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Complete List of Authors:	Liu, Danmeng; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Cheng, Yue; Xi'an Jiaotong University Health Science Center, Department of Nutrition Dang, Shaonong; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Wang, Duolao; Liverpool University, Liverpool School of Tropical Medicine Zhao, Yaling; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Li, Chao; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Li, Shanshan; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Lei, Fangliang; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Qu, Pengfei; Northwest women's and children's Hospital, Translational Medicine Center Mi, Baibing; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Zhang, Ruo; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Li, Jiamei; Department of Emergency Medicine, the Second Affiliated Hospital, Xi'an Jiaotong University, Department of Emergency Medicine Zeng, L; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Yan, H; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics; Nutrition and Food Safety Engineering Research Center of Shaanxi Province
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Rational maternal micronutrient supplementations is still a burning issue for public health: based on a large-scale cross-sectional survey of Northwestern China

Danmeng Liu[1], Yue Cheng[2], Shaonong Dang[1], Duolao Wang[3], Yaling Zhao[1], Chao Li[1], Shanshan Li[1], Fangliang Lei[1], Pengfei Qu[4], Baibing Mi[1], Ruo Zhang[1], Jiamei Li[5], Lingxia Zeng[1] *, Hong Yan[1 6 7] *

[1]Department of Epidemiology and Health Statistics, School of Public Health, Xi'an Jiaotong University Health Science Center, No. 76 Yanta West Road, Xi'an, Shaanxi, 710061, China

[2]Department of Nutrition, School of Public Health, Xi'an Jiaotong University Health Science Center, No. 76 Yanta West Road, Xi'an, Shaanxi, 710061, China

[3]Liverpool School of Tropical Medicine, Liverpool University, Pembroke Place, Liverpool, L3 5QA, UK

[4]Translational Medicine Center, Northwest women's and children's Hospital, No. 1616 Yanxiang Road, Xi'an, Shaanxi, 710061, China

[5]Department of Emergency Medicine, The Second Affiliated Hospital of Xi'an Jiaotong University, No. 157 West Fifth Road, Xi'an, Shaanxi, 710004, China

[6]Nutrition and Food Safety Engineering Research Center of Shaanxi Province, Xi'an, Shaanxi, 710061, China

[7]Key Laboratory of Environment and Genes Related to Diseases, Xi'an Jiaotong University, Ministry of Education, Xi'an, Shaanxi, 710061, China

*Corresponding author:

Lingxia Zeng, Health Science Center, Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, China. Fax +86 29 82655104, email tjzlx@mail.xjtu.edu.cn

Hong Yan, Health Science Center, Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, China. Fax +86 29 82655104, email xjtu_yh.paper@aliyun.com

Abstract

Objectives This study aims to examine the prevalence and factors related to rational micronutrient supplementations before and during pregnancy among women in Northwestern China, under the background of lack of dietary intake in this region [1].

Design A large-scale cross-sectional survey.

Setting Twenty counties and ten districts of Shaanxi Province.

Participants Total 28678 women (aged 16-49 years) who had live birth babies during 2010-2013 and who provided clear information about maternal micronutrient supplementations were selected by using stratified multistage random sampling method in this study.

Outcomes The use of micronutrient supplements including folic acid (FA), iron, calcium, and multiple micronutrients (MMN). Rational use of micronutrient supplements according to initiation time and total days of use. Generalized estimating equation (GEE) models were performed to analyze the factors associated with rational micronutrient supplementations.

Results In total, 83.9% of women took micronutrient supplements before or during their recent pregnancy. FA (67.6%) and calcium (57.5%) were the primarily used micronutrient supplements, but small parts of participants used MMN (14.0%) or iron (5.4%). The prevalence of rational uses were very low for most micronutrients (7.4% for FA, 0.8% for iron, 3.2% for MMN and 23.2% for calcium).

Higher education and income levels, urban residents, as well as better antenatal cares including had aristogenesis consultation and a higher frequency of antenatal visits were usually associated with the increased rational micronutrient supplementations.

Conclusion Maternal micronutrient supplementations in Northwestern China were far from qualified according to the Chinese guideline or WHO recommendation. Targeted health education and future nutritional guidelines are suggested to improve rational maternal micronutrient supplementations, especially for women with disadvantaged sociodemographic conditions.

Keywords: Micronutrient supplementation; Pregnancy; Prevalence; Initiation time of use; Total use days; Associated-factors

Running Head: Rational maternal micronutrient supplementations

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Strengths and limitations of this study

- This is the first study that detailed describing the situation of rational maternal micronutrient supplementations in Northwestern China, which could serve as a data basis for developing health education strategies in the future.
- Sample representativeness in Northwestern China is guaranteed by a large sample of 28678 women that recruited using a stratified multistage random sampling method
- The recall bias is ineluctable owing to the retrospective and self-reported information.
- The study does not provide an insight into the dosage of specific micronutrient supplementations due to the uncertain specifications of some supplements.

- The generalisability of our findings to other geographical areas may be limited.

Introduction

Pregnancy is a process that involves the increasing of macro- and micronutrients requirement induced by maternal physiological changes and fetal growth [2]. During pregnancy, adequate micronutrient intake is hard to achieve just from the daily diet [3], and maternal micronutrient deficiencies could cause severe adverse outcomes including stillbirth, low birth weight and birth defects [4]. Maternal micronutrient supplementation is an alternative in addition to the adjustment of diet pattern and quality to fulfill the increased nutrition demands during pregnancy [5]. Growing evidence showed that supplementation of certain micronutrients during pregnancy could improve maternal health status as well as birth outcomes [6-9]. Routine micronutrient supplementations were recommended in developed countries as well as by WHO. Many developed countries implemented folic acid (FA) supplementation before and during the first trimester for protecting against neural tube defects (NTDs) [10,11]. Additionally, WHO provide targeted recommendations of micronutrient supplementations, such as FA, iron, and calcium, for diverse populations to reduce the risk of adverse pregnancy outcomes [12,13]. However, adherence to these recommendations varied from countries [3,5,14].

In China, National Health Commission (NHC) promotes the nutritional intervention that supplementation of FA (400 μg) daily during the periconceptional period to prevent congenital NTDs, especially for women in rural areas [15,16]. In addition, Chinese nutrition society recommends women who preparing for pregnancy or being pregnant to take daily FA supplement during the time from 3-

months before pregnancy to the time at delivery for the prevention of NTDs and pregnancy-induced hypertension [17]. There are no more guidelines to direct other micronutrient supplementations so that the use of micronutrient supplements during pregnancy varied in geographic areas and socioeconomic groups. Previous studies reported that 81.8% of women in Sichuan Province of China consumed micronutrient supplements during pregnancy and calcium (63.9%) were the most popular to use among the participants [5]. In addition, the result of a cross-sectional research showed that the overall prevalence of micronutrient supplementations among pregnant women in urban and rural areas were 81.8% and 57.8%, respectively, along with the consumption of specific micronutrients in urban were all significantly higher than that in rural [18].

To ensure the effectiveness of micronutrient supplementations for prevention of adverse pregnancy outcomes, health policies or recommendations on the topic of micronutrient supplementations all emphasized the timing and sustainability of use. For instance, daily use during the periconceptional period is recommended for FA supplementation in preventing NTDs. Additionally, daily iron and folic acid supplementation are recommended as part of the antenatal care to reduce the risk of low birth weight, maternal anemia, and iron deficiency. Evidence showed that low compliance that determined according to timing and days of use was a major reason for the low effectiveness of micronutrient supplementations [9,19], which indicated the importance of rational use of micronutrient supplements rather than merely using. However, few of the previous studies focused on the rationality of maternal micronutrient supplementation.

Shaanxi Province is a developing area in Northwestern China and can be geographically divided into 3 regions, which are northern, central and southern Shaanxi. The climate, culture and economic development of these three regions vary significantly, as well as the diet habit of residents [1].

According to previous researches in this region, most of the micronutrients took from the diet were inadequate among pregnant women [1,20], and therefore, micronutrient supplementation seems to be very pivotal for improving the health status of both mothers and infants. However, data about the maternal micronutrient supplementation is still not available, especially lack of information on the rational use of supplements. This article investigates the condition of maternal micronutrient supplementations in Shaanxi, focuses on analyzing the prevalence and associated-factors of rational supplement use, and aims to provide evidence for future evaluation of health policy effectiveness and development of health education strategies.

Methods

Data source and participants

The study employed data from a large-scale cross-sectional survey, which was conducted between August to November 2013 in Shaanxi province with the purpose of investigating the prevalence and risk factors of birth defects among newborns, along with the maternal dietary condition and nutritional supplements use. The target population were women aged from 16 to 49 years, pregnant during 2010-2013 and had specific pregnant outcomes before the survey. The sample of the study was acquired from twenty counties and ten districts of Shaanxi with applying a stratified multistage random sampling method [1,21]. Twenty counties and ten districts were randomly selected firstly from the eighty rural counties and twenty-four urban districts in Shaanxi Province according to the difference in size, distribution and fertility rates of population between rural and urban areas. Subsequently, in the rural area, six townships were randomly obtained from each chosen county, and then six villages were randomly selected from each sampled township. Finally, thirty eligible women were randomly

selected in each village. In the urban area, three streets were randomly selected from each sampled district, six communities were randomly chosen from each selected street, and then sixty eligible women were selected in each community. Data collection was completed with a structured-questionnaire via face-to-face survey by trained interviewers. Information including maternal sociodemographic characteristics, lifestyle, health condition, health care utilization, and supplements consumption, etc. were collected. Strict quality control process was utilized to guarantee data integrity and accuracy [1].

