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Folic acid supplementation, dietary folate intake and risk of small for gestational age in China

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Abstract

Objective: To investigate the hypothesis that folic acid supplementation and dietary folate intake before conception and during pregnancy reduce the risk of small for gestational age (SGA) and to examine the joint effect of folic acid supplementation and dietary folate intake on the risk of SGA.

Design: Participants were interviewed by trained study interviewers using a standardized and structured questionnaire. Information on birth outcomes and maternal complications was abstracted from medical records and dietary information was collected via a semi-quantitative FFQ before conception and during pregnancy.

Setting: A birth cohort data analysis using the 2010–2012 Gansu Provincial Maternity and Child Care Hospital.

Participants: Women (*n* 8758) and their children enrolled in the study.

Results: Folic acid supplementation was associated with a reduced risk of SGA (OR = 0·72, 95 % CI 0·60, 0·86), with the reduced risk seen mainly for SGA at ≥37 weeks of gestational age (OR = 0·70, 95 % CI 0·58, 0·85) and nulliparous SGA (OR = 0·67, 95 % CI 0·54, 0·84). There was no significant association between dietary folate intake and SGA risk.

Conclusions: Our study suggested that folic acid supplementation was associated with a reduced risk of SGA and the risk varied by preterm status and parity.

Keywords
Folic acid supplementation
Dietary folate intake
Small for gestational age
Cohort study

Small for gestational age (SGA) increases neonatal mortality and various infant morbidities, including chronic lung disease, necrotizing enterocolitis, perinatal acidosis, hypoglycaemia, hypothermia, coagulation abnormalities and selected immunological deficiencies[1,2]. It also leads to chronic diseases in later life such as type 2 diabetes, hypertension, obesity, CVD and mental health problems[3–9]. The associated economic costs due to immediate neonatal intensive care, ongoing long-term complex health needs and lost economic productivity can be substantial. Unfortunately, modern obstetrics is still unable to predict, prevent or treat SGA[10].

Folate acts as a coenzyme in the biosynthesis of purine nucleotides and deoxythymidylic acid which are essential for DNA and RNA synthesis[11]. While folic acid supplementation has been recommended for prevention of neural tube defects, its impact on other birth outcomes is not fully understood. Epidemiological studies investigating the associations of folic acid supplementation and dietary folate intake with SGA have provided conflicting results[12–34]. Eleven studies found that folic acid supplementation before and/or during pregnancy reduced the risk of SGA[15–17,20,22,26,28,30,32–34], but three studies reported no association between folic acid supplementation and

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SGA[14,25,31]. In addition, three studies suggested that a high dosage of folic acid may be associated with an increased risk of SGA at birth[23,24,27]. Two studies found that dietary folate intake during periconception or pregnancy was a protective factor for SGA[17,27], but one study found that SGA was not associated with dietary folate intake during the second trimester[25]. Five studies reported that higher folate concentrations in blood (erythrocyte or serum) during preconception or pregnancy had a protective effect on SGA[12,13,18,19,21], but one study found that SGA was not associated with folate concentrations[29]. Today, folic acid supplementation and dietary folate intake are recommended to women in many countries. A recommendation to take folic acid supplements starting from 3 months before pregnancy until the end of the first trimester of pregnancy to prevent neural tube defects has been exercised in China since 2009 and users take 400 μg folic acid daily[35]. National health authorities in many countries recommend periconceptional folic acid supplementation, and some countries have introduced mandatory folate fortification of foods[36–40]. By taking account of the joint effect of folic acid supplementation and dietary folate intake, it might be possible to define the folic acid supplementation scheme mostly likely to affect SGA risk. However, no study has examined the joint effect of folic acid supplementation and dietary folate intake on the risk of SGA.

Approximately one-fifth of the world's population is Chinese. The rate of SGA infants has increased over recent years, with the reported rate of SGA ranging from 5·82 to 17·5 %[22,31,33,34]. The typical diet of northern China is characterized by low amounts of fresh vegetables and fruits, particularly during the winter, resulting in low blood concentrations of folate[41]. Only 10–15 % of women of childbearing age routinely take folic acid supplements[42–44]. Given the low percentage of folic acid supplementation among women of childbearing age, seasonal variation of dietary folate intake and the lack of folic acid fortification in staple foods in China, the Lanzhou birth cohort study provides a unique opportunity to concurrently study the impact of folic acid supplementation and dietary folate intake on SGA.

