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ORIGINAL CONTRIBUTION

Folic acid supplementation, dietary folate intake and risk of preterm birth in China

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Abstract

Purpose Folic acid supplementation has been suggested to reduce the risk of preterm birth. However, results from previous epidemiologic studies have been inconclusive. We investigated the hypothesis that folic acid supplementation and dietary folate intake during pre- and post-conception reduces the risk of preterm birth.

Methods We analyzed data from a birth cohort study conducted between 2010 and 2012 in Lanzhou, China, including 10,179 pregnant women with live singleton births.

Results Compared to non-users, folic acid supplement users with >12-week duration had a reduced risk of preterm birth (OR 0.67, 95 % CI 0.55–0.83) with a significant dose–response relationship (*P* for trend = 0.01). A similar pattern was observed for spontaneous preterm birth. Stronger associations were seen for ever use of folic acid supplement and very preterm birth (OR 0.50, 95 % CI 0.36–0.69) and spontaneous very preterm birth (OR 0.42, 95 % CI 0.29–0.63). Dietary folate intake during preconception and pregnancy were also associated with reduced risk of preterm birth (OR 0.68, 95 % CI 0.56–0.83, OR 0.57, 95 % CI 0.47–0.70 for the highest quartiles, respectively), particularly for spontaneous very preterm (OR 0.41, 95 % CI 0.24–0.72, OR 0.26, 95 % CI 0.15–0.47 for the highest quartiles, respectively). There were also decreased risks of preterm birth observed per 10-μg increase in dietary folate intake, and similar associations were found after stratification by folic acid supplementation status.

Conclusions Our results suggest that folic acid supplementation and higher dietary folate intake during preconception and pregnancy reduces the risk of preterm birth, and the protective effect varies by preterm subtypes.

Keywords Dietary folate · Epidemiology · Folic acid supplements · Preterm birth

Abbreviations

PB	Preterm birth
PPROM	Preterm premature rupture of membranes
OR	Odds ratio
CI	Confidence interval
BMI	Body mass index

Introduction

Preterm birth (PB) is the leading cause of neonatal morbidity and mortality [1], and the second leading cause of death in children <5 years of age [2]. Neonatal morbidity and mortality are inversely associated with gestational age at delivery, with most adverse outcomes associated with delivery before 32 weeks gestation [1]. Infants born PB are also more likely to be diagnosed with motor, cognitive, visual, hearing, behavioral, health, and growth problems

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compared to term infants [3, 4]. Approximately 15 million PB infants are born each year worldwide [5, 6], and the numbers continue to increase [7]. The World Health Organization's Millennium development goals have named prevention of preterm birth as a global health priority [6].

Folate plays an essential role in DNA synthesis, repair, and methylation [8]. It is particularly important in pregnancy and infancy, which involve rapid cell division and growth. Folic acid supplementation before conception and during the first trimester of pregnancy has been recommended for prevention of neural tube defects [9]. Its role in other pregnancy outcomes, however, has been largely controversial [10]. Randomized controlled trials linking maternal folic acid supplementation to PB have reported inconsistent findings [10–16]. Epidemiologic studies examining folic acid supplementation/dietary folate and PB have also reported mixed results, including positive [17], negative [18–27], and null findings [28–30].

China has one-fifth of the world population, and also the second largest number of PB [31] with PB rates ranges from 4.1 to 18.9 % [7]. A recent study reported that dietary folate intake among Chinese women of childbearing age was far from optimal, especially among women living in northern China [32]. Although taking 400 μg of folic acid daily has been recommended to women of childbearing age by the Chinese Ministry of Health since 1993 [32], the percentage of women who actually took folic acid supplements before and during pregnancy was only around 12 % based on a recent national survey [33]. While folic acid fortification of certain staple foods began in the USA in 1998 [34], no such fortification has been instituted in China. A recent Chinese study found that preconception folic acid supplementation use decreased risk of PB; however, the study did not address dietary folate intake or qualify duration of use [26].

Because studies examining the association between PB and folic acid supplements have provided inconsistent results, and limited studies have been conducted in the Chinese population, we conducted a birth cohort study in Lanzhou, China, to systemically examine the association between folic acid supplementation, dietary folate, and risk of PB.

Materials and methods

Study population

The study population has been described previously [35–37]. In brief, a birth cohort study was conducted during 2010–2012 at the Gansu Provincial Maternity & Child Care Hospital, the largest maternity and child care hospital in Lanzhou, China. Eligible women were recruited upon their arrival at the hospital for delivery. After obtaining written consent, an in-person interview was conducted at the hospital by trained study interviewers using a standardized and structured questionnaire to collect information on demographic, environmental, and lifestyle factors. The majority of women (84 %) were interviewed within 1–3 days after delivery. Information on birth outcomes and maternal complications was abstracted from medical records. A total of 14,359 eligible women were approached for participation, and 10,542 (73.4 %) women completed in-person interviews, with 10,179 women having singleton live birth. All study procedures were approved by the Human Investigation Committees at the Gansu, Provincial Maternity & Child Care Hospital and Yale University.