A total sample of 30027 women were enrolled in the survey after excluding women with limited cognitive capacity or without informed consent. In order to obtain more accurate analysis results, the present study only regarded women who had live birth babies in the recent pregnancy and who provided clear information about maternal nutritional supplements use as eligible participants. Total 28678 women were chosen for the final analysis. (**Figure 1**)

Maternal sociodemographic characteristics, birth history, and antenatal care information

Maternal characteristics were collected according to the unified questionnaire. Maternal age at delivery was divided into three categories (<25, 25-34 and ≥35years), as well as education level (Junior high school or below, senior high school and college or above), geographic area (Southern Shaanxi, Central Shaanxi and Northern Shaanxi) and per capita annual household income (Low: <8800, Medium: 8800-15200 and High: ≥15200 Yuan, where 1 Yuan=0·144 $US on 26 Nov 2018). Residence (urban and rural) and parity (primiparous and multiparous) were classified into two categories. antenatal care information including the number of antenatal visits (<5 and ≥5), the type of hospitals for antenatal visit (hospitals below the county level and county level hospitals or above)

and aristogenesis consultation (yes and no, referred to the participation of health counseling that related to maternal health care and fetal development before or during pregnancy) were investigated.

Micronutrient supplementations

Information about the use of micronutrient supplements in forms of tablet and capsule were mainly collected, including folic acid (FA), iron, multiple-micronutrients that contain FA and iron (MMN), calcium, vitamin C, B vitamins and others. Women who consumed any micronutrient supplement before or during their recent pregnancy were considered as micronutrient supplement users, otherwise, were considered as non-users.

The timing of supplementation we focused was from 3-month before the last menstrual period to the time at delivery. 3-month before the last menstrual period was defined as the preconceptional period; the time through the preconceptional period to the first trimester was defined as the periconceptional period; the time of the second and third trimester was defined as the after-periconceptional period.

Rational micronutrient supplementations were evaluated according to Chinese guideline and WHO recommendation as mentioned in the introduction section. The initiation time and total days of use were the two factors that determined the classification of rational use. In the present study, initiated from the periconceptional period with longer than180 days of use was considered as rational use of FA, otherwise, was irrational use. Similarly, initiated from the periconceptional period with longer than 90 days of use was considered as rational use of iron, and the same to MMN. For calcium, rational use was defined as supplementation before or during pregnancy with total days of use longer than 90.

Statistical analysis

Dataset was established using Epidata 3.1 (The Epidata Association, Odense, Denmark) with double entry. Multiple imputation was used to attribute values for the missing variables including income level (n=5830), maternal age group (n=434), and the type of hospitals for antenatal visits (n=327), taking education level, geographic area, residence, parity, the number of antenatal visits and aristogenesis consultation as covariates with 5 imputed data sets [22]. Percentages (%) were estimated for reporting categorical variables, as well as for examining the prevalence of micronutrient supplements use among different groups. Comparisons between groups were completed by the Chi-square test. Prevalence of main supplements use according to initiation time and total days of use were exhibited with percentage stacked column chart using Microsoft Excel software version 2016. Because of the hierarchical structure of the data derived from the stratified multistage random sampling design, GEE models [23] with random effect at county level were applied to estimate adjusted odds ratio (OR) and 95% confidence interval (CI) for rational use of main micronutrient supplementations. Maternal characteristics including age, education, residence, income, parity, aristogenesis consultation, the number of antenatal visit and type of hospitals for antenatal visits were the fixed effects in the GEE models. Rational use of main micronutrient supplementations were binary outcomes so that binomial distribution and logit link function were used in the GEE analysis. An exchangeable covariance structure was used for all GEE models. Model 1 analyzed the relationship between rational use of main micronutrient supplementations and the sociodemographic characteristics including age, education, residence and income. Model 2 analyzed the relationship between rational use of main micronutrient supplementations and sociodemographic characteristics (all the variables in model 1) as well as parity, and antenatal care characteristics. The criteria for

statistical significance was $P < 0.05$. All analysis were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Result

Maternal characteristics according to micronutrient supplementations among participants

There were significant differences in the aspects of the maternal sociodemographic condition, birth history and antenatal care characteristics between users and non-users of micronutrient supplements (**Table 1**). Users of micronutrient supplements were more likely aged between 25-34 years at delivery, with higher education and income level, from central Shaanxi and lived in rural area, as well as primiparous and had better antenatal care including took part in aristogenesis consultations, chose higher-level hospitals, and had a higher frequency of antenatal visits.

Prevalence of overall and rational micronutrient supplementations among participants

In total, 83.9% of women took at least one micronutrient supplement during their last pregnancy. The main supplements used by participants were folic acid (FA) (67.6%), calcium (57.5%), MMN (14.0%), and iron (5.4%) (**Table 2**). Most of micronutrient supplements users did not reach the rational use requirements according to the total days and timing of use. Although FA had a relatively higher prevalence of use during the periconceptional period (64.5%), only 7.4% of women adhered to used FA for longer than 180 days. Compare to the prevalence that who begin to use iron, MMN or calcium in the after-periconceptional period (3.7% for iron, 8.2% for MMN and 39.0% for calcium), smaller proportion of women commence to take them during periconceptional period (1.7% for iron, 5.8% for MMN and 18.5% for calcium). Additional, few of the participants who used iron, MMN or

calcium met the rational use requirements (0.8% for iron, 3.2% for MMN and 23.2% for calcium). (**Table 3 and Figure 2**). Because that MMN contains FA and iron ingredients, we further examined the rational supplementation of FA and iron by combining the use of FA or iron with MMN. Still, the prevalence of rational supplementation of FA and iron were low (8.5% for FA, 3.8% for iron, not shown in table).

Factors associated with rational micronutrient supplementations among participants

Table 4 showed the results of GEE analysis. Higher education and income levels, urban residents, as well as better antenatal care including had aristogenesis consultation and a higher frequency of antenatal visits were usually associated with the increased rational micronutrient supplementations. Multipara were less likely to use micronutrient supplements rationally. Moreover, women aged in 25-34 were more likely to increase the probability of rational use of FA, but elder than 35 was associated with decreased probability of rational use of calcium. The type of hospitals for antenatal visits was not related with rational micronutrient supplementations.

Discussion

Maternal micronutrient supplementations is a common way to compensate for the insufficient nutrition intake from daily diet, which could contribute to healthy pregnancy outcomes as indicated in many studies. The present study reports the maternal micronutrient supplementations among pregnant women in Northwestern China, and focuses to examine the prevalence and associated-factors of rational micronutrient supplementations according to initiation time and total days of use. The results reveals two main problems of maternal micronutrient supplementations among our

population. On the one hand, the prevalence of micronutrient supplementations was lower than expected. On the other hand, the micronutrient supplementations among our population, particularly in the sociodemographic-disadvantageous groups, were far from rational according to Chinese guideline and WHO recommendations.

Totally, the prevalence of maternal micronutrient supplementations in Shaanxi during 2010-2013 was 83.9%. Compared with other countries, our prevalence was higher than that of United States in 1999-2006 (77.6%) [3] but lower than those of Sydney, Australia in 2014 (93.8%) [24], Seoul, Korea in 2012 (88%) [25]. Compared with the domestic data, it was similar to that of Sichuan Province (81.8%) in 2010 [5] and higher than the overall prevalence of eight Provinces of China in 2009 (66.4%) [18]. FA, calcium, MMN, and iron were the four supplements primarily used by participants. Maternal FA supplementation is associated with the prevention of NTDs as well as the reduced risk of preterm delivery and small for gestational age (SGA) births [26]. Both WHO and CNS developed guidelines for promoting daily FA supplementation before and during pregnancy [12,17]. In our population, among all kinds of investigated micronutrient supplements, FA was the most popular one used before and during pregnancy, but there were still over than 30% of women did not take FA during their recent pregnancy. Additionally, the NHC of China recommends FA supplementation at least during the six months of the periconceptional period [16], but only a small part of women took FA supplement for preparing for pregnancy, most of the women start to take FA supplement after they were pregnant. In addition, the more serious reality is merely 7.4% of women rationally use FA supplement initiated from the periconceptional period with longer than 180 total days of use. Even though considering the contribution of MMN use to the total prevalence of rational FA supplementation, less than 10% of women achieved the requirement. Because of the low intake of dietary folate (249 μg) among

pregnant women in this region [1], qualified timing and continuity of use are essential for the effectiveness of FA supplementation in the aspect of preventing adverse birth outcomes.

