Architect system (Architect i2000SR, Abbott Diagnostics). Standard solution and external quality control were carried out according to the requirements from Abbott Laboratories (Abbott Laboratories). The RBC folate concentration was adjusted for hematocrit.

2.4 | Assessment of infant AD

The primary outcome was infant AD that occurred within 6 months of age. The AD was diagnosed using Williams' criteria.¹⁸ Suspected AD with atypical symptoms onset before 6 months of age was treated by a pediatric dermatologist and followed up for subsequent assessment of symptoms. Final diagnosis was confirmed at 1 year of age by three experienced pediatric dermatologists through panel discussion. The associations of AD within 6 months (primary outcome) or within 12 months (secondary outcome) were analyzed separately based on the finalized diagnosis.

2.5 | Covariates

Maternal demographic characteristics were collected by questionnaire, including maternal age at enrollment, education level,

preconception body mass index (BMI), gestational week at enrollment, parity, self and family history of allergic disease (ie AD, allergic rhinitis, and asthma), as well as alcohol consumption, smoke exposure, hair coloring, home decoration, and pet keeping for 3 months around conception. After delivery, data of birthweight, delivery mode, infant's gender, and gestational age were collected by reviewing electronic medical records.

2.6 | Statistical analyses

Statistical analyses were performed using Stata 15.0 (Stata Corp). General characteristics of participants were analyzed using conventional descriptive statistical methods for the overall cohort. Continuous variables are presented as mean (standard deviation) or median (IQR); categorical variables are presented as absolute numbers and percentage (%). Higher RBC folate levels were defined as those above the 80th percentile level (620 ng/mL) of the non-AD subgroup; this value was close to the high folate levels of the US general population of child-bearing age.¹⁹ Folic acid supplement intake was grouped into "no use," "<400 µg/d," "400-799 µg/d," and "more than 800 µg/d." Differences between the two groups were compared by using the chi-square test for categorical variables, and the Wilcoxon rank test or independent Student's *t* test was used for continuous variables. Correlations between RBC folate and serum folate levels were tested by the Spearman rank correlation test.

The association of maternal folate status with infant AD was initially investigated by univariate logistic regression models for higher RBC folate (binary variable), RBC folate concentration (continuous variable), folic acid supplement intake (categorical variable), and serum folate (continuous variable) levels. Then, a multivariate logistic model was used to adjust for possible covariates, including maternal age at enrollment, education, preconception BMI, parity, maternal allergy history, paternal allergy history, maternal smoke exposure, maternal alcohol consumption, maternal hair coloring, maternal pet keeping, maternal house decoration, and infant's gender and birthweight. Odds ratio (OR) and 95% confidence interval (CI) were reported. $P < .05$ was considered statistically significant.

The sample size was calculated based on the hypothesis of a maternal higher RBC folate status and onset of infant AD within 6 months. We supposed an incidence of infant AD being 25% in the population with RBC folate levels below the 80th percentile folate level and 60% higher risk in the group with higher RBC folate concentrations. A type I error of 0.05 (2-sided) and power of 0.8 would require 455 infants.

3 | RESULTS

3.1 | Participants

A total of 475 pregnant women in early gestation were recruited, and the infant cohort consisted of 459 newborn babies at birth.

Among them, 458 completed the investigation at the 6-month visit (Figure 1).

Pregnant women were 29.4 years old and at 12.8 weeks of gestation on average at enrollment, and their babies were born at 39.1 weeks of gestation (Table 1). In total, 107 (23.4%) infants developed AD within 6 months, and the number increased to 121 (26.5%) by the 12th month. The AD group had more male infants and a greater birthweight, more maternal allergy history, paternal allergy history, and maternal hair coloring history during the periconceptional period than in the non-AD group (Table 1). The other maternal and child characteristics did not significantly differ between the two groups.