Preterm birth

Gestational age was calculated in completed weeks from the first day of the last menstrual period until delivery based on medical records and self-reported questionnaire. According to the World Health Organization, a child born before 37 completed weeks of gestation is defined as PB [6]. Term birth is defined as a child born ≥37 completed weeks of gestation. According to gestational age, PB was divided into moderate PB (32 to <37 completed weeks of gestation), very PB (28 to <32 completed weeks), and extremely PB (<28 completed weeks). We combined very and extremely PB together as very PB to increase statistical power. PB was further classified as medically indicated or spontaneous [38, 39]. A medically indicated PB occurs when a placental, uterine, fetal, or maternal condition exists prompting the medical team to proceed with delivery after the risks and benefits of continuing pregnancy versus early delivery are weighed. Examples of risky conditions prompting a decision include: placental abruption, placenta accreta, placenta or vasa previa, prior classical cesarean, uterine rupture or dehiscence, fetal intrauterine growth restriction, select fetal anomalies, severe preeclampsia, uncontrolled gestational or chronic hypertension, complicated pregestational diabetes, and oligohydramnios. Medically indicated PB does not include pregnancies delivered as a result of spontaneous PB labor with or without PB premature rupture of membranes (PPROM).

Folic acid supplementation and dietary folate intake

Data collection on folic acid supplementation and dietary folate intake has been described previously [37]. Briefly, information on folic acid supplements was asked for the following four time periods: preconception (12 months before pregnancy), first trimester (1–13 weeks), second trimester (14–27 weeks), and third trimester (>27 weeks). For each time period, duration and frequency of folic acid

Table 1 Distributions of selected characteristics of the study population between term and preterm births ($N = 10,179$)

Characteristics	Term ($n = 9160$)		Preterm ($n = 1019$)		P value[a]
	n	%	n	%	
Maternal age (years)					
<25	1395	15.2	242	23.7	<0.001
25–29	4498	49.1	363	35.6	
≥30	3276	35.8	414	40.6	
Maternal employment					
No	4327	47.2	601	59.0	<0.001
Yes	4833	52.8	418	41.0	
Family monthly income per capita (RMB)					
<3000	4475	48.9	662	65.0	<0.001
≥3000	3794	41.4	275	27.0	
Missing	891		82		
Highest education level					
<College	3411	37.2	587	57.6	<0.001
≥College	5586	61.0	410	40.2	
Missing	163		22		
Pre-pregnancy BMI					
<18.5	1879	20.5	195	19.1	0.02
18.5–23.9	6043	66.0	633	62.1	
≥24.0	948	10.3	132	13.0	
Missing	290		59		
Weight gain during pregnancy					
<15 kg	3333	36.4	585	57.4	<0.001
15–18.5 kg	2147	23.4	153	15.0	
>18.5 kg	3342	36.5	192	18.8	
Missing	338		89		
Alcohol consumption during pregnancy					
No	9143	99.8	1016	99.7	0.46
Yes	17	0.2	3	0.3	
Smoking (passive and active) during pregnancy					
No	7405	80.8	783	76.8	0.002
Yes	1755	19.2	236	23.2	
Physical activity during pregnancy					
No	1587	17.3	187	18.4	0.42
Yes	7573	82.7	832	81.6	
Parity					
Primiparous	6734	73.5	615	60.4	<0.001
Multiparous	2426	26.5	404	39.6	
Preeclampsia					
No	8973	98.0	891	87.4	<0.001
Yes	187	2.0	128	12.6	
History of preterm					
No	9128	99.7	970	95.2	<0.001
Yes	32	0.3	49	4.8	
Maternal diabetes					
No	9074	99.1	1002	98.3	0.03
Yes	86	0.9	17	1.7	
History of abortion					
No	8318	90.8	924	90.7	0.89
Yes	842	9.2	95	9.3	
C-section					
No	5718	62.9	488	49.9	<0.001
Yes	3370	37.1	490	50.1	
Missing	72		41		
Gender					
Male	4799	52.6	559	55.2	0.11
Female	4334	47.5	454	44.8	
Missing	27		6		

[a] Estimated by Pearson's Chi-square test

supplement use alone and folic acid-containing multivitamins were ascertained. Folic acid supplement users were defined as those who took folic acid supplements alone or folic acid-containing multivitamins during preconception and/or pregnancy. Non-users were defined as those who never took folic acid supplements alone or folic acid-containing multivitamins during preconception and pregnancy. Dietary information was collected via a semi-quantitative food frequency questionnaire. Daily dietary folate intake was estimated from the frequency of consumption and portion size of food items using the Chinese Standard Tables of Food Consumption [40], for each time period [37].