Pregnant anemia in China is a moderate or severe public health problem due to its high prevalence among women [27]. Iron deficiency (ID) is the most common cause of anemia [28] and iron deficiency anemia (IDA) was one of the most important factors contributing to increased morbidity and mortality in pregnant women [29]. Reviews stated that daily or intermittent iron supplementation in pregnancy could be effective in improving iron status and reduce the risk of maternal IDA, which finally promotes birth outcomes [7,30,31]. Although daily maternal iron supplementation during pregnancy is recommended by WHO for the prevention of adverse pregnancy outcomes [12], our participants rarely used iron supplement before or during pregnancy. What was worse, unreasonable supplementations of iron exist in our population as well. Previous studies demonstrated that prophylactic iron supplementation from early in pregnancy benefited for improving birth weight, iron status and reducing preterm birth [30,32]. Nevertheless, among our participants, many users took iron after the periconceptional period, and few women insisted on taking it longer than 90 days. This may indicate that most women took iron for curing ID or IDA during the second half of pregnancy, but the prophylactic supplementation was very rare. When taking the use of both iron and iron-containing MMN into consideration, the prevalence of rational iron supplementation was still very low (3.8 %). This situation possibly attributed to the lack of maternal iron supplementation guideline in China and the popular use of antianemic Chinese patent medicines in this region [33].

The evidence demonstrated that periconceptional MMN supplementation with iron and folic acid could promote iron status and some birth outcomes in term of reducing the risk of LBW, SGA and congenital abnormalities [34-37]. Meanwhile, besides the effects on pregnancy outcomes,

periconceptional MMN supplementation with adequate total dose was associated with the long-term intellectual development of offspring [38]. The developed country like Australia had a high prevalence of periconceptional MMN intake (79.2%) [24]. However, the prevalence of MMN supplementation among our participants was only 14.0%, and merely 5.6% of women met its rational use requirement. Consideration of situations including high incidence of adverse birth outcomes [39], low intakes of most micronutrients from daily diet [1] and disadvantageous-sociodemographic conditions among many pregnant women, the suggestion that to replace iron and folic acid with MMN supplement for pregnant women in low-income areas [35] might be an useful strategy to comprehensively improve maternal micronutrient supplementations in this region.

For calcium supplementation, WHO recommends that in populations with low dietary calcium intake, pregnant women should take daily oral calcium supplementation (1.5 g - 2.0 g) to reduce the risk of pre-eclampsia and further to prevent maternal deaths and preterm births [13]. In our population, daily intake of calcium from diet among pregnant women (512 mg) was lower than the recommended nutrient intakes (RNI) based on *Chinese Dietary Reference Intakes 2013* [1], however, more than 40% of women did not take calcium supplements during their last pregnancy. Moreover, less than a quarter of participants supplement with calcium rationally without consideration of initiation time and the dose of use, which suggested that there is still a gap between the situation of calcium supplementation and the WHO recommendation.

When examining the population distribution of rational micronutrient supplementations, we found that better sociodemographic conditions including urban residence, higher education and income levels, along with better antenatal care in aspects of taking aristogenesis consultation and higher frequency of antenatal visits were associated with increased prevalence of rational micronutrient

supplementations. Although the relationship between education level, prenatal health counseling and the micronutrient supplementations were demonstrated in researches of the developed country like Finland [40] or of the domestic region like Sichuan [5], few studies reported the information of rational micronutrient supplementations. Our finding of higher age and primiparity were the predictors of rational use of FA was consistent with the previous report in Ireland [41]. We did not find the difference of rational FA supplementation between women who took antenatal visits in higher-level hospitals and in township hospitals. This may reflect the balanced implement of national health policy on maternal FA supplementation in the health system of the study region.

To our knowledge, this is the first study investigated the maternal micronutrient supplementations in Northwestern China. Meanwhile, the prevalence and population distribution of rational micronutrient supplementations were detailed analyzed according to initiation time and total days of use, which could serve as a data basis for developing health education strategies in the future. In addition, according to the proportion of rural to urban residents, population size and fertility rate in Shaanxi, a large sample of 28678 women were recruited from twenty counties and ten districts of Shaanxi using a stratified multistage random sampling method to guarantee its representativeness. Nonetheless, several limitations of the present study should be stated. First, this study was retrospective and all the information of micronutrient supplementations were self-reported from participants, and therefore the recall bias were ineluctable. Second, the specifications of some supplements were uncertain, so that the accurate dosage used by our participants could not be calculated. As a result, we only define rational micronutrient supplementations according to initiation time and total days of use, without consideration of dose of use. Third, the sources of recommendation regarding the use of supplements were not recorded, hence, the approach that more proper for future interventions could not be known.

Finally, due to the diversities of economy, culture, lifestyle, as well as eating habits in different geographical areas of China, the generalisability of our findings to other geographical areas may be limited. Further quantitative analysis of the association between micronutrient supplementations and pregnancy health and the investigation of the better way for health education are recommended to be conducted in the future.

Conclusion

In conclusion, maternal micronutrient supplementations in Shaanxi failed to meet the Chinese guideline or WHO recommendation according to initiation time and total days of use. Improving rational micronutrient supplementations before or during pregnancy is still a burning issue for maternal and child health in Northwestern China. Targeted health education and future guidelines of micronutrient supplementations are suggested to be implemented, especially for women with disadvantaged sociodemographic conditions.

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Ethics

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Ethic Review Committee and Academic Committee of Xi'an Jiaotong University Health Science Center (number 2012008). Written informed consent was obtained from all participants.

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Competing interests

None.

Contributors

D.L., Y.C., L.Z., and H.Y. conceived and designed the study; D.L., S.L., F.L., B.M., R.Z., J.L. collected and cleared the data; D.L., D.W., Y.Z., C.L., S.L., F.L., and P.Q. analyzed and interpreted the data; D.L., Y.C., S.D., and L.Z. drafted and revised the manuscript. All authors read and approved the final version of the manuscript.

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Figure legends

Figure 1 Flow diagram of sampling strategy with exclusion criteria

Figure 2 Prevalence of main supplements use according to total days and initiation time of use among Chinese women in Shaanxi, 2010-2013. FA, folic acid; MMN, multiple-micronutrients. For FA, iron and MMN, the two classes from the right side represent the prevalence of rational use (shown in red dashed box); for calcium, the three classes from the right side represent the prevalence of rational use (shown in red dashed box).

Table 1 Maternal characteristics according to micronutrient supplementations among Chinese women in Shaanxi, 2010-2013

Characteristics	Micronutrient supplementations				*P*[a]
	Yes (n=24051)		No (n=4627)		
	n	%	*n*	%	
Sociodemographic characteristics					
Age (years)					<0.001
<25	7843	32.6	1615	34.9	
25-34	14299	59.5	2465	53.3	
≥35	1909	7.9	547	11.8	
Education					<0.001
Junior high school or below	14113	58.7	3611	78.0	
Senior high school	5114	21.3	627	13.6	
College or above	4824	20.0	389	8.4	
Geographic area					<0.001
Southern Shaanxi	5099	21.2	776	16.8	
Central Shaanxi	13731	57.1	1725	37.3	
Northern Shaanxi	5221	21.7	2126	45.9	
Residence					<0.001
Rural	15846	65.9	3455	74.7	
Urban	8205	34.1	1172	25.3	
Per capita annual household income (RMB)					<0.001
Low	7990	33.2	1714	37.0	
Medium	7819	32.5	1604	34.7	
High	8242	34.3	1309	28.3	
Birth history and antenatal care information					
Parity					<0.001
Primiparous	14651	60.9	2152	46.5	
Multiparous	9400	39.1	2475	53.5	
Aristogenesis consultation[b]					<0.001
No	17404	72.4	3981	86.0	
Yes	6647	27.6	646	14.0	
The number of antenatal visit					<0.001
<5	6310	26.2	2298	49.7	
≥5	17741	73.8	2329	50.3	
Type of hospitals for antenatal visits					<0.001
Township hospitals	2783	11.6	622	13.4	
County hospitals or above	21268	88.4	4005	86.6	

[a] *P* values for the differences among groups were derived from the $\chi 2$ tests or Fisher's exact test.
[b] Refered to the participation of health counselling that related to maternal healthcare and fetal development before or during pregnancy.

Table 2 Prevalence of maternal micronutrient supplementations among Chinese women in Shaanxi, 2010-2013

Micronutrient supplements	n	%
Folic acid	19352	67.6
Calcium	16414	57.5
Multi-micronutrients	4018	14.0
Iron	1547	5.4
Vitamin C	1147	4.0
B Vitamins	814	2.8
Vitamin E	173	0.6
Others[a]	1271	4.4

[a] Including vitamin A, vitamin D and fish oil.

Table 3 Prevalence of main supplements use according to initiation time among Chinese women in Shaanxi, 2010-2013[a]

Initiation time	FA[b] (N=28629)	Iron (N=28644)	MMN[b] (N=28628)	Calcium (N=28548)
Periconceptional period	18469 (64.5)	499 (1.7)	1665 (5.8)	5292 (18.5)
3 months before pregnancy	4966 (17.4)	79 (0.3)	212 (0.8)	272 (1.0)
First trimester	13503 (47.2)	420 (1.5)	1453 (5.1)	5020 (17.6)
After-periconceptional period	883 (3.1)	1048 (3.7)	2353 (8.2)	11122 (39.0)

[a] N=28678. The number of missing values for supplementation of FA, iron, MMN and calcium were 49, 34, 50 and 130. Values are numbers and percentage, n(%).
[b] FA, folic acid; MMN, multiple-micronutrients.