3.2 | Maternal folate status

The median maternal RBC folate concentration was 414.1 (315.2, 575.2) ng/mL for the entire cohort, and the AD group had higher levels than the non-AD group (442.0 (341.9, 626.8) vs 401.8 (310.5, 554.0), $P = .031$; Table 2). According to the WHO recommendations,²⁰ 46.2% of mothers had insufficient RBC folate concentrations, and the proportion was lower in the AD group than in the non-AD group (37.1% vs 49.0%, respectively, $P = .033$; Table 2). The median serum folate level was 14.6 (12.0, 16.3) ng/mL, and levels did not differ between the two groups ($P = .67$; Table 2). In total, 61.5% women did not take any folic acid supplements before conception, and the proportion decreased to 6.0% in the first trimester. The percentage of pre- and post-conception folic acid supplementation, serum folate, vitamin B-12, and homocysteine levels did not significantly differ between the AD and non-AD groups (Table 2). We found that during early gestation, the RBC folate concentrations showed skewed but deflected distributions compared with the serum levels (Figure 2A, B), and more participants had lower RBC folate values, whereas more participants had higher serum folate values; the two folate biomarkers showed weak correlation ($\rho = 0.30$, $P < .001$; Figure 2C).

3.3 | Association of maternal folate status and infant AD

A significant association was found between maternal RBC folate concentrations at early gestation and the AD risk within 6 months (OR = 1.12, 95% CI 1.01-1.25; Table 3). The association remained after adjustment for covariates (aOR 1.16, 95% CI 1.04-1.31; Table 3) and was independent of established risk factors of infant AD, including child sex, parental allergy history, and maternal hair coloring history (Table S1). In the univariate analysis, we observed a non-significant association between higher maternal RBC folate status (≥ 620 ng/mL, the 80th percentile) and infant AD (Table 3). After adjustment for covariates, this association became significant, and a higher RBC folate status was significantly related to an increased risk of AD by 91% (aOR = 1.91, 95% CI 1.09-3.36). Results were similar