Statistical analyses

Chi-square tests were employed to compare selected characteristics between PB and term-birth groups. Unconditional logistic regression models were used to estimate odds ratios (OR) and 95 % confidence intervals (95 % CI) for the associations between use of folic acid supplements, dietary folate intake, and risk of PB and its clinical subtypes. Folic acid supplements were classified into two levels by midpoint of duration of use, dietary folate intake was categorized to quartiles, and dose–response relationship (P for trend) was calculated based on those categorical levels. Potential confounding variables included maternal age (≤24, 25–29, ≥30 years), education level (<college, ≥college), household monthly income per capita (<3000, ≥3000 RMB), parity (primiparous, multiparous), maternal

pre-pregnancy body mass index (BMI) (<18.5, 18.5–23.9, ≥24), employment status during pregnancy (yes, no), maternal diabetes (yes, no), preeclampsia (yes, no), and previous PB (yes, no). Additional adjustment for active and passive smoking, alcohol consumption, cesarean section (C-section), history of abortion, infant gender, and physical activity did not result in material changes in the observed associations, and thus these covariates were not included in the final models. The analyses examining dietary folate intake excluded subjects with missing dietary data ($N = 212$). All analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results

Of the 10,179 women in our study, 1019 women had PB (<37 completed weeks of gestation). Distributions of selected characteristics for study population are presented in Table 1. Compared to women who delivered term birth, women who delivered PB were more likely to be either younger (<25 year-old) or older (≥30 year-old), have lower education and income, be unemployed, and be smokers. Women who delivered PB were also more likely to be multiparous, have higher BMI, less weight gain during pregnancy, previous PB, and C-section, and be diagnosed with preeclampsia and maternal diabetes. Distributions of alcohol consumption, history of abortion, physical activity during pregnancy, and infant's gender were similar between term and PB groups.

A total of 7864 women reported to be folic acid supplement users, and 2315 women reported to be non-users (Table 2). Compared to non-users, users were more likely to be older, be employed, have higher education and income, have more weight gain during pregnancy, and physically active during pregnancy. Women who reported using folic acid supplement were less likely to be multiparous, be diagnosed preeclampsia and maternal diabetes.

Compared to non-users, folic acid supplement users had a reduced risk of PB (OR 0.80, 95 % CI 0.68–0.94, Table 3). The significant reduced risk was mainly seen for those who had used folic acid supplements for more than 12 weeks (OR 0.67, 95 % CI 0.55–0.83) with a significant dose–response (P for trend = 0.01). After stratifying by time periods of use, significant associations were observed for those who took supplements during both preconception and pregnancy (OR 0.75, 95 % CI 0.61–0.92) or during pregnancy only (OR 0.82, 95 % CI 0.69–0.97). A significant dose–response for duration of use was only observed for those who used during pregnancy only (P for trend = 0.005). No significant association was observed among women who took supplements during preconception only.

After stratifying by PB subtypes (Table 3), significant protective effects of folic acid supplement use were seen for very PB (OR 0.50, 95 % CI 0.36–0.69 for ever users; OR 0.47, 95 % CI 0.30–0.75 for during both preconception and pregnancy; OR 0.21, 95 % CI 0.59–0.88 for during preconception only; and OR 0.53, 95 % CI 0.37–0.75 for during pregnancy only) and spontaneous PB (OR 0.77, 95 % CI 0.64–0.93 for ever users; OR 0.73, 95 % CI 0.57–0.93 for during both preconception and pregnancy; and OR 0.77 95 % CI 0.63–0.94 for during pregnancy only). A significantly reduced risk of moderate PB was also seen for ever users who used for more than 12 weeks (OR 0.74, 95 % CI 00.59–0.94) and users who used during pregnancy only for more than 8 weeks (OR 0.79, 95 % CI 0.63–0.99).

