



**Figure S1.** Flowchart of the pregnancies included in the study.

**Table S1.** Characteristics of pregnant women according to maternal response status between 2010 and 2016.

Maternal characteristics	Response				Total	
	Yes		No			
	(N=67,439)		(N=29,485)		(N=96,924)	
	n	%	n	%	n	%
Maternal periconceptional FA supplementation						
No supplementation	15,461	22.93	5,411	18.35	20,872	22.93
Starting after conception	17,926	26.58	7,260	24.62	25,186	26.58
Starting 1-2 months prior to conception	12,258	18.18	6,069	20.58	18,327	18.18
Starting at least 3 months prior to conception	21,794	32.32	10,745	36.44	32,539	32.32
Maternal age (years)						
20–24	31,318	46.44	13,210	44.80	44,528	46.44
25–29	26,516	39.32	11,473	38.91	37,989	39.32
30–34	6,666	9.88	3,259	11.05	9,925	9.88
≥35	2,721	4.03	1,432	4.86	4,153	4.03
Missing	218	0.32	111	0.38	329	0.32
Maternal ethnicity						
Han	62,740	93.03	27,338	92.72	90,078	93.03
Others	2,926	4.34	1,899	6.44	4,825	4.34
Missing	1,773	2.63	248	0.84	2,021	2.63
Maternal education						
Primary school or below	2,771	4.11	1,224	4.15	3,995	4.11
Junior high school	28,124	41.70	12,289	41.68	40,413	41.70
Senior high school	16,075	23.84	6,932	23.51	23,007	23.84
College /University or above	17,058	25.29	8,261	28.02	25,319	25.29
Missing	3,411	5.06	779	2.64	4,190	5.06
Maternal employment						
Farmer	28,618	42.44	12,845	43.56	41,463	42.78
Worker	6,646	9.85	2,752	9.33	9,398	9.70

waiter	7,253	10.75	2,948	10.00	10,201	10.52
Merchant	2,332	3.46	1,063	3.61	3,395	3.50
Housewife	3,767	5.59	1,458	4.94	5,225	5.39
Teacher/civil servant/staff	9,897	14.68	4,759	16.14	14,656	15.12
Others	6,222	9.23	3,171	10.75	9,393	9.69
Missing	2,704	4.01	489	1.66	3,193	3.29
Maternal household registration						
Rural	49,631	73.59	21,489	72.88	71,120	73.59
Urban	17,802	26.40	7,995	27.12	25,797	26.40
Missing	6	0.01	1	0.00	7	0.01
Maternal BMI before pregnancy (kg/m <sup>2</sup> )						
<18.5	10,029	14.87	4,350	14.75	14,379	14.87
18.5–23.9	48,180	71.44	20,957	71.08	69,137	71.44
24–27.9	6,662	9.88	3,235	10.97	9,897	9.88
≥28	1,155	1.71	556	1.89	1,711	1.71
Missing	1,413	2.10	387	1.31	1,800	2.10
Passive smoking before pregnancy						
No	54,948	81.48	25,212	85.51	80,160	81.48
Occasional	9,485	14.06	3,405	11.55	12,890	14.06
Often	1,367	2.03	460	1.56	1,827	2.03
Missing	1,639	2.43	408	1.38	2,047	2.43
Husbands' smoking in early pregnancy						
No	47,825	70.92	20,440	69.32	68,265	70.92
Decreased	9,960	14.77	4,623	15.68	14,583	14.77
Yes	9,571	14.19	4,356	14.77	13,927	14.19
Missing	83	0.12	66	0.22	149	0.12
parity						
0	48,248	71.54	20,068	68.06	68,316	71.54
≥1	19,191	28.46	9,417	31.94	28,608	28.46