Materials and methods

Study population

A birth cohort was conducted in 2010–2012 at the Gansu Provincial Maternity and Child Care Hospital (GPMCCH), the largest maternity and child care hospital in Lanzhou, China[45–48]. 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. Maternal characteristics (age, income, education level, parity, BMI, etc.), social factors (employment status, height of partner, etc.), lifestyle factors (smoking status, drinking, etc.) and pre-existing medical and previous obstetric history (history of preterm birth, caesarean section, etc.) were self-reported. Pregnancy complications and birth outcomes (pre-eclampsia, gestational diabetes, birth weight, gender of live birth, etc.) were based on diagnoses from the medical records. All women were interviewed within 1–3 d after delivery. A total of 14 359 eligible women were approached for participation and 10 542 (73·4 %) women completed in-person interviews, with 10 179 singleton live births. Among 363 fetuses, 323 were multiple fetuses and forty fetuses died *in utero* (>32 weeks) or were stillborn. All study procedures were approved by the human investigation committees at the GPMCCH and Yale University.

Gestational age at delivery was calculated in completed weeks from the first day of the last menstrual period. All self-reported last menstrual period dates were further verified by ultrasound examinations during antenatal care in the hospital. SGA was defined as a birth weight below the 10th percentile of the gestational-age- and gender-specific birth weight standard for Chinese newborns[49]; large for gestational age was defined as a birth weight greater than the 90th percentile of the standard; while appropriate for gestational age (AGA) was defined as a birth weight between the 10th and 90th percentile of the standard. The range of gestational age in the Chinese national standard was from 28 to 44 weeks[49]. For neonates with a gestational age of 22–27 weeks, the US national reference based on 2009–2010 live births was applied as a surrogate[50]. After exclusion of large-for-gestational-age births, 8758 (784 SGA and 7974 AGA) were included in the final analysis.

Folic acid supplementation and dietary folate intake

Data collection on folic acid supplementation and dietary folate intake has been described in a previous study and the FFQ was validated[47]. Folic acid supplementation started from 3 months before pregnancy through to the end of the first trimester of pregnancy and users took 400 μg folic acid daily. 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, the duration and frequency of folic acid supplementation alone and of folic acid-containing multivitamins were ascertained. Folic acid supplementation users were defined as those who took folic acid supplements alone or folic acid-containing multivitamins before conception or during pregnancy. Preconception and pregnancy users were defined as those who took folic acid supplements alone or folic acid-containing multivitamins before conception and during pregnancy. Preconception-only users were defined as those who took folic acid supplements alone or folic acid-containing multivitamins before conception

only. Pregnancy-only users were defined as those who took folic acid supplements alone or folic acid-containing multivitamins during pregnancy only. Non-users were defined as those who never took folic acid supplements alone or folic acid-containing multivitamins before conception and/or during pregnancy. The final variables included folic acid supplement users and non-users; folic acid supplements were classified into three levels by duration of use: before conception and during pregnancy, before conception only and during pregnancy only.

Dietary information was collected via a semi-quantitative FFQ. 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[51].

Statistical analysis

Pearson's χ^2 tests were used to compare selected characteristics between AGA and SGA. Unconditional logistic regression models were used to estimate the odds ratio and 95 % confidence interval for single associations of folic acid supplementation and dietary folate intake with SGA. The interaction analysis of multiplication models, done by logistic regression modelling, estimated the joint effect of folic acid supplementation and dietary folate intake on SGA. Dose–response relationships (and P_{trend}) were calculated by including those categorical levels. According to the literature and the results of univariate analysis, potential confounders including maternal age, monthly income per capita, maternal education level, smoking, maternal employment, pre-pregnancy BMI, weight gain during pregnancy, pre-eclampsia, parity, caesarean section, height of the child's father, history of preterm birth, total energy intake, dietary folate intake and folic acid supplementation were adjusted for in the multivariable logistic regression model. In some previous studies, the results showed that high dosage of folic acid may be associated with an increased risk of SGA at birth[23,24,27]. Therefore, we conducted a sensitivity analysis restricted to participants with <24 weeks of gestational of age. We assessed goodness-of-fit of the models in the present study and all showed a good fit by the Homser–Lemeshow test ($P > 0{\cdot}05$). All analyses were performed using the statistical software package SAS version 9.4.