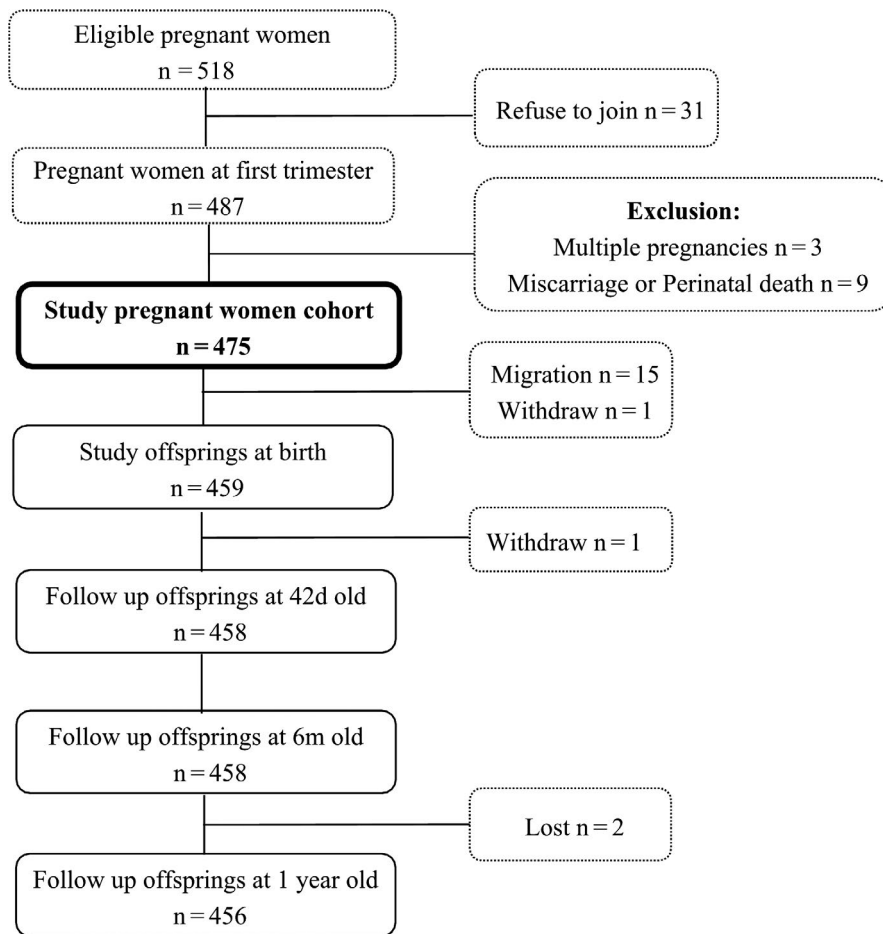


FIGURE 1 Flowchart of the Maternal Key Nutritional Factors and Offspring's Atopic Dermatitis (MKNFOAD) study. A total of 475 pregnant women were recruited in the study, 459 infants were enrolled after birth, and 458 infants completed the primary outcome follow-up visit at 6 mo of age

for the incidence of AD within 12 months (aOR = 1.81, 95% CI 1.05–3.10; Table 3).

No significant associations were found between consumption of maternal folic acid supplements before conception or during early gestation and serum folate at early gestation with the risk of AD in infants after adjustment for covariates (Table 4 and Table S2).

4 | DISCUSSION

Our prospective cohort study revealed an association between higher maternal RBC folate concentrations during early gestation and an increased risk of early-onset AD in infants. Increments (100 ng/mL) of RBC folate were each associated with a 16% increased risk of AD occurring before 6 months of age. Compared with lower RBC folate levels, infants of mothers with RBC folate levels over 620 ng/mL (corresponding to the 80th percentile of population levels) had a 91% higher risk of developing AD before 6 months of age. This association was independent of multiple covariates, such as a parental history of allergy, a well-known predictive factor for allergic diseases in children. We did not find significant associations between maternal serum folate levels in early gestation or folic acid supplements before or after conception and the risk of AD in infants.

Several studies have investigated the association between maternal folate status and AD, but with mixed findings possibly due to the different timings of folate measurements and outcome assessments.

Two prospective cohort studies reported that higher maternal intake of folic acid supplements or higher serum folate levels during pregnancy were associated with an increased risk of developing AD.^{11,12} However, Kim et al reported a reverse association between higher maternal serum folate levels during mid-pregnancy and a lower risk of AD in 2-year-old infants,¹⁴ and other cohort studies found no such associations.^{13,15,17,21} One study by Fabienne et al examined maternal RBC folate concentrations, as an intercellular folate biomarker, in 837 mothers during late pregnancy.¹⁷ While they found a significant association and dose-response relationship with childhood asthma, no association with onset of infant AD before 2 years of age was observed. To our knowledge, our study is the first to investigate the association between maternal RBC folate levels during early pregnancy and the incidence of infant AD before 6 months of age. Contradictory to the non-significant findings from Fabienne et al's study,¹⁷ we showed a significantly positive association. Two possibilities may account for the disparities. First, considering that maternal circulating and tissue folate levels alter dramatically during pregnancy, as reflected by a marked increase during early pregnancy and a subsequent decline by about 20% at mid-gestation that last to later gestation,²² any effect of the maternal RBC folate concentrations on the fetal development may differ by stages of gestation. Second, the incidence of early-onset AD may be significantly affected by the epigenetic effects of maternal folate on immune gene regulation across the entire period of gestation, whereas a later onset of AD

TABLE 1 Characteristics of pregnant women and infants with and without atopic dermatitis