	<18.5	3,240	15.29	1,838	15.54	2,669	15.35	2,078	13.64	9,825
	18.5–23.9	15,323	<b>72.33</b>	8,453	71.47	12,373	71.14	10,776	70.71	46,925
	24–27.9	1,943	9.17	1,089	9.21	1,746	10.04	1,620	10.63	6,398
	≥28	328	1.55	190	1.61	256	1.47	317	2.08	1,091
	Missing	350	1.65	258	2.18	348	2.00	448	2.94	1,404
	Gravidity									
	0	9,910	46.78	5,871	49.64	8,480	48.76	6,767	44.41	31,028
	≥1	10,909	51.50	5,694	48.14	8,556	49.20	8,015	52.60	33,174
	Missing	365	1.72	263	2.22	356	2.05	457	3.00	1,441
	Parity									
	0	15,752	74.36	8,948	75.65	12,748	73.30	9,843	64.59	47,291
	≥1	5,432	25.64	2,880	24.35	4,644	26.70	5,396	35.41	18,352
Maternal history of adverse pregnancy outcomes										
	No	12,558	59.28	7,348	62.12	10,748	61.80	9,527	62.52	40,181
	Yes	8,626	<b>40.72</b>	4,480	37.88	6,644	38.20	5,712	37.48	25,462
Maternal history of chronic diseases										
	No	21,008	99.17	11,755	99.38	17,302	99.48	15,174	99.57	65,239
	Yes	176	<b>0.83</b>	73	0.62	90	0.52	65	0.43	404
Maternal birth defects or history of a birth defect in a previous delivery										
	No	20,966	98.97	11,705	98.96	17,267	99.28	15,113	99.17	65,051
	Yes	218	<b>1.03</b>	123	<b>1.04</b>	125	0.72	126	0.83	592
Recruiting Year										
	2010	3,476	<b>16.41</b>	1,126	9.52	1,268	7.29	1,266	8.31	7,136
	2011	2,349	11.09	1,554	13.14	1,500	8.62	1,208	7.93	6,611
	2012	3,376	15.94	2,211	18.69	3,142	18.07	3,374	22.14	12,103
	2013	4,012	18.94	2,094	17.70	3,902	22.44	4,537	29.77	14,545
	2014	3,603	17.01	2,017	17.05	3,547	20.39	3,116	20.45	12,283
	2015	4,368	20.62	2,826	23.89	4,033	23.19	1,738	11.40	12,965
Areas in Chongqing										
	Urban core area	6,758	<b>31.90</b>	2,930	24.77	4,158	23.91	3,124	20.50	16,970
	New urban district	10,540	<b>49.75</b>	5,661	47.86	7,868	45.24	6,490	42.59	30,559
Northeast ecological conservation area		2,990	14.11	2,599	21.97	4,276	24.59	3,984	26.14	13,849
Southeast ecological protection area		896	4.23	638	5.39	1,090	6.27	1,641	10.77	4,265
Compliance of FA supplementation										
	Irregular	831	3.92	841	7.11	1,795	10.32			
	regular	20,353	<b>96.08</b>	10,987	92.89	15,597	89.68			

**Table S3.** Risk ratios and 95% CIs for spontaneous abortion according to maternal periconceptional folic acid (FA) supplementation in sensitivity analysis.

	Sensitivity 1 <sup>a</sup>		Sensitivity 2 <sup>b</sup>		Sensitivity 3 <sup>c</sup>	
	aRR	95% CI	aRR*	95% CI	aRR*	95% CI
No supplementation	1.00		1.00		1.00	
Having supplementation	0.51	0.48,0.55	0.51	0.47,0.55	0.49	0.46,0.52
Starting at least 3 months prior to conception	0.45	0.41,0.50	0.45	0.41,0.50	0.43	0.40,0.47
Starting 1-2 months prior to conception	0.55	0.50,0.61	0.54	0.48,0.60	0.52	0.47,0.58
Starting after conception	0.55	0.50,0.59	0.55	0.50,0.60	0.52	0.48,0.57

<sup>a</sup> This sensitivity analyses additionally were adjusted for maternal reproductive tract infection, cytomegalovirus, and toxoplasma infection before pregnancy. <sup>b</sup> This sensitivity analyses were excluded pregnancies of women without information of any covariates. <sup>c</sup> This sensitivity analyses were excluded pregnancies ended with induced abortion/still birth. **Abbreviations:** cRR, crude risk ratio; aRR, adjusted risk ratio; CI, confidence interval.