Table 1 Distributions of selected participant characteristics, according to small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) births, among women (*n* 8758) and their children enrolled in the 2010–2012 Gansu Provincial Maternity and Child Care Hospital birth cohort, Lanzhou, China

	AGA (*n* 7974)		SGA (*n* 784)		
Characteristic	*n*	%	*n*	%	*P* value
Maternal age (years)					
<25	1812	88·78	229	11·22	<0·001
25–29	3330	92·35	276	7·65	
≥30	2832	91·03	279	8·97	
Monthly income per capita (RMB)					
<3000	4193	89·48	493	10·52	<0·001
≥3000	3781	92·85	291	7·15	
Maternal education level					
<College	4903	89·67	565	10·33	<0·001
≥College	3071	93·34	219	6·66	
Smoking (passive and active)					
No	6430	91·65	586	8·35	<0·001
Yes	1544	88·63	198	11·37	
Drink during pregnancy					
No	7959	91·05	782	8·95	0·684*
Yes	15	88·24	2	11·76	
Maternal employment					
No	3812	89·69	438	10·31	<0·001
Yes	4162	92·32	346	7·68	
Pre-pregnancy BMI (kg/m^2)					
<18·5	1724	89·70	198	10·30	0·005
18·5–23·9	5292	91·76	475	8·24	
≥24·0	958	89·62	111	10·38	
Weight gain during pregnancy (kg)					
<15	2524	88·34	333	11·66	<0·001
15–18·5	2560	91·72	231	8·28	
>18·5	2890	92·93	220	7·07	
Pre-eclampsia					
No	7768	91·87	687	8·13	<0·001
Yes	206	67·99	97	32·01	
Gestational diabetes					
No	7913	91·02	781	8·98	0·230
Yes	61	95·31	3	4·69	
Parity					
Primipara	5826	91·59	535	8·41	0·027
Multipara	2148	89·61	249	10·39	
Caesarean section					
No	5164	92·30	431	7·70	<0·001
Yes	2810	88·84	353	11·16	
History of preterm birth					
No	7920	91·12	772	8·88	0·008
Yes	54	81·82	12	18·18	
Height of child's father (cm)					
≤175	5416	90·43	573	9·57	0·003
>175	2558	92·38	211	7·62	
Gender of live birth					
Male	4186	91·52	388	8·48	0·108
Female	3788	90·54	396	9·46	

*Fisher's exact test.

Results

Table 1 shows the distributions of selected characteristics in participants with SGA and AGA births. Women who had SGA births were more likely to be younger than 25 years old, have less family income and lower education level, be exposed to smoke, be unemployed during pregnancy, have a lower pre-pregnancy BMI, gain less weight during pregnancy, be diagnosed with pre-eclampsia, be multipara, undergo caesarean delivery and have a history of preterm birth. Paternal height of SGA was more likely to be shorter than 175 cm compared with paternal height of AGA. Distributions of alcohol drinking during pregnancy, gestational diabetes and infant's gender were similar between SGA and AGA.

Compared with non-users, folic acid supplement users had a reduced risk of SGA (OR = 0·72, 95 % CI 0·60, 0·86; Table 2). The significant reduced odds was seen mainly

Table 2 Associations of folic acid supplementation and dietary folate intake with the risk of small for gestational age (SGA) among women (*n* 8758) and their children enrolled in the 2010–2012 Gansu Provincial Maternity and Child Care Hospital birth cohort, Lanzhou, China