Table 4 Prevalence and adjusted OR (95%CI) of rational use of main micronutrient supplements among Chinese women in Shaanxi, 2010-2013[a]

Characteristics	n	FA		Iron		MMN		Calcium	
		Rational use[b] (%)	Adjusted OR (95%CI)	Rational use[c] (%)	Adjusted OR (95%CI)	Rational use[c] (%)	Adjusted OR (95%CI)	Rational use[d] (%)	Adjusted OR (95%CI)
Sociodemographic characteristics (Model 1)[e]									
Age (years)									
<25	9458	5.3	Ref	0.5	Ref	2.0	Ref	21.1	Ref
25-34	16764	8.7	**1.30 (1.11, 1.52)***	0.9	**1.34 (1.06, 1.69)***	3.8	**1.31 (1.10, 1.55)***	24.9	**1.08 (1.02, 1.15)***
≥35	2456	6.3	1.22 (0.98, 1.51)	0.7	1.41 (0.81, 2.48)	2.8	1.33 (1.67, 1.65)	18.7	**0.80 (0.70, 0.92)***
Education									
Junior high school or below	17724	4.9	Ref	0.4	Ref	1.8	Ref	19.3	Ref
Senior high school	5741	7.3	**1.38 (1.18, 1.61)***	1.1	**2.01 (1.42, 2.86)***	3.1	**1.49 (1.22, 1.82)***	26.7	**1.30 (1.20, 1.40)***
College or above	5213	15.9	**2.59 (2.21, 3.05)***	1.6	**2.13 (1.43, 3.17)***	7.8	**2.93 (2.36, 3.65)***	32.0	**1.51 (1.39, 1.65)***
Residence									
Rural	19301	5.9	Ref	0.5	Ref	2.3	Ref	20.5	Ref
Urban	9377	10.4	**1.72 (1.08, 2.72)***	1.4	**1.98 (1.28, 3.08)***	4.9	**1.56 (1.01, 2.43)***	28.4	1.30 (0.92, 1.83)
Per capita annual household income (RMB)									
Low	9689	5.0	Ref	0.5	Ref	2.0	Ref	20.9	Ref
Medium	9402	6.4	1.07 (0.94, 1.23)	0.6	1.05 (0.71, 1.57)	2.5	1.12 (0.91, 1.37)	22.3	1.07 (0.99, 1.15)
High	9538	10.7	**1.27 (1.11, 1.45)***	1.3	1.41 (0.94, 2.11)	5.0	**1.39 (1.11, 1.73)***	26.2	**1.14 (1.05, 1.24)***
Birth history and antenatal care information (Model 2)[f]									
Parity									
Primiparous	16803	9.2	Ref	0.9	Ref	3.9	Ref	25.3	Ref
Multiparous	11875	4.8	**0.70 (0.58, 0.84)***	0.6	1.19 (0.85, 1.67)	2.1	0.86 (0.70, 1.05)	20.0	1.03 (0.97, 1.10)
Aristogenesis consultation									
No	21385	5.6	Ref	0.6	Ref	2.6	Ref	20.7	Ref
Yes	7293	12.6	**1.91 (1.71, 2.14)***	1.2	**1.47 (1.28, 1.69)***	4.7	**1.41 (1.22, 1.63)***	30.2	**1.33 (1.22, 1.44)***
The number of antenatal visit									

<5	8608	3.8	Ref	0.4	Ref	1.8	Ref	15.4	Ref
≥5	20070	8.9	**1.59 (1.35, 1.87)***	0.9	**1.36 (1.13, 1.64)***	3.7	**1.26 (1.04, 1.53)***	26.4	**1.32 (1.22, 1.44)***
Type of hospitals for antenatal visits									
Township hospitals	3405	5.9	Ref	0.7	Ref	1.9	Ref	19.3	Ref
County hospitals or above	25273	7.6	0.88 (0.73, 1.06)	0.8	0.81 (0.53, 1.24)	3.3	1.15 (0.93, 1.43)	23.6	1.11 (0.99, 1.23)

[a] N=28678. FA, folic acid; MMN, multiple-micronutrients. The number of missing values for supplementation of FA, iron, MMN and calcium were 49, 34, 50 and 130. Adjusted OR and 95% CI were derived from GEE models with random effects at county level.

[b] Rational use of FA was defined as that supplementation of FA initiated from periconceptional period with total days of use longer than 180, otherwise, defined as irrational.

[c] Rational use of iron/MMN was defined as that supplementation of iron/MMN initiated from periconceptional period with total days of use longer than 90, otherwise, defined as irrational.

[d] Rational use of calcium was defined as supplementation of calcium before or during pregnancy with total days of use longer than 90, otherwise, defined as irrational.

[e] Model 1 adjusted for the sociodemographic characteristics including maternal age, education, residence and income, and the OR and 95% CI of these characteristics was derived from model 1.

[f] Model 2 adjusted for all variables in model 1 plus parity and antenatal care characteristics, and the OR and 95% CI of parity and antenatal care characteristics was derived from model 2.

* Refers to P-value <0.05.