Reduced risk of PB was also associated with higher estimated intake of dietary folate (Table 4). During preconception, a significant protective effect was seen for the highest quartile of dietary folate intake compared to the lowest quartile (OR 0.68, 95 % CI 0.56–0.83). Similar associations were observed for each clinical subtype. During pregnancy, a protective effect was shown for higher levels of dietary folate intake (OR 0.70, 95 % CI 0.59–0.84 for the second quartile; OR 0.67, 95 % CI 0.55–0.80 for the third quartile; and OR 0.57, 95 % CI 0.47–0.70 for the highest quartile) with significant dose–response (P for trend <0.001), and there was 0.2 % increased risk observed per 10-μg increase in dietary folate. Similar patterns were observed for moderate PB, medically indicated PB, and spontaneous PB. Stronger protective effect was seen for very PB (OR 0.62, 95 % CI 0.43–0.90 for the second quartile; OR 0.33, 95 % CI 0.21–0.52 for the third quartile; OR 0.28, 95 % CI 0.17–0.47 for the highest quartile, P for trend <0.001; and OR 0.949, 95 % CI 0.931–0.968 per 10-μg increase in dietary folate).

Although similar associations were observed for spontaneous PB with and without PPROM (Table 5), significantly reduced risk was observed for spontaneous PB with PPROM for folic acid users (OR 0.49, 95 % CI 0.33–0.73) and spontaneous PB without PPROM for higher estimated dietary folate intake (OR 0.60, 95 % CI 0.44–0.81 for the highest quartile level during preconception; OR 0.47, 95 % CI 0.35–0.63 for the highest quartile level during pregnancy; and OR 0.979, 95 % CI 0.969–0.990 per 10-μg increase in dietary folate).

We also stratified medically indicated and spontaneous PB into moderate and very PB (Table 6). The strongest association with folic acid supplements and estimated dietary folate intake was mainly seen for spontaneous very PB (OR 0.43, 95 % CI 0.29–0.63 for ever use folic acid supplements; OR 0.40 95 % CI 0.23–0.70 for the highest quartile intake of dietary folate during preconception with P for trend = 0.001; OR 0.26, 95 % CI 0.14–0.46 for the highest quartile intake of dietary folate during pregnancy with P for trend <0.001; and OR 0.942, 95 % CI 0.920–0.965 per 10-μg increase in dietary folate).

Table 2 Distributions of selected characteristics of the study population between folic acid users and non-users ($N = 10,179$)

Characteristics	Non-users ($n = 2315$)		Users ($n = 7864$)		P value[a]
	n	%	n	%	
Maternal age (years)					
<25	626	27.0	1008	12.8	<0.001
25–29	853	36.8	4002	50.9	
≥30	836	36.1	2854	36.3	
Maternal employment					
No	1466	63.3	3462	44.0	<0.001
Yes	849	36.7	4402	56.0	
Family monthly income per capita (RMB)					
<3000	1391	69.3	3746	52.0	<0.001
≥3000	616	30.7	3453	48.0	
Missing	208		665		
Highest education level					
<College	1425	64.7	2573	33.0	<0.001
≥College	776	35.3	5220	67.0	
Missing	114		71		
Pre-pregnancy BMI					
<18.5	443	21.2	1631	21.1	0.70
18.5–23.9	1409	67.4	5267	68.1	
≥24.0	240	11.5	840	10.9	
Missing	223		126		
Weight gain during pregnancy (kg)					
<15	992	48.2	2926	38.0	<0.001
15–18.5	407	19.8	1893	24.6	
>18.5	659	32.0	2875	37.4	
Missing	257		170		
Alcohol consumption during pregnancy					
No	2310	99.8	7849	99.8	0.81
Yes	5	0.2	15	0.2	
Smoking (passive and active) during pregnancy					
No	1842	79.6	6346	80.7	0.23
Yes	473	20.4	1518	19.3	
Physical activity during pregnancy					
No	686	29.6	1088	13.8	<0.001
Yes	1629	70.4	6776	86.2	
Parity					
Primiparous	1261	54.5	6088	77.4	<0.001
Multiparous	1054	45.5	1776	22.6	
Preeclampsia					
No	2206	95.3	7658	97.4	<0.001
Yes	109	4.7	206	2.6	
History of preterm					
No	2298	99.3	7800	99.2	0.71
Yes	17	0.7	64	0.8	
Maternal diabetes					
No	2302	99.4	7774	98.9	0.014
Yes	13	0.6	90	1.1	
History of abortion					
No	2102	90.8	7140	90.8	0.99
Yes	213	9.2	724	9.2	
C-section					
No	1444	63.3	4762	61.2	0.074
Yes	839	36.8	3021	38.8	
Missing	32		81		
Gender					
Male	1253	54.3	4105	52.4	0.095
Female	1053	45.7	3735	47.6	
Missing	9		24		

[a] Estimated by Pearson's Chi-square test

Stratified analysis by folic acid supplementation was also conducted (Table 7). Similar effects of estimated dietary intake on risk of preterm birth were found between folic acid supplement users and non-users, although slightly stronger protective effects were observed among non-users.