Folic acid/folate intake duration	AGA (*n* 7974)	SGA (*n* 784)	OR	95 % CI	OR*	95 % CI
Folic acid supplement						
Non-users	1762	252	1·00	Ref.	1·00	Ref.
Users	6212	532	0·60	0·51, 0·70	0·72	0·60, 0·86
≤12 weeks	3239	321	0·69	0·58, 0·83	0·79	0·66, 0·96
>12 weeks	2973	211	0·70	0·64, 0·78	0·78	0·70, 0·87
P_{trend}			<0·001		<0·001	
Per 2-week increase			0·943	0·928, 0·959	0·962	0·945, 0·979
Before conception and during pregnancy	2344	155	0·46	0·37, 0·57	0·58	0·46, 0·75
<24 weeks	1101	78	0·50	0·38, 0·65	0·61	0·45, 0·81
≥24 weeks	1243	77	0·66	0·58, 0·75	0·77	0·66, 0·90
P_{trend}			<0·001		<0·001	
Per 2-week increase			0·937	0·919, 0·954	0·955	0·935, 0·976
Before conception only	294	28	0·67	0·44, 1·01	0·84	0·54, 1·29
≤8 weeks	123	12	0·68	0·37, 1·25	0·76	0·41, 1·41
>8 weeks	171	16	0·81	0·62, 1·05	0·95	0·72, 1·26
P_{trend}			0·061		0·471	
Per 2-week increase			0·936	0·870, 1·008	0·975	0·904, 1·052
During pregnancy only	3574	349	0·68	0·58, 0·81	0·78	0·65, 0·94
≤8 weeks	1415	164	0·81	0·66, 1·00	0·85	0·68, 1·06
>8 weeks	2159	185	0·77	0·70, 0·86	0·85	0·76, 0·95
P_{trend}			<0·001		0·002	
Per 2-week increase			0·948	0·925, 0·970	0·966	0·942, 0·991
Dietary folate intake (μg/d)						
Before pregnancy						
Q1 < 115·63	1963	232	1·00	Ref.	1·00	Ref.
Q2 = 115·63–157·42	2002	157	0·66	0·54, 0·82	0·78	0·62, 1·00
Q3 = 157·42–218·91	1959	206	0·94	0·85, 1·04	1·04	0·93, 1·16
Q4 ≥ 218·91	2050	189	0·92	0·86, 1·00	1·02	0·93, 1·12
P_{trend}			0·124		0·311	
Per 10-μg increase			0·996	0·982, 1·010	1·014	0·997, 1·031
During pregnancy						
Q1 < 149·47	1971	240	1·00	Ref.	1·00	Ref.
Q2 = 149·47–197·56	1967	185	0·77	0·63, 0·95	0·92	0·73, 1·15
Q3 = 197·56–263·21	1988	166	0·83	0·75, 0·92	0·97	0·86, 1·10
Q4 ≥ 263·21	2048	193	0·92	0·86, 0·98	1·06	0·96, 1·18
P_{trend}			0·005		0·418	
Per 10-μg increase			0·985	0·971, 0·998	1·012	0·995, 1·030

AGA, appropriate for gestational age; Q, quartile; ref., reference category.
Multiplicative interaction on SGA: OR = 0·85 (95 % CI 0·71, 1·01), *P* = 0·062.
*OR adjusted for maternal age, monthly income per capita, maternal education level, smoking, maternal employment, pre-pregnancy BMI, weight gain during pregnancy, pre-eclampsia, parity, caesarean section, height of child's father, history of preterm birth, total energy intake, dietary folate intake or folic acid supplement.

for those who had used folic acid supplements for more than 12 weeks (OR = 0·78, 95 % CI 0·70, 0·87, P_{trend} < 0·001; OR = 0·962, 95 % CI 0·945, 0·979 per 2-week increase in folic acid supplement use). After stratifying by time period of use, significant associations were observed for those who took supplements before conception and during pregnancy (OR = 0·58, 95 % CI 0·46, 0·75, P_{trend} < 0·001; OR = 0·955, 95 % CI 0·935, 0·976 per 2-week increase) or during pregnancy only (OR = 0·78, 95 % CI 0·65, 0·94, P_{trend} = 0·002; OR = 0·966, 95 % CI 0·942, 0·991 per 2-week increase). No significant association was observed among women who took supplements before conception only. We did not observe significant associations between dietary folate intake and SGA. In addition, we assessed the joint effect of folic acid supplementation and dietary folate intake on SGA and found no significant interaction between them ($P_{interaction}$ = 0·062). Additionally, in the sensitivity analysis restricted to the participants with <24 weeks of gestational age (see online supplementary material, Supplemental Table S1), the results were consistent with the findings of Table 2; significant associations also were observed for those who took supplements before conception and during pregnancy (OR = 0·62, 95 % CI 0·48, 0·81, P_{trend} < 0·001; OR = 0·953, 95 % CI 0·927, 0·980 per 2-week increase).