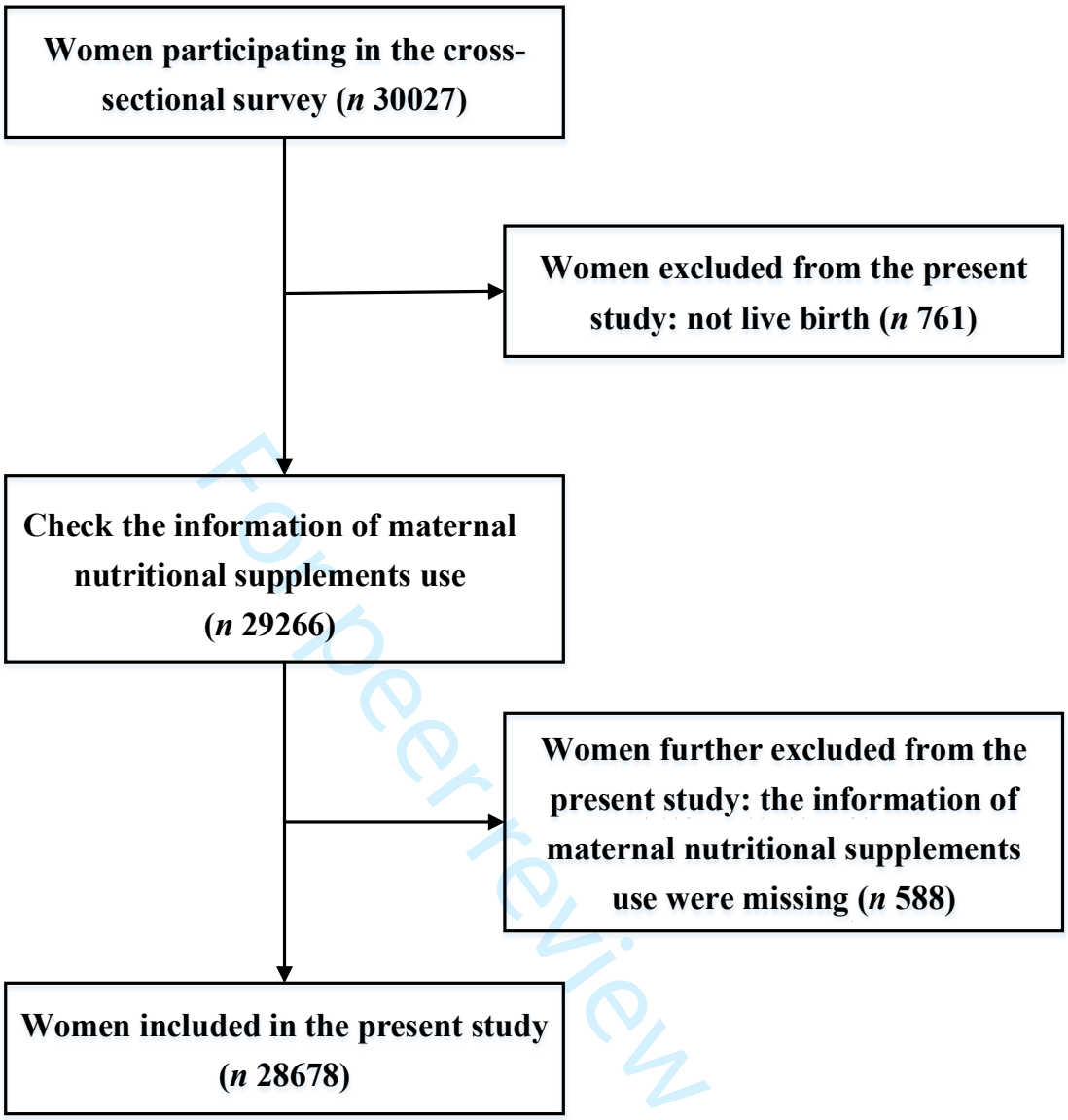

Figure 1 Flow diagram of sampling strategy with exclusion criteria

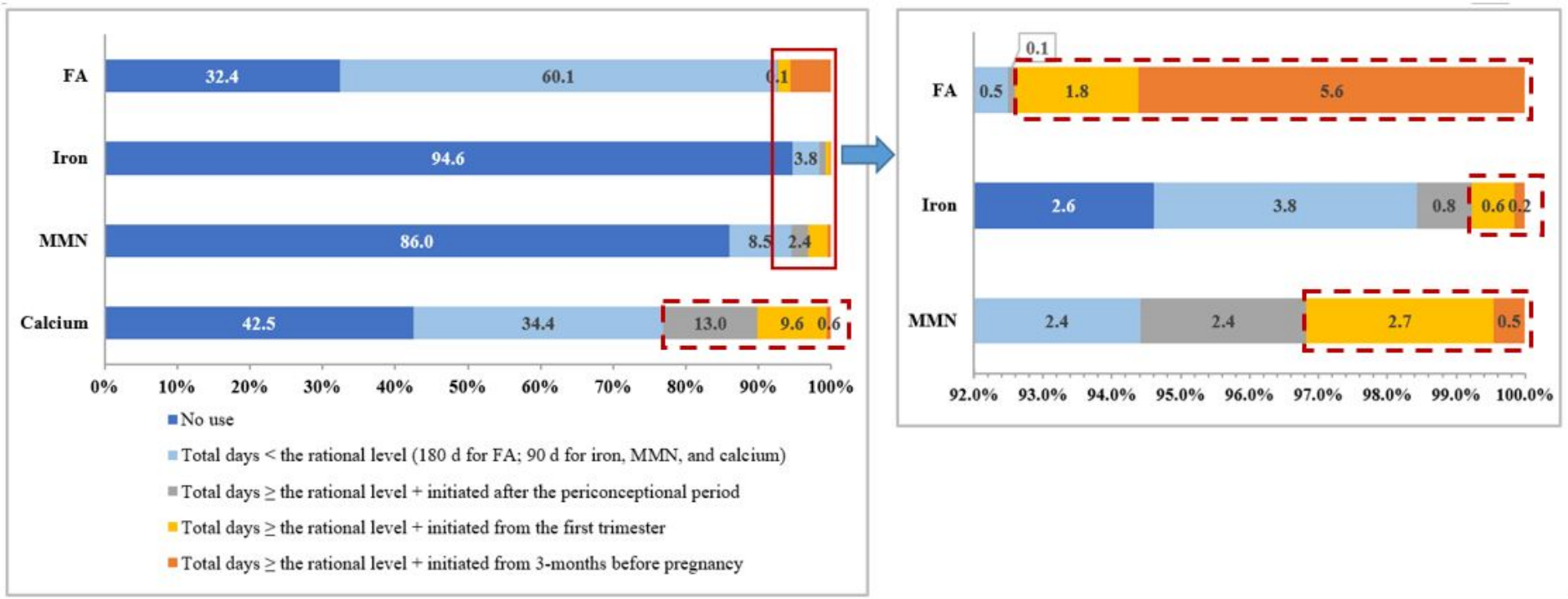

Figure 2 Prevalence of main supplements uses according to total days and initiation time of use among Chinese women in Shaanxi, 2010-2013. FA, folic acid; MMN, multiple-micronutrients. For FA, iron, and MMN, the two classes from the right side represent the prevalence of rational use (shown in red dashed box); for calcium, the three classes from the right side represent the prevalence of rational use (shown in red dashed box).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	None
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	None
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 3-4
Outcome data	15*	Report numbers of outcome events or summary measures	Table 1-4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 4
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	None
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	None
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16-17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Low adherence to maternal micronutrient supplementation is still a burning issue for public health: based on a large-scale cross-sectional survey of Northwestern China

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Complete List of Authors:	Liu, Danmeng; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Cheng, Yue; Xi'an Jiaotong University Health Science Center, Department of Nutrition Dang, Shaonong; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Wang, Duolao; Liverpool University, Liverpool School of Tropical Medicine Zhao, Yaling; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Li, Chao; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Li, Shanshan; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Lei, Fangliang; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Qu, Pengfei; Northwest women's and children's Hospital, Translational Medicine Center Mi, Baibing; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Zhang, Ruo; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Li, Jiamei; Department of Emergency Medicine, the Second Affiliated Hospital, Xi'an Jiaotong University, Department of Emergency Medicine Zeng, L; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Yan, H; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics; Nutrition and Food Safety Engineering Research Center of Shaanxi Province
Primary Subject Heading:	Public health
Secondary Subject Heading:	Public health, Nutrition and metabolism
Keywords:	Micronutrient supplementation, Pregnancy, Adherence, Associated-factors

Low adherence to maternal micronutrient supplementation is still a burning issue for public health: based on a large-scale cross-sectional survey of Northwestern China

Danmeng Liu[1], Yue Cheng[2], Shaonong Dang[1], Duolao Wang[3], Yaling Zhao[1], Chao Li[1], Shanshan Li[1], Fangliang Lei[1], Pengfei Qu[4], Baibing Mi[1], Ruo Zhang[1], Jiamei Li[5], Lingxia Zeng[1] *, Hong Yan[1 6 7] *

[1]Department of Epidemiology and Health Statistics, School of Public Health, Xi'an Jiaotong University Health Science Center, No. 76 Yanta West Road, Xi'an, Shaanxi, 710061, China

[2]Department of Nutrition, School of Public Health, Xi'an Jiaotong University Health Science Center, No. 76 Yanta West Road, Xi'an, Shaanxi, 710061, China

[3]Liverpool School of Tropical Medicine, Liverpool University, Pembroke Place, Liverpool, L3 5QA, UK

[4]Translational Medicine Center, Northwest women's and children's Hospital, No. 1616 Yanxiang Road, Xi'an, Shaanxi, 710061, China

[5]Department of Emergency Medicine, The Second Affiliated Hospital of Xi'an Jiaotong University, No. 157 West Fifth Road, Xi'an, Shaanxi, 710004, China

[6]Nutrition and Food Safety Engineering Research Center of Shaanxi Province, Xi'an, Shaanxi, 710061, China

[7]Key Laboratory of Environment and Genes Related to Diseases, Xi'an Jiaotong University, Ministry of Education, Xi'an, Shaanxi, 710061, China

*Corresponding author:

Lingxia Zeng, Health Science Center, Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, China. Fax +86 29 82655104, email tjzlx@mail.xjtu.edu.cn

Hong Yan, Health Science Center, Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, China. Fax +86 29 82655104, email xjtu_yh.paper@aliyun.com

Abstract

Objectives This study aims to report the situation of maternal micronutrient supplementation before and during pregnancy, and examine the rates of and factors related to the adherence to micronutrient supplementation in Northwestern China where dietary micronutrients deficiency is common.

Design A large-scale population-based cross-sectional survey.

Setting Twenty counties and ten districts of Shaanxi Province.

Participants Total 28678 women (aged 16-49 years) who provided clear information about maternal micronutrient supplementation were selected by using stratified multistage random sampling method in this study.

Main outcome measures The adherence to micronutrient supplements (including folic acid, iron, calcium, and multiple-micronutrients) are the outcomes. Factors associated with the adherence to micronutrient supplementation are analyzed using Generalized Estimating Equation (GEE) models.

Results In total, 83.9% of women took micronutrient supplements before or during pregnancy. FA (67.6%) and calcium (57.5%) were the primarily used micronutrient supplements, but small parts of participants used MMN (14.0%) or iron (5.4%). The adherence was low to all micronutrient supplementation (7.4% for FA, 0.8% for iron, 23.2% for calcium and 3.2% for MMN) according to the Chinese guideline (for FA) and WHO recommendations (for iron, calcium, and MMN). Higher

education and income levels, urban residents, as well as better antenatal cares including had pregnancy consultation and a higher frequency of antenatal visits were usually associated with the high adherence to micronutrient supplementation.

Conclusion Maternal micronutrient supplementation in Northwestern China was far from qualified according to the Chinese guideline or WHO recommendation. Targeted health education and future nutritional guidelines are suggested to improve this situation, especially for women with disadvantaged sociodemographic conditions.

Keywords: Micronutrient supplementation; Pregnancy; Adherence; Associated-factors

Running Head: Adherence to maternal micronutrient supplementation

Word count: 4128

Strengths and limitations of this study

- This is the first large-scale and representative study that detailed describing the adherence to maternal micronutrient supplementation in Northwestern China, which could serve as a data basis for developing health education strategies in the future.
- Sample representativeness in Northwestern China is guaranteed by a large sample of 28678 women that recruited using a stratified multistage random sampling method
- The recall bias is ineluctable owing to the retrospective and self-reported information.
- The study does not provide an insight into the dosage of specific micronutrient supplementation due to the uncertain specifications of some reported supplements.
- The generalizability of our findings to other geographical areas may be limited.

Introduction

Pregnancy is a process that involves the increasing of macro- and micronutrients requirement induced by maternal physiological changes and fetal growth [1]. During pregnancy, adequate micronutrient intake is hard to achieve just from the daily diet [2], and maternal micronutrient deficiencies could cause severe adverse outcomes, including stillbirth, low birth weight (LBW) and birth defects [3]. Micronutrients supplementation is an alternative in addition to the adjustment of diet pattern and quality to fulfill the increased nutrition demands during pregnancy [4]. In recent decades, maternal micronutrients supplementation during pregnancy attracts more and more attention as growing evidence showed that it has significant benefits in the improvement of maternal health status as well as birth outcomes [5-8].