We explored potential effect modifications of maternal age, pre-pregnancy BMI, and parity on the associations between folic acid supplements and dietary folate intake and risk of PB. None of these variables modified the associations (data not shown). We did not observe a synergistic effect between dietary folate intake and folic acid supplement use (data not shown). Fewer subjects were folic acid-containing multivitamin users compared to folic acid supplement-alone users (21 vs. 79 %), and similar inverse associations were observed for using either type of folic acid supplements (data not shown).We analyzed the data by excluding birth defects and reached the same conclusion (data not shown). We also conducted a sensitivity analysis for dietary folate intake to exclude poor quality of either under- or over-reporting of the calculated energy intake [41], 892 (8.8 %) participants with energy intake of <4.5 MJ/day (1075 kcal/day) and 50 (0.5 %) participants with energy intake of >20 MJ/day (4777 kcal/day) were excluded, and similar results were observed (data not shown).

Discussion

Our study results suggest that folic acid supplements and high dietary folate intake are associated with a reduced risk of PB, and the reduced risk may vary by PB subtype.

Table 3 Associations between folic acid supplementation and risk of preterm birth

Folic acid supplement use	Controls	Preterm (<37 weeks)			Moderate preterm (32 to < 37 weeks)			Very preterm (<32 weeks)			Medically indicated preterm			Spontaneous preterm		
		Cases	OR[a]	95 % CI	Cases	OR[a]	95 % CI	Cases	OR[a,c]	95 % CI	Cases	OR[b,c]	95 % CI	Cases	OR[b]	95 % CI
Non-users	1982	333	1.00		252	1.00		81	1.00		120	1.00		213	1.00	
Users	7178	686	0.80	0.68, 0.94	580	0.92	0.77, 1.09	106	0.50	0.36, 0.69	218	0.82	0.63, 1.05	468	0.77	0.64, 0.93
≤12 weeks	4405	481	0.85	0.72, 1.01	411	0.99	0.82, 1.18	70	0.50	0.35, 0.71	153	0.85	0.65, 1.11	328	0.82	0.68, 1.00
>12 weeks	2773	205	0.67	0.55, 0.83	169	0.74	0.59, 0.94	36	0.49	0.31, 0.77	65	0.73	0.52, 1.03	140	0.64	0.51, 0.82
P for trend			0.01			0.004			0.91			0.30			0.03	
Preconception																
During pregnancy	2734	217	0.75	0.61, 0.92	183	0.85	0.68, 1.07	34	0.47	0.30, 0.75	66	0.79	0.56, 1.12	151	0.73	0.57, 0.93
≤12 weeks	569	59	0.88	0.64, 1.21	52	1.06	0.75, 1.49	7	0.40	0.18, 0.91	16	0.78	0.44, 1.36	43	0.93	0.65, 1.34
>12 weeks	2165	158	0.71	0.57, 0.89	131	0.79	0.61, 1.01	27	0.50	0.30, 0.81	50	0.80	0.55, 1.16	108	0.67	0.52, 0.87
P for trend			0.21			0.098			0.71			1.00			0.10	
Preconception only	339	35	0.88	0.60, 1.31	33	1.12	0.75, 1.68	2	0.21	0.59, 0.88	8	0.72	0.38, 1.38	27	0.98	0.63, 1.51
≤4 weeks	89	12	1.01	0.52, 1.95	10	1.17	0.58, 2.37	2	0.61	0.14, 2.69	3	0.88	0.30, 2.60	9	1.18	0.57, 2.45
>4 weeks	250	23	0.83	0.52, 1.33	23	1.10	0.69, 1.76	0		–	5	0.66	0.30, 1.45	18	0.91	0.54, 1.52
P for trend			0.80			0.99			0.73			0.56			0.79	
During pregnancy only	4105	434	0.82	0.69, 0.97	364	0.93	0.77, 1.12	70	0.53	0.37, 0.75	144	0.84	0.64, 1.09	290	0.77	0.63, 0.94
≤8 weeks	1871	246	0.94	0.77, 1.13	206	1.07	0.87, 1.32	40	0.59	0.39, 0.88	80	0.93	0.69, 1.27	166	0.91	0.72, 1.13
>8 weeks	2234	188	0.70	0.57, 0.85	158	0.79	0.63, 0.99	30	0.46	0.29, 0.72	64	0.74	0.53, 1.02	124	0.64	0.50, 0.81
P for trend			0.005			0.007			0.42			0.16			0.003	

[a] Adjusted for maternal age, education level, smoking, parity, preeclampsia, maternal diabetes, preeclampsia, pre-pregnancy BMI, family monthly income per capita, maternal employment during pregnancy, history of preterm, and dietary folate intake