We then analysed the data separately for SGA at ≥37 weeks of gestational age and SGA at <37 weeks of gestational age (Table 3). Significant protective effects of folic acid supplement use were seen on SGA at ≥37 weeks of gestational age (OR = 0·70, 95 % CI 0·58, 0·85 for users; OR = 0·59, 95 % CI 0·45, 0·77 for use before conception and during pregnancy, with OR = 0·953, 95 % CI 0·931, 0·976 per 2-week increase in folic acid supplement use; and OR = 0·76, 95 % CI 0·62, 0·93 for use during pregnancy only, with OR = 0·968, 95 % CI 0·941, 0·994 per 2-week increase) and no significant association was observed among women who took supplements before conception only. We did not observe significant associations between

Table 3 Associations of folic acid supplementation and dietary folate intake with the risk of small for gestational age (SGA) at ≥37 weeks of gestational age and SGA at <37 weeks of gestational age among women (*n* 8758) and their children enrolled in the 2010–2012 Gansu Provincial Maternity and Child Care Hospital birth cohort, Lanzhou, China

	SGA at ≥37 weeks of gestational age						SGA at <37 weeks of gestational age					
Folic acid/folate intake duration	Controls (*n* 7211)	Cases (*n* 632)	OR	95 % CI	OR*	95 % CI	Controls (*n* 763)	Cases (*n* 152)	OR	95 % CI	OR*	95 % CI
Folic acid supplement												
Non-users	1531	197	1·00	Ref.	1·00	Ref.	231	55	1·00	Ref.	1·00	Ref.
Users	5680	435	0·60	0·50, 0·71	0·70	0·58, 0·85	532	97	0·77	0·48, 1·25	0·76	0·53, 1·10
≤12 weeks	2901	258	0·69	0·57, 0·84	0·79	0·64, 0·97	338	63	0·78	0·53, 1·17	0·77	0·49, 1·21
>12 weeks	2779	177	0·70	0·63, 0·78	0·77	0·68, 0·87	194	34	0·86	0·68, 1·08	0·79	0·59, 1·06
P_{trend}			<0·001		<0·001				0·177		0·137	
Per 2-week increase			0·944	0·927, 0·961	0·961	0·943, 0·980			0·971	0·935, 1·010	0·966	0·925, 1·011
Before conception and during pregnancy	2173	128	0·46	0·36, 0·58	0·59	0·45, 0·77	171	27	0·66	0·40, 1·10	0·58	0·32, 1·07
<24 weeks	1007	65	0·50	0·38, 0·67	0·64	0·46, 0·88	94	13	0·58	0·30, 1·11	0·47	0·23, 1·00
≥24 weeks	1166	63	0·65	0·56, 0·75	0·76	0·64, 0·91	77	14	0·87	0·63, 1·20	0·84	0·58, 1·24
P_{trend}			<0·001		<0·001				0·221		0·271	
Per 2-week increase			0·936	0·917, 0·955	0·953	0·931, 0·976			0·970	0·929, 1·015	0·971	0·921, 1·023
Before conception only	266	25	0·73	0·47, 1·13	0·92	0·58, 1·45	28	3	0·45	0·13, 1·53	0·38	0·11, 1·47
During pregnancy only	3241	282	0·68	0·56, 0·82	0·76	0·62, 0·93	333	67	0·85	0·57, 1·25	0·80	0·50, 1·26
≤8 weeks	1252	124	0·77	0·61, 0·98	0·81	0·64, 1·04	163	40	1·03	0·66, 1·62	0·95	0·56, 1·59
>8 weeks	1989	158	0·79	0·70, 0·88	0·86	0·76, 0·96	170	27	0·82	0·64, 1·05	0·77	0·57, 1·03
P_{trend}			<0·001		0·006				0·144		0·080	
Per 2-week increase			0·950	0·926, 0·975	0·968	0·941, 0·994			0·968	0·914, 1·026	0·947	0·887, 1·010
Dietary folate intake (μg/d)												
Before pregnancy												
Q1 < 115·63	1736	172	1·00	Ref.	1·00	Ref.	227	60	1·00	Ref.	1·00	Ref.
Q2 = 115·63–157·42	1815	128	0·71	0·56, 0·91	0·83	0·65, 1·07	187	29	0·59	0·36, 0·96	0·59	0·32, 1·06
Q3 = 157·42–218·91	1773	173	0·99	0·89, 1·11	1·09	0·97, 1·23	186	33	0·82	0·65, 1·04	0·93	0·70, 1·24
Q4 ≥ 218·91	1887	159	0·95	0·88, 1·02	1·03	0·93, 1·13	163	30	0·89	0·76, 1·05	1·02	0·81, 1·29
P_{trend}			0·609		0·194				0·119		0·718	
Per 10-μg increase			1·001	0·986, 1·016	1·020	0·993, 1·037			0·982	0·948, 1·017	0·992	0·953, 1·036
During pregnancy												
Q1 < 149·47	1705	183	1·00	Ref.	1·00	Ref.	266	57	1·00	Ref.	1·00	Ref.
Q2 = 149·47–197·56	1788	146	0·76	0·61, 0·96	0·84	0·65, 1·09	179	39	1·02	0·65, 1·59	1·29	0·75, 2·24
Q3 = 197·56–263·21	1822	135	0·83	0·74, 0·93	0·98	0·86, 1·12	166	31	0·93	0·74, 1·19	0·99	0·72, 1·37
Q4 ≥ 263·21	1896	168	0·94	0·87, 1·00	1·04	0·93, 1·17	152	25	0·92	0·77, 1·09	1·35	0·99, 2·.01
P_{trend}			0·063		0·369				0·276		0·951	
Per 10-μg increase			0·992	0·977, 1·007	1·018	0·998, 1·036			0·976	0·943, 1·010	0·988	0·944, 1·034