Characteristics	Overall subjects (n = 458)	Infants with AD (n = 107)	Infants without AD (n = 351)	P value
Pregnant women				
Age (year)	29.4 (4.0)	29.4 (4.3)	29.4 (3.9)	.94
Education				
High school	100 (21.9%)	20 (18.7%)	80 (22.9%)	.61
Bachelor	320 (70.2%)	77 (72.0%)	243 (69.4%)	
Master	37 (8.1%)	10 (9.3%)	27 (7.7%)	
Parity = 1	184 (40.2%)	37 (34.6%)	147 (41.9%)	.18
Gestational week at enrollment (weeks)	12.8 (0.9)	12.8 (1.0)	12.8 (0.9)	.77
Preconception weight (kg)	54.1 (7.8)	54.1 (7.8)	54.0 (7.9)	.89
Preconception BMI (kg/cm ²)	20.8 (2.7)	20.7 (2.6)	20.8 (2.7)	.81
Allergy history				
Self-allergy history	100 (21.8%)	36 (33.6%)	64 (18.2%)	.001
Husband's allergy history	75 (16.4%)	26 (24.3%)	49 (14.0%)	.011
Environmental exposures in 3 mo pre- and post-conception				
Smoking	81 (17.7%)	18 (16.8%)	63 (18.0%)	.80
Alcohol consumption	74 (16.2%)	21 (19.6%)	53 (15.1%)	.27
Hair coloring	31 (6.8%)	13 (12.2%)	18 (5.1%)	.011
Home decoration	53 (11.6%)	12 (11.2%)	41 (11.7%)	.90
Pet keeping	65 (14.2%)	16 (15.0%)	49 (14.0%)	.80
Infants				
Male	240 (52.4%)	70 (65.4%)	170 (48.4%)	.002
Birthweight (g)	3369 (404)	3457 (454)	3342 (384)	.010
Gestational age (weeks)	39.1 (1.3)	39.2 (1.1)	39.1 (1.3)	.63
Cesarean	219 (50.2%)	59 (55.1%)	160 (48.6%)	.24
Turbid amniotic fluid	78 (18.1%)	17 (15.9%)	61 (18.8%)	.50
Breast feeding within 6 mo of age	265 (61.9%)	59 (55.7%)	206 (64.0%)	.13
Solid food within 6 mo of age	230 (53.7%)	59 (55.7%)	171 (53.1%)	.65
AD (6 mo)	107 (23.4%)			
AD (12 mo)	121 (26.5%)			

Note: Data shown as mean (standard deviation) or number (%), as appropriate.

Abbreviations: AD, atopic dermatitis; BMI, body mass index.

or allergic diseases may be attributed to more complex additional exposures during childhood. Indeed, the epigenetic effect of maternal folic acid use during pregnancy on offspring airway remodeling via histological modification and subsequently increased offspring allergic responses has been documented in animal study,²³ although whether this can be applicable to human population^{24,25} needs further investigations.

We did not find any associations of maternal serum folate concentrations in early gestation and periconceptional folic acid supplement intake with AD in infants, which were in agreement with previous studies.^{17,21} Although serum folate and RBC folate levels are recommended biomarkers for pregnant women,^{16,26,27} their responses to folic acid supplements within a certain period of time during early gestation and potential effects on methylation patterns in offspring, if any, may differ. The non-significant association for folic acid supplementation

may be explained by less reliable measurement by questionnaire. In addition, the genetic effect of multiple gene polymorphisms on folate metabolism, such as MTHFR 677 C > T, has not been considered.

We acknowledge that, for pregnancies with insufficient folate status (RBC folate concentrations < 400 ng/mL, the recommended folate level for reducing NTD), our findings indicating a potential risk of infant AD should be considered secondary to the importance of folate for fetal neurodevelopment given the well-established benefits for NTD prevention.⁸ However, possible adverse effects of RBC folate exceeding 400 ng/mL upon AD and other outcomes warrant further investigation.

Our study had several strengths. First, our cohort was well retained. Second, the diagnosis of AD was accurate with small chance of misclassification. Third, maternal folate status was examined by multiple measurements (RBC folate, serum folate, and