[b] Adjusted all variables above except for preeclampsia and maternal diabetes

[c] Estimated by using Fisher's exact test for the number of cases in a category <5

Table 4 Associations between estimated dietary folate intake and risk of preterm birth

Dietary folate duration and intake levels (μg/day)	Controls	Preterm (<37 weeks)			Moderate preterm (32 to <37 weeks)			Very preterm (<32 weeks)			Medically indicated preterm			Spontaneous preterm		
		Cases	OR[a]	95 % CI	Cases	OR[a]	95 % CI	Cases	OR[a]	95 % CI	Cases	OR[b]	95 % CI	Cases	OR[b]	95 % CI
Preconception																
Q1 < 118.6	2248	313	1.00		252	1.00		61	1.00		109	1.00		204	1.00	
Q2 118.6–161.8	2236	246	0.90	0.75, 1.08	197	0.91	0.74, 1.11	49	0.91	0.62, 1.35	73	0.99	0.76, 1.29	173	0.95	0.76, 1.17
Q3 161.8–224.6	2241	242	0.84	0.70, 1.01	196	0.85	0.69, 1.04	46	0.82	0.55, 1.21	79	0.76	0.57, 1.01	163	0.87	0.70, 1.08
Q4 ≥ 224.6	2245	196	0.68	0.56, 0.83	172	0.76	0.61, 0.94	24	0.44	0.27, 0.71	67	0.60	0.44, 0.81	129	0.69	0.54, 0.87
P for trend			<0.001			0.009			0.001			<0.001			0.002	
Per 10-μg increase			0.996	0.990, 1.001		0.998	0.993, 1.003		0.975	0.958, 0.992		0.991	0.981, 1.000		0.993	0.986, 1.000
During pregnancy																
Q1 < 155.8	2245	373	1.00		285	1.00		88	1.00		124	1.00		249	1.00	
Q2 155.8–202.8	2239	228	0.70	0.59, 0.84	182	0.74	0.60, 0.90	46	0.62	0.43, 0.90	72	0.53	0.40, 0.70	156	0.69	0.56, 0.85
Q3 202.8–272.1	2245	212	0.67	0.55, 0.80	187	0.78	0.64, 0.95	25	0.33	0.21, 0.52	72	0.50	0.38, 0.67	140	0.63	0.51, 0.79
Q4 ≥ 272.1	2241	184	0.57	0.47, 0.70	163	0.67	0.54, 0.83	21	0.28	0.17, 0.47	60	0.47	0.34, 0.63	124	0.57	0.45, 0.71
P for trend			<0.001			<0.001			<0.001			<0.001			<0.001	
Per 10-μg increase			0.998	0.982, 0.995		0.994	0.988, 1.000		0.949	0.931, 0.968		0.979	0.969, 0.990		0.985	0.977, 0.993

[a] Adjusted for maternal age, education level, smoking, parity, preeclampsia, maternal diabetes, preeclampsia, pre-pregnancy BMI, family monthly income per capita, maternal employment during pregnancy, history of preterm, folic acid supplementation

[b] Adjusted all variables above except for preeclampsia and maternal diabetes

Table 5 Associations between folic acid supplementation, estimated dietary folate intake, and risk of spontaneous preterm birth

Folic acid/folate intake duration	Controls	Spontaneous preterm w/ PPROM[b]			Spontaneous preterm w/o PPROM[b]		
		Cases	OR[a]	95 % CI	Cases	OR[a]	95 % CI
Folic acid supplements							
Non-users	1982	90	1.00		123	1.00	
Users	7178	195	0.49	0.33, 0.73	273	0.87	0.64, 1.20
Dietary folate intake (μg/day)							
Preconception							
Q1 < 118.6	2248	80	1.00		124	1.00	
Q2 118.6–161.8	2236	63	0.89	0.64, 1.26	110	0.99	0.76, 1.29
Q3 161.8–224.6	2241	77	1.06	0.76, 1.46	86	0.76	0.57, 1.01
Q4 ≥ 224.6	2245	61	0.86	0.61, 1.21	68	0.60	0.44, 0.81
P for trend			0.62			<0.001	
Per 10-μg increase			0.996	0.985, 1.006		0.991	0.981, 1.000
During pregnancy							
Q1 < 155.8	2245	84	1.00		165	1.00	
Q2 155.8–202.8	2239	76	1.01	0.73, 1.40	80	0.53	0.40, 0.70
Q3 202.8–272.1	2245	65	0.88	0.63, 1.23	75	0.50	0.38, 0.67
Q4 ≥ 272.1	2241	56	0.76	0.53, 1.08	68	0.47	0.35, 0.63
P for trend			0.10			<0.001	
Per 10-μg increase			0.992	0.981, 1.003		0.979	0.969, 0.990