Q, quartile; ref., reference category.
Multiplicative interaction on SGA at ≥37 weeks of gestational age: OR = 1·04 (95 % CI 0·84, 1·29), *P* = 0·698.
Multiplicative interaction on SGA at <37 weeks of gestational age: OR = 0·64 (95 % CI 0·38, 1·06), *P* = 0·085.
*OR adjusted for maternal age, monthly income per capita, education level, smoking, employment, pre-pregnancy BMI, weight gain during pregnancy, pre-eclampsia, parity, caesarean section, height of child's father, history of preterm birth, total energy intake, dietary folate intake or folic acid supplement.

Table 4 Associations of folic acid supplementation and dietary folate intake with the risk of nulliparous small for gestational age (SGA) and multiparous SGA among women (*n* 8758) and their children enrolled in the 2010–2012 Gansu Provincial Maternity and Child Care Hospital birth cohort, Lanzhou, China

	Nulliparous SGA						Multiparous SGA					
Folic acid/folate intake duration	Controls (*n* 5826)	Cases (*n* 535)	OR	95 % CI	OR*	95 % CI	Controls (*n* 2148)	Cases (*n* 249)	OR	95 % CI	OR*	95 % CI
Folic acid supplement												
Non-users	982	138	1·00	Ref.	1·00	Ref.	780	114	1·00	Ref.	1·00	Ref.
Users	4844	397	0·58	0·48, 0·72	0·67	0·54, 0·84	1368	135	0·68	0·52, 0·88	0·80	0·61, 1·06
≤12 weeks	2379	224	0·67	0·54, 0·84	0·73	0·58, 0·93	860	97	0·77	0·58, 1·03	0·90	0·67, 1·22
>12 weeks	2465	173	0·71	0·63, 0·80	0·79	0·69, 0·91	508	38	0·72	0·59, 0·87	0·77	0·63, 0·95
P_{trend}			<0·001		<0·001				<0·001		0·022	
Per 2-week increase			0·949	0·932, 0·967	0·965	0·946, 0·985			0·933	0·902, 0·966	0·951	0·917, 0·985
Before conception and during pregnancy	1971	132	0·48	0·37, 0·61	0·62	0·46, 0·83	373	23	0·42	0·27, 0·67	0·52	0·32, 0·85
<24 weeks	889	64	0·51	0·35, 0·70	0·64	0·45, 0·91	212	14	0·62	0·44, 0·88	0·70	0·48, 1·01
≥24 weeks	1082	68	0·67	0·58, 0·78	0·79	0·66, 0·94	161	9	0·45	0·25, 0·80	0·53	0·29, 0·97
P_{trend}			<0·001		0·002				<0·001		0·010	
Per 2-week increase			0·941	0·921, 0·962	0·960	0·937, 0·984			0·920	0·879, 0·964	0·938	0·893, 0·986
Before conception only	224	21	0·67	0·41, 1·08	0·85	0·51, 1·41	70	7	0·68	0·31, 1·53	0·83	0·36, 1·88
During pregnancy only	2649	244	0·66	0·53, 0·82	0·71	0·56, 0·90	925	105	0·78	0·59, 1·03	0·90	0·67, 1·21
≤8 weeks	983	110	0·80	0·61, 1·04	0·78	0·59, 1·03	432	54	0·86	0·61, 1·21	0·97	0·68, 1·39
>8 weeks	1666	134	0·76	0·67, 0·86	0·83	0·72, 0·95	493	51	0·71	0·50, 1·01	0·79	0·54, 1·14
P_{trend}			<0·001		0·002				0·051		0·265	
Per 2-week increase			0·954	0·925, 0·982	0·969	0·941, 0·998			0·943	0·902, 0·996	0·958	0·915, 1·004
Dietary folate intake (μg/d)												
Before pregnancy												
Q1 < 115·63	1399	147	1·00	Ref.	1·00	Ref.	564	85	1·00	Ref.	1·00	Ref.
Q2 = 115·63–157·42	1523	122	0·76	0·59, 0·99	0·90	0·68, 1·18	479	35	0·49	0·32, 0·73	0·56	0·36, 0·90
Q3 = 157·42–218·91	1450	139	0·96	0·85, 1·08	1·07	0·94, 1·23	509	67	0·94	0·79, 1·11	0·96	0·79, 1·17
Q4 ≥ 218·91	1454	127	0·94	0·87, 1·02	1·02	0·91, 1·14	596	62	0·88	0·79, 0·99	1·02	0·87, 1·19
P_{trend}			0·338		0·440				0·182		0·713	
Per 10-μg increase			1·004	0·988, 1·021	1·022	1·004, 1·041			0·979	0·956, 1·003	1·001	0·973, 1·031
During pregnancy												
Q1 < 149·47	1294	156	1·00	Ref.	1·00	Ref.	677	84	1·00	Ref.	1·00	Ref.
Q2 = 149·47–197·56	1484	127	0·71	0·56, 0·91	0·85	0·65, 1·12	483	58	0·97	0·68, 1·38	1·08	0·73, 1·60
Q3 = 197·56–263·21	1560	113	0·78	0·68, 0·88	0·90	0·78, 1·05	428	53	0·99	0·83, 1·20	1·18	0·95, 1·47
Q4 ≥ 263·21	1488	139	0·92	0·85, 0·99	1·06	0·93, 1·20	560	54	0·92	0·82, 1·04	1·11	0·92, 1·34
P_{trend}			0·019		0·794				0·223		0·373	
Per 10-μg increase			0·992	0·975, 1·009	1·019	0·998, 1·040			0·975	0·952, 0·999	0·999	0·969, 1·030