As a result, some micronutrients which greatly contribute to maternal and fetal health is highly recommended for routine use as a part of antenatal care. Many countries implemented periconceptionally folic acid (FA) supplementation for protecting against neural tube defects (NTDs) [9,10]. WHO also provide several guidelines for micronutrient supplementation for pregnant women to reduce the risk of adverse pregnancy outcomes [11]. WHO recommends daily use of FA (400 μg) start at 2-month before the planned pregnancy until 12 weeks of pregnancy for the prevention of NTDs [12], and daily oral folic acid combined with iron supplementation (400 μg FA and 30-60 mg iron) throughout pregnancy is recommended to reduce the risk of LBW, maternal anemia and iron deficiency [13]. In addition, daily oral calcium supplementation (1.5-2.0 g) in the second half of pregnancy is recommended for pregnant women in the area of low dietary calcium intake, to reduce the risk of pre-eclampsia [14].

China is the most populated developing country with a considerable incidence of adverse pregnancy outcomes, including maternal anemia [15], LBW [16], small gestational age [8], etc., but the implementation of folic acid supplementation project (take daily FA (400 μg) initiate from 3-month before pregnancy to the end of the first trimester) to prevent NTDs, especially in rural areas, is the only nutritional intervention promoted by the National Health Commission (NHC) for pregnant women and women planning to be pregnant [17,18]. Also, the only routine antenatal micronutrient supplementation recommended by the Chinese Nutrition Society (CNS) for childbearing-aged women is daily use of FA (400 μg) start at 3-month before the planned pregnancy until the end of pregnancy [19], which is similar to the WHO recommendation. There are no more guidelines for routine supplementation of other micronutrients, so that the use of micronutrient supplements during pregnancy varied in Chinese geographic areas and socioeconomic groups [4,20].

Health policies and recommendations of micronutrient supplementations all emphasized the timing, dosage, sustainability of use, as well as the target population. Evidence showed that low compliance was a major reason for the low effectiveness of micronutrient supplementation [8,21], and thus the exploration of the determinants of the adherence is important for guiding the appropriate use to guarantee the efficacy. Many factors were reported in relation to the adherence to micronutrient supplementation, including maternal age, education background, occupation, antenatal care, etc. Previous studies reported the compliance of micronutrient supplementation in the Western countries like the United States and Norway [22,23], as well as in the Africa countries like Ethiopia and Kenya [24,25]. Few of the studies focused on the adherence to maternal micronutrient supplementation in China. Shaanxi Province is a developing area in Northwestern China where most of the micronutrients took from the diet among pregnant women were lower than the Chinese recommended nutrient intake

(RNI) [26,27], especially the intake of folate and calcium [26,27]. Although the dietary iron intake was close to the RNI for the first and second trimester, most iron from diet was the non-heme iron, which is not efficiently absorbed and utilized by the human body [28]. Additionally, about 40% of the childbearing-aged women in the region suffered anemia [29], and the incidence of adverse birth outcomes, including LBW and preterm birth, were high in this region [30]. Therefore, maternal micronutrient supplementation seems to be a relatively inexpensive and low-risk method for compensating for inadequate dietary intake and improving the health status of both mothers and infants. However, representative data from large-scale study on the maternal micronutrient supplementation in this region is not available.

Accordingly, this article aims to investigate the condition of maternal micronutrient supplementation in Shaanxi, focuses on analyzing the rates of and associated-factors related to the adherence to supplement use according to existing recommendations, and to provide evidence for future evaluation of health policy effectiveness and development of health education strategies.

Methods

Data source and participants

The study employed data from a large-scale population-based cross-sectional survey, which was conducted between August to November 2013 in Shaanxi province with the purpose of investigating the prevalence and risk factors of birth defects among newborns, along with the maternal dietary condition and nutritional supplements use. The target population were women aged from 16 to 49 years, pregnant during 2010-2013 and had specific pregnant outcomes before the survey. The sample of the study was acquired from twenty counties and ten districts of Shaanxi with applying a stratified

multistage random sampling method [27,31]. Twenty counties and ten districts were randomly selected firstly from the eighty rural counties and twenty-four urban districts in Shaanxi Province according to the difference in size, distribution and fertility rates of population between rural and urban areas. Subsequently, in the rural area, six townships were randomly obtained from each chosen county, and then six villages were randomly selected from each sampled township. Finally, thirty eligible women were randomly selected in each village. In the urban area, three streets were randomly selected from each sampled district, six communities were randomly chosen from each selected street, and then sixty eligible women were selected in each community. Data collection was completed with a structured-questionnaire via face-to-face survey by trained interviewers. Information including maternal sociodemographic characteristics, lifestyle, health condition, health care utilization, and supplements consumption, etc. were collected. Strict quality control process was utilized to guarantee data integrity and accuracy [27].

A total sample of 30027 women were enrolled in the survey after signing the informed consent and excluding women with limited cognitive capacity. In order to obtain more accurate analysis results, we further excluded who did not provide clear information about maternal nutritional supplementation (total 1349 women, among them, 761 women had no live birth babies in the recent pregnancy and refused to provide detailed information). Total 28678 women were chosen for the final analysis.

Maternal sociodemographic characteristics, parity, and antenatal care information

Maternal characteristics were collected according to the questionnaire. Maternal age at delivery was divided into three categories (<25, 25-34 and ≥35years), as well as education level (Junior high

school or below, senior high school and college or above), geographic area (Southern Shaanxi, Central Shaanxi and Northern Shaanxi) and per capita annual household income (Low: <8800, Medium: 8800-15200 and High: ≥ 15200 Yuan, where 1 Yuan=0·149 $US on 17 Mar 2019). Residence (urban and rural) and parity (primiparous and multiparous) were classified into two categories. Antenatal care information including the number of antenatal visits (<5 and ≥5), the type of hospitals for antenatal visit (hospitals below the county level and county level hospitals or above) and pregnancy consultation (yes and no, referred to the participation of health counseling that related to maternal health care and fetal development before or during pregnancy) were investigated.

Micronutrient supplementation

Information about the micronutrient supplements in forms of tablet and capsule were mainly collected. We asked the participants to choose the supplements they used during pregnancy from a list of the brand of supplements that were commonly provided in the local hospital or pharmacy, and they should further tell the brand and kind of supplement they consumed if it was not shown in the list. We did not list iron-FA supplement in the questionnaire due to that few supplements on the market are the two-nutrient formulation of iron and FA. In the analysis, FA supplements referred to those contains only FA; iron supplements referred to those contains only iron; calcium supplements referred to those contains only calcium or calcium plus another micronutrient (including calcium-vitamin D and calcium-zinc); multiple-micronutrient (MMN) supplements referred to those contains FA, iron and other micronutrients. Women who consumed any micronutrient supplement before or during their recent pregnancy were considered as micronutrient supplement users, otherwise, were regarded as non-users.

We further obtained the time and total days of use of each supplement they reported. The participants were required to select the time of supplement use from the four pregnant periods (3-month before the last menstrual period, the first trimester, the second trimester, and the third trimester) and report the total days of supplementation for each supplement they used. 3-month before the last menstrual period was defined as the preconceptional period; the time through the 3-month before the last menstrual period to the end of first trimester was defined as the periconceptional period; the time of the second and third trimester was defined as the after-periconceptional period.

Adherence to micronutrient supplementation was determined by the initiation time and total days of use according to Chinese guideline (for FA) and WHO recommendations (for iron, calcium, and MMN). Although WHO did not universally recommend MMN supplementation (MMS) for pregnant women, due to its components of iron and FA, we still examine the compliance of MMS by referencing the WHO recommendation for iron and FA supplementation. We applied total days of use instead of the total amounts because most of our investigated supplements were taken one tablet per day. In the present study, the thresholds used to define the adhered total days of use were 180 days for FA and 90 days for others. Therefore, adhered to FA supplementation was defined as initiated from the periconceptional period with ≥ 180 days of use, otherwise, was regarded as non-adhered; adhered to iron supplementation was considered as initiated from the first trimester with ≥ 90 days of use, otherwise, was regarded as non-adhered. For calcium supplementation, 20 weeks of gestation is the initiation time recommended by WHO. Because of we did not collect the specific weeks of gestation of micronutrient supplementation, adhered to calcium supplementation was considered as initiated from the second trimester with ≥ 90 days of use, otherwise, was regarded as non-adhered; adhered to MMS was defined as initiated from the first trimester with ≥ 90 days of use, otherwise,

was considered as non-adhered.

Statistical analysis

Dataset was established using Epidata 3.1 (The Epidata Association, Odense, Denmark) with double entry. Multiple imputation was used to attribute values for the missing variables, including income level (n=5830), maternal age group (n=434), and the type of hospitals for antenatal visits (n=327), taking education level, geographic area, residence, parity, the number of antenatal visits and pregnancy consultation as covariates with 5 imputed data sets [32]. Numbers and percentages (n (%)) were estimated for reporting the rate of micronutrient supplementation in different groups and for presenting the adherence to micronutrient supplementation. Comparisons between groups were completed by the Chi-square test or Fisher's exact test.