[a] Adjusted for maternal age, education level, smoking, parity, pre-pregnancy BMI, family monthly income per capita, maternal employment during pregnancy, history of preterm, and dietary folate intake/folic acid supplementation

[b] Preterm premature rupture of membranes

Earlier epidemiological studies investigating the associations between PB and folic acid supplements/dietary folate intake have provided conflicting results [17–30, 42]; among them, Dunlop et al. [43] investigated plasma level of folate. While ten studies have reported a protective effect of folic acid supplements/dietary folate intake on PB [18–27], one study reported that risk of PB associated with folic acid supplement use varied by time periods of use (preconception, first trimester, and second trimester) [17] and four studies found no association [28–30, 42]. Variations in dosage of folic acid use, selected pregnancy period of use, definitions of PB by gestational age, and lack of consideration of PB clinical subtypes among different populations might partially contribute to the inconsistent results.

PB is a complex phenotype and different subtypes may have different etiologies [44]. Our study found a stronger reduced risk of spontaneous very preterm associated with folic acid supplements, which was consistent with some of the previous reports [19, 21]. Spontaneous very PB has been strongly associated with intrauterine infection [45]. Bacterial vaginosis has been shown to double the risk of spontaneous preterm delivery [46–48]. Lower folate concentration in maternal blood has been associated with impaired immune function, and subsequent high prevalence of urinary tract infection and bacterial vaginosis in pregnancy [43, 49]. Therefore, it is biologically plausible that folic acid supplements reduce the risk of spontaneous PB through promotion of immune function and prevention of infection [50].

Our study suggested that starting folic acid supplementation during preconception and early pregnancy, but not late pregnancy, decreased the risk of PB. Studies have suggested that intrauterine infection may occur early in pregnancy and remain undetected for months, resulting in spontaneous preterm labor or rupture of the membranes [45]. Folate concentration in serum continues to decrease for several weeks after pregnancy [51, 52] with folate total body half-life of 100 days [53]. Starting folic acid supplementation from preconception or the first trimester would maximize folate concentration in plasma and suppression of inflammatory processes as early as possible. Insufficient folic acid supplementation leads to lower concentrations of folate in plasma or red blood cells [54, 55].

Our study also found significant association between duration of folic acid supplementation and risk of overall PB and spontaneous PB during preconception and pregnancy, indicating that longer duration of intake had a beneficial effect on reduction in PB risk. Bukowski et al.

Table 6 Associations between folic acid supplementation, estimated dietary folate intake, and risk of medically indicated and spontaneous preterm birth

Folic acid/folate intake duration	Controls	Medically indicated preterm						Spontaneous preterm					
		Moderate preterm			Very preterm			Moderate preterm			Very preterm		
		Cases	OR[a]	95 % CI	Cases	OR[a]	95 % CI	Cases	OR[a]	95 % CI	Cases	OR[a]	95 % CI
Folic acid supplements													
Non-users	1982	94	1.00		26	1.00		158	1.00		55	1.00	
Users	7178	186	0.88	0.66, 1.16	32	0.61	0.34, 1.09	394	0.90	0.73, 1.11	74	0.42	0.29, 0.63
Dietary folate intake (μg/day)													
Preconception													
Q1 < 118.6	2248	95	1.00		14	1.00		157	1.00		47	1.00	
Q2 118.6–161.8	2236	56	0.69	0.49, 0.98	17	1.54	0.75, 3.17	141	1.01	0.79, 1.28	32	0.76	0.48, 1.21
Q3 161.8–224.6	2241	62	0.72	0.51, 1.00	17	1.41	0.68, 2.89	134	0.93	0.73, 1.19	29	0.68	0.42, 1.09
Q4 ≥ 224.6	2245	61	0.68	0.48, 0.96	6	0.51	0.19, 1.35	111	0.78	0.61, 1.01	18	0.41	0.24, 0.72
P for trend			0.03			0.28			0.06			0.001	
Per 10-μg increase			1.000	0.994, 1006		0.980	0.951, 1.009		0.996	0.989, 1.004		0.971	0.951, 0.992
During pregnancy													
Q1 < 155.8	2245	100	1.00		24	1.00		185	1.00		64	1.00	
Q2 155.8–202.8	2239	58	0.68	0.48, 0.95	14	0.75	0.38, 1.47	124	0.74	0.58, 0.94	32	0.57	0.37, 0.88
Q3 202.8–272.1	2245	62	0.77	0.55, 1.08	10	0.53	0.25, 1.12	125	0.76	0.60, 0.97	15	0.26	0.15, 0.46
Q4 ≥ 272.1	2241	54	0.61	0.43, 0.87	6	0.32	0.13, 0.81	109	0.68	0.53, 0.87	15	0.26	0.15, 0.47
P for trend			0.01			0.007			0.003			<0.001	
Per 10-μg increase			0.995	0.985, 1.005		0.962	0.931, 0.994		0.992	0.984, 1.000		0.942	0.920, 0.965