Q, quartile; ref., reference category.
Multiplicative interaction on nulliparous SGA: OR = 0·88 (95 % CI 0·72, 1·08), *P* = 0·228.
Multiplicative interaction on multiparous-SGA: OR = 0·79 (95 % CI 0·56, 1·11), *P* = 0·174.
*OR adjusted for maternal age, monthly income per capita, education level, smoking, employment, pre-pregnancy BMI, weight gain during pregnancy, pre-eclampsia, caesarean section, height of child's father, history of preterm, total energy intake, dietary folate intake or folic acid supplement.

folic acid supplement use and SGA at <37 weeks of gestational age. Nor did we observe any significant associations of SGA at ≥37 weeks of gestational age and SGA at <37 weeks of gestational age with dietary folate intake. In addition, we assessed the joint effect of folic acid supplementation and dietary folate intake on SGA at ≥37 weeks of gestational age and SGA at <37 weeks of gestational age; there was no significant interaction on SGA at ≥37 weeks of gestational age ($P_{interaction}$ = 0·698) or on SGA at <37 weeks of gestational age ($P_{interaction}$ = 0·085).

We further stratified the analysis by parity (Table 4). A significant protective effect on nulliparous SGA was observed among folic acid supplementation users (OR = 0·67, 95 % CI 0·54, 0·84), but folic acid supplementation was not related to multiparous SGA (OR = 0·80, 95 % CI 0·61, 1·06). The significant protective effect on nulliparous SGA was observed for those who took supplements before conception and during pregnancy (OR = 0·62, 95 % CI 0·46, 0·83, P_{trend} = 0·002; OR = 0·960, 95 % CI 0·937, 0·984 per 2-week increase in folic acid supplement use) and during pregnancy only (OR = 0·71, 95 % CI 0·56, 0·90, P_{trend} = 0·002; OR = 0·969, 95 % CI 0·941, 0·998 per 2-week increase), but not before conception only (OR = 0·85, 95 % CI 0·51, 1·41). We did not observe significant associations of nulliparous SGA and multiparous SGA with dietary folate intake. In addition, we assessed the joint effect of folic acid supplementation and dietary folate intake on nulliparous SGA and multiparous SGA, and found no significant interaction (nulliparous SGA: $P_{interaction}$ = 0·228, multiparous SGA: $P_{interaction}$ = 0·174).