Because of the hierarchical structure of the data derived from the stratified multistage random sampling design, we adopted two-level analysis to examine the relationship between maternal characteristics and the adherence to micronutrient supplementation. Multivariable GEE models [33] with random effect at county level were applied in the two-level analysis to estimate adjusted odds ratio (OR) and 95% confidence interval (CI) for factors associated with the adherence to micronutrient supplementation. Maternal characteristics including age, education, residence, income, parity, pregnancy consultation, the number of antenatal visit and type of hospitals for antenatal visits were the fixed effects in the GEE models. Adherence to supplementation of FA, iron, calcium, and MMN were binary outcomes (adhered *vs.* non-adhered) so that binomial distribution and logit link function were used in the GEE analysis. An exchangeable covariance structure was used for all GEE models. Model 1 analyzed the relationship between the adherence to micronutrient supplementation

and the sociodemographic characteristics including age, education, residence and income. Model 2 analyzed the relationship between the adherence to micronutrient supplementation and sociodemographic characteristics (all the variables in model 1) as well as parity, and antenatal care characteristics. The criteria for statistical significance was $P < 0.05$. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Patient and public involvement

No patients were involved in developing the research question, outcome measure and design of the study. We were unable to disseminate the results of the research directly to study participants, and we informed the results to the local health authorities.

Result

Maternal characteristics according to micronutrient supplementation

There were significant differences in the aspects of the maternal sociodemographic condition, birth history and antenatal care characteristics between users and non-users of micronutrient supplements (**Table 1**). Users of micronutrient supplements were more likely aged between 25-34 years at delivery, with higher education and income level, from central Shaanxi and lived in rural area, as well as primiparous and had better antenatal care including took part in pregnancy consultations, chose higher-level hospitals, and had a higher frequency of antenatal visits.

Rates of and the adherence to micronutrient supplementation

In total, 83.9% of women took at least one micronutrient supplement during their last pregnancy. The

main supplements used by participants were folic acid (FA) (67.6%), calcium (57.5%), MMN (14.0%), and iron (5.4%) (**Table 2**). Although FA had a relatively higher rate of use during the periconceptional period (64.5%), only 7.4% of women insisted to use it from periconceptional period for longer than 180 days. Most of the users started to take calcium supplements during the second trimester (39%), which is basically compliant to the recommended initiation time, but only 11.7% met the recommendation after taking total days of use into consideration. Compare to the rate that who began to use iron or MMN in the after-periconceptional period (3.7% for iron, and 8.2% for MMN), smaller proportion of women commence to take them from the first trimester (1.7% for iron, and 5.8% for MMN), and few of them adhered to use iron or MMN more than 90 days (0.6% for iron, and 2.7% for MMN). (**Table 3**). We also found that very few women (0.2%) consumed FA plus iron starting at the first trimester with more than 90 days of use (not shown in table). We further examined the adherence to supplementation of FA, iron, and FA plus iron by taking the contribution of MMS into consideration. Still, the rates of compliant use were low (8.5% for FA, 3.2% for iron, and 2.9% for FA plus iron, not shown in table).

Factors associated with the adherence to micronutrient supplementation

Multivariable two-level analysis was used to identify factors related to the adherence to micronutrient supplementation. **Table 4** shows the results of multivariable two-level analysis by GEE models. Higher education and income levels, urban residents, as well as better antenatal care including had pregnancy consultation and a higher frequency of antenatal visits were usually associated with the adhered micronutrient supplementation. Women aged in 25-34 were more likely to adhere to the supplementation of FA, iron, and MMN, but elder than 35 was associated with a lower probability of

adhered use of calcium. Multipara was less likely related to adhered FA supplementation. The type of hospitals for antenatal visits was not linked to the adherence to micronutrient supplementation.

Discussion

In this large-scale cross-sectional study, we observed that micronutrient supplements were not used as commonly as expected, and the adherence to micronutrient supplementation among our population, particularly in women with sociodemographic-disadvantageous, were low based on the CNS and WHO recommendations. Totally, the prevalence of maternal micronutrient supplementation in Shaanxi during 2010-2013 was 83.9%. Compared with other countries, our overall use rate was higher than that of United States in 1999-2006 (77.6%) [2] but lower than those of Sydney, Australia in 2014 (93.8%) [34], Seoul, Korea in 2012 (88%) [35]. Compared with the domestic data, it was similar to that of Sichuan Province (81.8%) in 2010 [4] and higher than the overall prevalence of eight Provinces of China in 2009 (66.4%) [20]. FA, calcium, MMN, and iron were the four supplements primarily used by participants.

Maternal FA supplementation is associated with the prevention of NTDs as well as the reduced risk of preterm delivery and small for gestational age (SGA) births [36]. Both WHO and CNS developed guidelines for promoting daily FA supplementation before and during pregnancy [13,19], and the Chinese government also implemented the periconceptional FA supplementation to prevent NTDs since 2009. In our population, FA was the most popular one used before and during pregnancy, but there were still over than 30% of women did not take it. Additionally, most of the users start to take FA supplement after they were pregnant, and only a small part took FA supplement for preparing for pregnancy, which may indicate the high frequency of non-planning pregnancy or the lack of

knowledge about preconceptional FA supplementation. The more serious reality is merely 7.4% of women adhered to FA supplementation periconceptionally with more than 180 days, and this rate still less than 10% even considering the contribution of MMS. Therefore, the utilization of FA supplement was failed to reach the recommendation among pregnant women in Northwestern China although maternal routine folic acid supplementation is strongly promoted in China.

China has a high prevalence of pregnant anemia which is commonly caused by iron deficiency during pregnancy [15,37]. Reviews stated that daily iron supplementation in pregnancy could be useful in improving iron status and birth outcomes [6,38]. Only 5.4% of the participants consumed iron supplement during pregnancy, and the low rate of iron supplementation possibly attribute to the lack of routine maternal iron supplementation guideline in China and the popular use of antianemic Chinese patent medicines among pregnant women in this region [39]. The proportion of women who had compliant iron supplementation was very low in our population (0.6% for iron, 3.2% for iron and iron-containing MMS), which is much lower than that (20.4% for FA-iron) of Western Amhara of Ethiopia [21]. On the basis of the WHO recommendation, maternal iron supplementation should be started as early as possible during pregnancy [13], Our participants usually began to use iron supplement after the periconceptional period rather than from the beginning of pregnancy. The reason for it may be that most women only took iron supplement under the direction of physicians after the occurrence of ID or IDA during the second half of pregnancy, but the prophylactic supplementation was very rare.

Maternal calcium supplementation has a clear beneficial effect on hypertension-related disorders during pregnancy and is possibly related to the reduction of preterm birth risk [40]. To prevent pre-eclampsia, WHO recommends daily calcium supplementation from 20 weeks of gestation for

populations with low dietary calcium intake [14]. Under the background of the low dietary calcium intake among pregnant women (512 mg/d) [27] and the high prevalence of preterm birth [41], the WHO guideline may suitable for widespread implementation in our population. There is still a gap between the calcium supplementation in Northwestern China and the WHO recommendation according to the fact that more than 40% of women did not take calcium supplements during pregnancy, and only 11.7% of the participants adhered to take calcium initiated from the second trimester for more than 90 total days of use.

Evidence demonstrated that periconceptional MMN supplementation with iron and folic acid could promote maternal health status, reduce the risk of LBW, SGA, and congenital abnormalities[42,43], as well as improve the long-term intellectual development of the offspring [44]. Developed country like Australia had a high prevalence of periconceptional MMS (79.2%) [34], but the rate of MMS among our participants was 14.0%. WHO did not universally recommend MMS for pregnant women due to its potential neonatal mortality risks [11], but the recent evidence from a meta-analysis of 17 randomized control trials updated the WHO subgroup analysis and showed no increased risk of neonatal mortality [45], and the results are consistent with the findings of the 2017 Cochrane Review [43]. Moreover, the 2016 WHO guidelines stated that "policy-makers in populations with a high prevalence of nutritional deficiencies might consider the benefits of MMS on maternal health to outweigh the disadvantages, and may choose to give MMS that include iron and folic acid". Consideration of situations including high incidence of adverse birth outcomes, low intakes of most micronutrients from daily diet as well as from supplement, and disadvantageous-sociodemographic conditions among many pregnant women, the suggestion that to replace iron and folic acid with MMS for pregnant women in low-income areas might be an useful strategy to comprehensively improve maternal micronutrient intake

in this region [43].

When examining the factors associated with the adherence to micronutrient supplementation, we found that disadvantaged sociodemographic conditions and lower antenatal care were associated with low adherence to micronutrient supplementation. Similar associations between education level and prenatal health counseling with the adherence of micronutrient supplementation were reported in the published literature [10,24,46]. Our finding of higher age and primiparity were the predictors of compliant use of FA was consistent with the previous report in Ireland [47]. We did not find the relationship of the type of hospitals for antenatal visits and FA supplementation, which may reflect the balanced implementation of national health policy on maternal FA supplementation in the health system of the study region. In our population, more times of antenatal visits were associated with higher adherence of micronutrient supplementation. Besides routine obstetric examination, women accept the phased health education from the physicians or specialized staff of maternal and child health care during the antenatal care visits according to the gestation age. In addition, women planning to be pregnant or being pregnant (before the 12 weeks of gestation) can receive free FA provided by the Chinese government from the medical institutions when antenatal care visits and learn to appropriately use it under the professional guidance. Iron or calcium supplementation are usually recommended to pregnant women by physicians after the diagnosis of physical or pathological changes related to iron or calcium deficiency. For women with severe pregnancy reactions or multiple-micronutrient deficiency, the physician may recommend MMS. Thus, more times of antenatal care visits provide more opportunities for women to learn the knowledge, and increase the possibilities for physicians to know women's health condition and to give recommendations in time, which finally promotes the adherence to micronutrient supplementation.