Characteristics	Overall subjects (n = 458)	Infants with AD (n = 107)	Infants without AD (n = 351)	P value
RBC folate levels in early gestation (ng/mL)	414.1 (315.2, 575.2)	442.0 (341.9, 626.8)	401.8 (310.5, 554.0)	.031
RBC folate levels below WHO recommendations ⁽¹⁹⁾	209 (46.2%)	39 (37.1%)	170 (49.0%)	.033
Quintiles of RBC folate levels				
≥20th (<295 ng/mL)		18 (17.1%)	73 (21.0%)	.44
≥40th (<375 ng/mL)		18 (17.1%)	73 (21.0%)	
≥60th (<466 ng/mL)		19 (18.1%)	70 (20.2%)	
≥80th (<620 ng/mL)		23 (21.9%)	67 (19.3%)	
≥100th (≥620 ng/mL)		27 (25.8%)	64 (18.5%)	
Folic acid supplements				
Before conception				
No use	278 (61.5%)	65 (61.3%)	213 (61.6%)	.30
<400 µg/d	49 (10.8%)	16 (15.1%)	33 (9.5%)	
400-799 µg/d	88 (19.5%)	16 (15.1%)	72 (20.8%)	
≥800 µg/d	37 (8.2%)	9 (8.5%)	28 (8.1%)	
First trimester				
No use	27 (6.0%)	4 (3.8%)	23 (6.7%)	.74
<400 µg/d	93 (20.7%)	23 (21.7%)	70 (20.3%)	
400-799 µg/d	176 (39.1%)	42 (39.6%)	134 (39.0%)	
≥800 µg/d	154 (34.2%)	37 (34.9%)	117 (34.0%)	
Serum folate levels in early gestation (ng/mL)	14.6 (12.0, 16.3)	14.6 (12.6, 15.9)	14.6 (11.9, 16.3)	.67
Serum vitamin B-12 (pg/mL)	451.5 (188.3)	458.8 (206.9)	449.3 (182.5)	.65
Serum homocysteine (µmol/L)	6.4 (1.4)	6.3 (1.4)	6.5 (1.4)	.26

Note: Data shown are mean (standard deviation), median (interquartile range), or number (%), as appropriate.

Abbreviations: AD, atopic dermatitis; RBC folate, red blood cell folate.

TABLE 2 Periconception folic acid supplements and serum and red blood cell folate levels grouped by atopic dermatitis status in infants

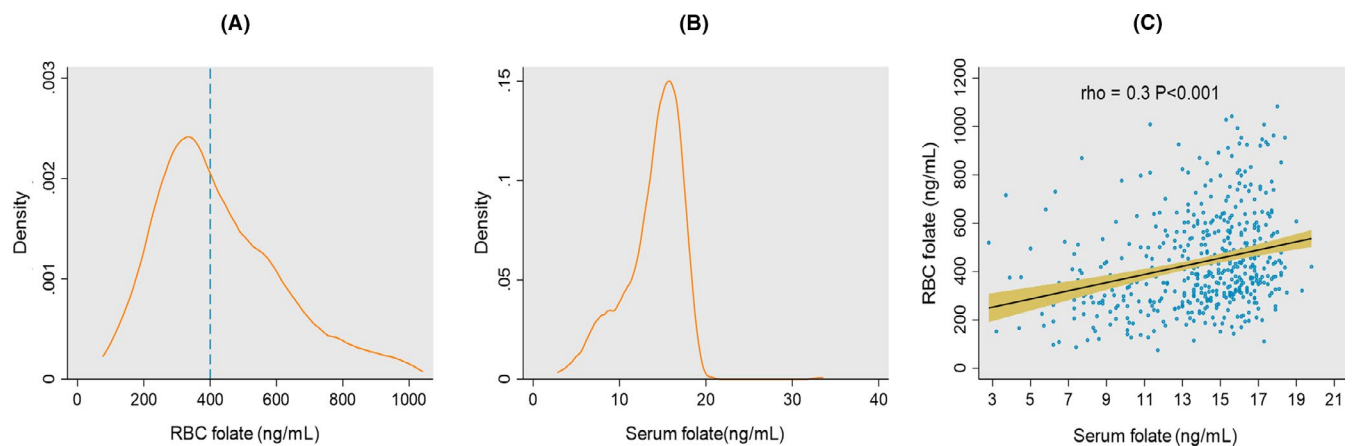


FIGURE 2 Density distributions and correlation of red blood cell (RBC) folate and serum folate levels during early gestation; (A). The distribution of maternal RBC folate (ng/mL) concentrations; (B). The distribution of serum folate (ng/mL) levels; (C). The correlation between RBC folate (ng/mL) and serum folate (ng/mL) levels. During early gestation, maternal RBC folate concentrations showed skewed but deflected distributions compared with serum levels (A, B); more participants had lower RBC folate values, whereas more participants had higher serum folate values. The two maternal folate biomarkers showed a weak correlation ($\rho = 0.30$, $P < .001$; (C))