Discussion

To our knowledge, our study represents the first one to concurrently examine folic acid supplementation and dietary folate intake in relation to the risk of SGA. Our study found that folic acid supplementation was associated with a reduced risk of SGA and the protective association was seen mainly for term births and births from nulliparous mothers. No significant interaction between folic acid supplementation and dietary folate intake was found for SGA, SGA at <37 weeks of gestational age, SGA at ≥37 weeks of gestational age, nulliparous SGA and multiparous SGA.

Earlier studies investigating the associations of folic acid supplementation and dietary folate intake with SGA provided conflicting results[12–22,25–30]. Variations in dosage of folic acid used, time periods and duration of folic acid supplementation, definition of SGA, and lack of consideration of effects of preterm birth and parity on SGA among different populations might partially contribute to the inconsistent results.

Our study found that folic acid supplementation was associated with a reduced risk of SGA overall. However, when data were stratified by time periods of folic acid supplementation, significant associations were observed for those who took supplements before conception and during pregnancy or during pregnancy only, but not for those taking supplements before conception only, which was consistent with some previous studies[13,17–22,26,28,30,33]. The magnitude of the protective effect of folic acid supplementation seemed greater for taking supplements before conception and during pregnancy compared with taking supplements during pregnancy only. While the strengthened association could be due to longer duration of intake, there are possible biological mechanisms that could explain the observed association. Folate is an essential ingredient in the synthesis of methionine and subsequent *S*-adenosylmethionine, which plays a key role in DNA methylation[52]. The epigenome is particularly susceptible during the early stages of embryogenesis[53]. Abnormal folate concentration may cause epigenetic modifications and subsequently result in altered placental and fetal growth patterns[54–58]. Furthermore, folate plays a critical role in protein and DNA synthesis[36,54]. Sufficient folate intake promotes a cell-rich placenta[59], which is beneficial later in the quantitatively important growth phase of the fetus, and insufficient folate intake during pregnancy will lead concentrations of folate in maternal plasma and erythrocytes to decrease from the fifth month of pregnancy onwards[60]. Significant fetal growth takes place during the later second trimester and the third trimester, therefore a sufficient supply of folate during pregnancy is critical to maintain normal fetal growth[61–63].

Our study found that folic acid supplementation was associated with SGA at ≥37 weeks of gestational age but not with SGA at <37 weeks of gestational age, suggesting that SGA at ≥37 weeks of gestational age and SGA at <37 weeks of gestational age are two different types of SGA and might have different aetiological profiles. To our knowledge, the current study is the first investigating the relationship between SGA at ≥37 weeks of gestational age and folic acid supplementation, and the second study investigating the relationship between SGA at <37 weeks of gestational age and folic acid supplementation, but Chen *et al.* found that taking folic acid supplementation more than 3 months before pregnancy was associated with a significant reduction in incidence of preterm SGA[16]. So, the biological processes should be studied further.

Our study also found a significant protective effect of folic acid supplementation on nulliparous SGA but not multiparous SGA. It has been suggested that multiparous women offer a more favourable environment for placental and fetal growth by remodelling of the maternal vascular structure in former pregnancies[36,55], which may attenuate the effect of folic acid supplementation on fetal growth. Actually, the biological processes should also be further studied.

Limitations should be considered when interpreting the study results. Information on folic acid supplementation

and dietary folate intake was based on self-report, thus potential recall bias was unavoidable. Since the benefit of folic acid on SGA was not well established, there was unlikely differential recall bias associated with SGA. A strong correlation between self-reported folate intake and serum folate concentrations during pregnancy has been suggested[63]. While we collected detailed information on potential confounding variables, residual confounding resulting from unknown sources cannot be ruled out. Although our study had relatively large sample size, limited statistical power was presented for stratified analysis, particularly for SGA at <37 weeks of gestational age. In addition, the representation of the sample in the study was limited because the participation rate was 74 %.

Conclusion

In conclusion, our study suggested a protective effect of folic acid supplementation on risk of SGA and the protective effect varied by preterm status and parity. Future studies are warranted to replicate the findings.

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Supplementary material

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