[a] Adjusted for maternal age, education level, smoking, parity, pre-pregnancy BMI, family monthly income per capita, maternal employment during pregnancy, history of preterm, and dietary folate intake/folic acid supplementation

Table 7 Associations between estimated dietary folate intake and risk of preterm birth stratified by folic acid supplement use

Dietary folate duration and intake levels (μg/day)	Folic acid supplement users				Folic acid supplement non-users			
	Controls	Cases	OR[a]	95 % CI	Controls	Cases	OR[a]	95 % CI
Preconception								
Q1 < 118.6	1765	197	1.00		483	116	1.00	
Q2 118.6–161.8	1882	180	0.91	0.73, 1.14	354	66	0.86	0.61, 1.21
Q3 161.8–224.6	1821	178	0.89	0.71, 1.12	420	64	0.70	0.50, 0.99
Q4 ≥ 224.6	1648	128	0.72	0.56, 0.92	597	68	0.58	0.41, 0.81
P for trend			0.01				<0.001	
Per 10-μg increase			0.999	0.994, 1.004			0.985	0.975, 0.995
During pregnancy								
Q1 < 155.8	1694	239	1.00		551	134	1.00	
Q2 155.8–202.8	1901	159	0.66	0.53, 0.83	338	69	0.84	0.60, 1.17
Q3 202.8–272.1	1819	159	0.70	0.56, 0.87	426	53	0.56	0.39, 0.80
Q4 ≥ 272.1	1702	126	0.58	0.45, 0.73	539	58	0.43	0.37, 0.75
P for trend			<0.001				<0.001	
Per 10-μg increase			0.990	0.982, 0.997			0.984	0.974, 0.995

[a] Adjusted for maternal age, education level, smoking, parity, pre-pregnancy BMI, family monthly income per capita, maternal employment during pregnancy, history of preterm, and dietary folate intake/folic acid supplementation

[19] reported that women with ≥1 year of preconception folic acid supplementation have a reduction in the risk of PB, compared to <1 year of intake. Other studies did not explore this association by duration of maternal supplementation.

Consistent with several earlier studies [22, 23, 27], but not all [17, 20, 29, 30], we found that higher dietary folate intake during pregnancy was associated with reduced risk of PB and certain subtypes. We did not observe a synergistic effect between dietary folate and folic acid supplements.

A major strength of our cohort is that we collected detailed information on both folic acid supplements and dietary folate intake. While our study had a relatively large sample size, statistical power was limited for stratified analyses. Although many important confounding factors have been adjusted for, we cannot rule out the potential for residual confounding. Because information on dietary folate and folic acid supplementation was collected through in-person interview at delivery, there was potential for recall bias. However, the relationships between folic acid supplementation, dietary folate intake, and risk of PB have not been well established and were unlikely to be known by the general public. Therefore, if there was any recall bias, it was likely to be non-differential and resulted in underestimation of the observed associations. Although the study was hospital based, which might impact generalizability, the PB rate (10.0 %) in our study population or (12.2 %) in the whole birth cohort were within the range of the reported rates (4.1–18.9 %) in other Chinese populations, as reviewed by Blencowe et al. [7]. A total of 87.4 % of the folic acid supplement users took 400 μg folic acid daily; therefore, we had limited power to examine the relationship with other doses. Recommendation of taking folic acid supplements starting from 3 months before pregnancy through the end of first trimester pregnancy has been exercised in China since 2009 to prevent neural tube defects [56]. While 77.2 % of women reported being folic acid users in our study population, only 29.0 % of women adhered to the recommendation. A survey in China conducted in 2008 reported an intake rate of 12 % among all women from the national-level poverty counties [33]. The higher intake rate in our study population could be because our study only focused on pregnant women in Lanzhou, which is an urban city in China with relatively higher education and income levels. Future studies are needed to identify women who would most benefit from folic acid supplementation.

In conclusion, our study supports the hypothesis that both folic acid supplementation and high dietary folate intake prior to and during pregnancy reduce the risk of PB, with stronger protective effect for spontaneous PB and very PB. The findings from our study have important public health implications and may facilitate acceptance of taking folic acid supplements during preconception and pregnancy.

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Conflict of interest None.

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