TABLE 3 Association of maternal red blood cell folate concentrations with infant atopic dermatitis

Outcomes	Maternal RBC folate concentration ^a		RBC folate status (≥ 620 vs < 620 ng/mL)	
	OR (95% CI)	P value	OR (95% CI)	P value
AD (6 mo)				
Univariate	1.12 (1.01-1.25)	.031	1.53 (0.91-2.56)	.11
Multivariate ^b	1.16 (1.04-1.31)	.011	1.91 (1.09-3.36)	.024
AD (12 mo)				
Univariate	1.13 (1.02-1.25)	.020	1.49 (0.90-2.45)	.12
Multivariate ^b	1.16 (1.04-1.30)	.008	1.81 (1.05-3.10)	.032

Abbreviations: AD, atopic dermatitis; CI, confidence interval; OR, odds ratio; RBC, red blood cell.

^aMaternal RBC folate concentration (ng/mL)/100 as an exposure variable.

^bAdjusted for maternal age at enrollment, education level, preconception body mass index, first gestation, maternal allergy history, paternal allergy history, maternal smoke exposure, maternal alcohol consumption, maternal hair coloring, maternal pet keeping, maternal house decoration, and infant's sex and birthweight.

TABLE 4 Association of maternal folic acid supplement consumption with infant atopic dermatitis

Outcomes	Folic acid supplement consumption						
	3 mo before conception, OR (95% CI)				First trimester, OR (95% CI)		
	No use	<400 μg	400-800 μg	≥ 800 μg	<400 μg ^a	400-800 μg	≥ 800 μg
AD (6 mo)							
Univariate	Reference	1.58 (0.82-3.06)	0.72 (0.39-1.33)	1.05 (0.47-2.34)	Reference	1.07 (0.62-1.87)	1.08 (0.61-1.91)
Multivariate ^b	Reference	1.64 (0.81-3.34)	0.81 (0.42-1.56)	1.52 (0.63-3.63)	Reference	1.19 (0.67-2.13)	1.15 (0.63-2.10)
AD (12 mo)							
Univariate	Reference	1.59 (0.84-3.01)	0.67 (0.37-1.21)	1.16 (0.55-2.47)	Reference	1.04 (0.61-1.76)	1.06 (0.61-1.82)
Multivariate ^b	Reference	1.59 (0.81-3.16)	0.73 (0.39-1.37)	1.67 (0.74-3.80)	Reference	1.17 (0.67-2.04)	1.17 (0.66-2.08)

Abbreviations: AD, atopic dermatitis; CI, confidence interval; OR, odds ratio.

^aThis group includes "No use."

^bAdjusted for maternal age at enrollment, education level, preconception body mass index, first gestation, maternal allergy history, paternal allergy history, maternal smoke exposure, maternal alcohol consumption, maternal hair coloring, maternal pet keeping, maternal house decoration, and infant's sex and birthweight.

folic acid supplements) to comprehensively capture the maternal short-term and long-term folate status. Although multiple methods are available for RBC folate examination,²⁶ using the 80th percentiles (620 ng/mL) for categorizing RBC folate concentrations makes our findings more interpretable and comparable with other studies. Additionally, the recruitment of participants from a primary healthcare setting enhances the generalizability of our findings.

Our study had limitations. The sample size of this cohort was relatively small. We lack data on maternal RBC folate concentrations before pregnancy, during mid- and late pregnancy, so the relations of this biomarker with infant AD need further studies. Although extensive parental covariates have been adjusted, effects of unmeasured covariates on our main finding cannot be completely controlled.