**Table S4.** The association between maternal periconceptional folic acid (FA) supplementation and the follow-ups time in gestation.

Maternal periconceptional FA supplementation	Follow-ups time in gestation				$\chi^2$	$p$
	$\leq 84$ days		$\geq 85$ days			
	N	%	N	%		
No supplementation	8,107	23.10	7,350	22.73		
Having supplementation	26,982	76.90	24,984	77.27		
Total	35,089		32,334		1.3223	0.250

**Table S5.** Risk ratios and 95% CIs for spontaneous abortion (SA) according to maternal periconceptional folic acid (FA) supplementation in a subpopulation recruited in 2010 (N=7 136).

Maternal periconceptional FA supplementation	No. of Pregnancies	SAs, No. (%)	Model 1		Model 2 <sup>a</sup>	
			cRR	95% CI	aRR	95% CI
No supplementation	1,266	52 (4.11)	1.00	-	1.00	-
Having supplementation	5,870	51 (0.87)	0.21	0.14,0.31	0.27	0.18,0.41
Starting at least 3 months prior to conception	3,476	18 (0.52)	0.13	0.07,0.21	0.19	0.11,0.34 <sup>b</sup>
Starting 1-2 months prior to conception	1,126	9 (0.80)	0.19	0.10,0.39	0.24	0.12,0.47 <sup>b</sup>
Starting after conception	1,268	24 (1.89)	0.46	0.29,0.74	0.41	0.25,0.67 <sup>b</sup>

<sup>a</sup> aRR adjusted for maternal BMI, passive smoking before pregnancy, history of adverse pregnancy outcomes, chronic diseases, birth defects or history of a birth defect in a previous delivery, and husbands' smoking in early pregnancy, in addition to maternal age, ethnicity, education, employment, household registration, and area of recruitment. <sup>b</sup> aRR for FA supplementation initiated at least 3months prior to conception was significantly lower than FA supplementation after conception ( $\chi^2=5.10$ ,  $p=0.0239$ ). **Abbreviations:** cRR, crude risk ratio; aRR, adjusted risk ratio; CI, confidence interval.

**Table S6.** Risk ratios and 95% CIs for pregnancies ending with still birth or induced abortion due to foetal abnormalities according to maternal periconceptional folic acid (FA).

Maternal periconceptional FA supplementation	No. of Pregnancies	Induced abortions or still births, No. (%)	Model 1		Model 2 <sup>a</sup>	
			cRR	95% CI	aRR	95% CI
No supplementation	13,878	1,028 (7.40)	1.00	-	1.00	-
Having supplementation	48,241	1,049 (2.17)	0.29	0.27,0.32	0.31	0.29,0.34
Starting at least 3 months prior to conception	20,383	388 (1.90)	0.26	0.23,0.29	0.28	0.25,0.32 <sup>b</sup>
Starting 1-2 months prior to conception	11,287	231 (2.05)	0.28	0.24,0.32	0.29	0.25,0.34 <sup>b</sup>
Starting after conception	16,571	430 (2.59)	0.35	0.31,0.39	0.35	0.31,0.39 <sup>b</sup>

<sup>a</sup> aRR adjusted for maternal BMI, passive smoking before pregnancy, history of adverse pregnancy outcomes, chronic diseases, birth defects or history of a birth defect in a previous delivery, and husbands' smoking in early pregnancy, in addition to maternal age, ethnicity, education, employment, household registration, year and area of recruitment. <sup>b</sup> aRR for FA supplementation initiated 3 months or more ( $\chi^2=8.60$ ,  $p=0.0034$ ), or initiated 1-2 months ( $\chi^2=4.62$ ,  $p=0.0315$ ) prior to conception was significantly lower than supplementation after conception. **Abbreviations:** cRR, crude risk ratio; aRR, adjusted risk ratio; CI, confidence interval