In conclusion, we provide the first evidence of the association between higher maternal RBC folate concentrations during early gestation and increased risk of early-onset AD in infants.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

Ying Ye: Conceptualization (equal); Investigation (lead); Project administration (lead); Writing-original draft (lead). **Li Min Dou:** Data curation (lead); Investigation (equal); Project administration (supporting); Writing-original draft (equal). **Yi Zhang:** Formal analysis (equal); Methodology (equal); Resources (supporting); Writing-original draft (supporting). **Ya Lan Dou:** Data curation (supporting); Formal analysis (supporting); Project administration (equal). **Piao Ping Zhao:** Data curation (equal);

Investigation (supporting); Project administration (supporting). **Yuan Jiang:** Formal analysis (equal); Methodology (supporting); Software (equal). **Wei Gao:** Data curation (supporting); Investigation (supporting); Project administration (supporting). **Mi Ji:** Data curation (supporting); Project administration (supporting). **Lin Feng He:** Investigation (supporting); Project administration (supporting). **Da Yan Niu:** Data curation (supporting); Resources (supporting); Software (supporting). **Lei Zhang:** Project administration (supporting); Resources (equal); Supervision (supporting). **Xiao Hua Gao:** Project administration (supporting); Resources (equal); Supervision (equal). **Yun Li:** Investigation (supporting); Project administration (supporting); Supervision (supporting). **Li Ping Xiao:** Resources (supporting); Supervision (supporting). **Jun Huang:** Resources (supporting); Supervision (supporting). **Xiao Hua Zhang:** Project administration (supporting); Resources (supporting). **Liu Hui Wang:** Conceptualization (equal); Funding acquisition (equal); Project administration (lead); Supervision (equal); Writing-review & editing (equal). **Weili Yan:** Conceptualization (equal); Funding acquisition (lead); Project administration (equal); Supervision (lead); Writing-review & editing (lead).

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Table S1 Associations of maternal red blood cell (RBC) folate concentrations with infant atopic dermatitis (6 months of age) by adjusting shown covariates.

Variables	OR (95% CI)	P value
RBC folate concentration [†]	1.16 (1.04–1.31)	0.011
Maternal age at enrollment	0.97 (0.90–1.03)	0.33
Education	1.31 (0.82–2.10)	0.25
Preconception BMI	0.97 (0.89–1.07)	0.56
Parity >1	1.59 (0.93–2.74)	0.09
Sex of infants (male=1; female=2)	0.50 (0.31–0.81)	0.005
Birth weight [†]	1.06 (1.00–1.12)	0.039
Maternal allergy history (yes=1, no=0)	2.31 (1.37–3.89)	0.002
Paternal allergy history (yes=1, no=0)	1.80 (1.00–3.24)	0.049
Smoke exposure 3 months around conception (yes=1, no=0)	0.96 (0.51–1.82)	0.91
Alcohol consumption (yes=1, no=0)	1.24 (0.67–2.30)	0.50
Hair coloring (yes=1, no=0)	2.30 (1.01–5.23)	0.048
Home decoration (yes=1, no=0)	0.70 (0.33–1.51)	0.37
Pet keeping (yes=1, no=0)	0.96 (0.49–1.88)	0.91

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

[†]RBC folate concentration (ng/mL) /100, birth weight (g) /100 as exposure variables.

Table S2 Associations of maternal serum folate with infant atopic dermatitis.

Outcomes	Serum folate concentration	
	OR (95% CI)	<i>P</i> value
AD (6 months)		
Univariate	0.98 (0.92-1.04)	0.49
Multivariate [†]	0.99 (0.92-1.06)	0.72
AD (12 months)		
Univariate	0.97 (0.91-1.03)	0.30
Multivariate [†]	0.97 (0.91-1.04)	0.43

Abbreviations: AD, Atopic Dermatitis.

[†]Adjusted OR controlled by maternal age at enrollment, education level, preconception BMI, first gestation, maternal allergy history, paternal allergy history, maternal smoke exposure, maternal alcohol consumption, maternal hair coloring, maternal pet keeping, maternal house decoration and infant's sex, birth weight.