To our knowledge, this is the first large-scale and representative study investigated the maternal micronutrient supplementation in Northwestern China. A large sample of 28678 women were recruited from twenty counties and ten districts of Shaanxi using a stratified multistage random sampling method according to the proportion of rural to urban residents, population size and fertility rate in Shaanxi. The results can serve as a data basis for developing health education strategies in the future. Nonetheless, several limitations of the present study should be stated. First, this study was retrospective and all the information of micronutrient supplementation was self-reported from participants, and therefore the recall bias was ineluctable. Second, we did not provide an insight into the dosage of use. Although we listed the possible brand of supplements that women might consume, many women could only recall the micronutrient they used without clear commodity information. Except for FA supplement of different brands usually have specified dosage of 400 μg per pill, the specifications of other supplements are varied from each other, and thus it is hard to calculate the accurate dosage used by our participants. But what is certain is that some supplements women consumed were not specialized for pregnant women, and thus the content of elemental iron or calcium in one tablet of the supplement is lower than the WHO recommended dosage, which may indicate the more severe situation of low adherence of micronutrient supplementation in our population. Third, the sources of recommendation regarding the use of supplements, as well as the access that women procured the supplements, were not recorded. Hence, the approach that more proper for future interventions could not be known. Finally, due to the diversities of economy, culture, lifestyle, as well as eating habits in different geographical areas of China, the generalizability of our findings to other geographical areas may be limited. More large-scale, in-depth and well-designed studies are recommended to explore the effectiveness of supplementation of iron, calcium, and MMN on

pregnancy outcomes according to the adherence of use, and further promote the establishment of new nutritional recommendation for pregnancy in China.

Conclusion

In conclusion, maternal micronutrient supplementation in Shaanxi failed to meet the Chinese guideline and WHO recommendation according to initiation time and total days of use. Improving the adherence to micronutrient supplementation before or during pregnancy is still a burning issue for maternal and child health in Northwestern China. Targeted health education and future guidelines of micronutrient supplementation are suggested to be implemented, especially for women with disadvantaged sociodemographic conditions.

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Ethics

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Ethic Review Committee and Academic Committee of Xi'an Jiaotong University Health Science Center (number 2012008). Written informed consent was obtained from all participants.

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Competing interests

None.

Contributions

D.L., Y.C., L.Z., and H.Y. conceived and designed the study; D.L., S.L., F.L., B.M., R.Z., J.L. collected and cleared the data; D.L., D.W., Y.Z., C.L., S.L., F.L., and P.Q. analyzed and interpreted the data; D.L., Y.C., S.D., and L.Z. drafted and revised the manuscript. All authors read and approved the final version of the manuscript.

Data sharing statement

There is no additional data available.

Reference

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Table 1 Maternal characteristics according to micronutrient supplementations among Chinese women in Shaanxi, 2010-2013

Characteristics	Micronutrient supplementations				*P* [a]
	Yes (n=24051)		No (n=4627)		
	n	%	*n*	%	
Sociodemographic characteristics					
Age (years)					<0.001
<25	7843	32.6	1615	34.9	
25-34	14299	59.5	2465	53.3	
≥35	1909	7.9	547	11.8	
Education					<0.001
Junior high school or below	14113	58.7	3611	78.0	
Senior high school	5114	21.3	627	13.6	
College or above	4824	20.0	389	8.4	
Geographic area					<0.001
Southern Shaanxi	5099	21.2	776	16.8	
Central Shaanxi	13731	57.1	1725	37.3	
Northern Shaanxi	5221	21.7	2126	45.9	
Residence					<0.001
Rural	15846	65.9	3455	74.7	
Urban	8205	34.1	1172	25.3	
Per capita annual household income (RMB)					<0.001
Low	7990	33.2	1714	37.0	
Medium	7819	32.5	1604	34.7	
High	8242	34.3	1309	28.3	
Birth history and antenatal care information					
Parity					<0.001
Primiparous	14651	60.9	2152	46.5	
Multiparous	9400	39.1	2475	53.5	
Pregnancy consultation [b]					<0.001
No	17404	72.4	3981	86.0	
Yes	6647	27.6	646	14.0	
The number of antenatal visits					<0.001
<5	6310	26.2	2298	49.7	
≥5	17741	73.8	2329	50.3	
Type of hospitals for antenatal visits					<0.001
Township hospitals	2783	11.6	622	13.4	
County hospitals or above	21268	88.4	4005	86.6	

[a] *P* values for the differences among groups were derived from the $\chi 2$ tests or Fisher's exact test.
[b] Referred to the participation of health counselling that related to maternal healthcare and fetal development before or during pregnancy.

Table 2 Rates of maternal micronutrient supplementation among Chinese women in Shaanxi, 2010-2013

Micronutrient supplements	n	%
Folic acid	19352	67.6
Calcium	16414	57.5
Multiple micronutrient	4018	14.0
Iron	1547	5.4
Vitamin C	1147	4.0
B Vitamins	814	2.8
Vitamin E	173	0.6
Others [a]	1271	4.4

[a] Including vitamin A, vitamin D and fish oil.

Table 3 Maternal micronutrient supplementation recommendations from WHO and CNS; rates of main micronutrient supplementation by initiation time and total days of use, and adherence to micronutrient supplementation among Chinese women in Shaanxi, 2010-2013

	FA (N=28629)	Iron (N=28644)	Calcium (N=28548)	MMN (N=28628)
Recommendations				
WHO recommendation	1. **Purpose**: NTDs prevention **Settings**: all **Supplementation**: daily use of FA (400 μg) **Duration**: start at 2-month before the planned pregnancy until 12 weeks of pregnancy 2. See recommendation for iron and FA supplementation in the right column	**Purpose**: pregnancy outcome improvement **Settings**: all **Supplementation**: daily use of iron (30-60 mg)-FA (400 μg) **Duration**: throughout pregnancy	**Purpose**: pre-eclampsia prevention **Settings**: areas with low calcium intake **Supplementation**: daily use of calcium (1.5-2.0 g) **Duration**: from 20 weeks' gestation until the end of pregnancy	N/A
CNS recommendation	**Purpose**: NTDs prevention and pregnancy outcome improvement **Settings**: all regions in China **Supplementation**: daily use of FA (400 μg) **Duration**: start at 3-month before the planned pregnancy until the end of pregnancy	No routine iron supplementation is recommended for pregnant women; Pregnant women with severe anemia should appropriately take iron supplements under the guidance of physicians	N/A	N/A
Micronutrient supplementation in our population (n (%))				
Start at periconceptional period	18469 (64.5)	499 (1.7)	5292 (18.5)	1665 (5.8)
Start at 3-month before pregnancy	4966 (17.4)	79 (0.3)	272 (1.0)	212 (0.8)
< 90 days (180 days for FA)	3373 (11.8)	35 (0.1)	104 (0.4)	81 (0.3)
≥ 90 days (180 days for FA)	1593 (5.6)	44 (0.2)	168 (0.6)	131 (0.5)
Start at first trimester	13503 (47.2)	420 (1.5)	5020 (17.6)	1453 (5.1)

< 90 days (180 days for FA)	12992 (45.4)	243 (0.9)	2291 (8.0)	683 (2.4)
≥ 90 days (180 days for FA)	511 (1.8)	177 (0.6)	2729 (9.6)	770 (2.7)
Start at after-periconceptional period	883 (3.1)	1048 (3.7)	11122 (39.0)	2353 (8.2)
Start at second trimester	737 (2.6)	633 (2.2)	8947 (31.4)	1844 (6.4)
< 90 days	524 (1.8)	454 (1.6)	5614 (19.7)	1238 (4.3)
≥ 90 days	213 (0.7)	179 (0.6)	3333 (11.7)	606 (2.1)
Start at third trimester	146 (0.5)	415 (1.5)	2175 (7.6)	508 (1.8)
< 90 days	127 (0.4)	365 (1.3)	1810 (6.3)	435 (1.5)
≥ 90 days	19 (0.1)	50 (0.2)	365 (1.3)	73 (0.3)
Adherence to micronutrient supplementation (n (%)) [a]				
Non-adhered	26525 (92.7)	28467 (99.4)	25215 (88.3)	27858 (97.3)
Adhered	2104 (7.4)	177 (0.6)	3333 (11.7)	770 (2.7)

FA, folic acid; MMN, multiple-micronutrients; WHO, World Health Organization; CNS, Chinese Nutrition Society.

[a] Adhered to FA supplementation was defined as initiated from the periconceptional period with ≥ 180 days of use, otherwise, was regarded as non-adhered; adhered to iron supplementation was considered as initiated from the first trimester with ≥ 90 days of use, otherwise, was regarded as non-adhered; adhered calcium supplementation was considered as initiated from the second trimester with ≥ 90 days of use, otherwise, was regarded as non-adhered; adhered to MMS was defined as initiated from the first trimester with ≥ 90 days of use, otherwise, was considered as non-adhered.

Table 4 Rates of adhered use of supplements by maternal characteristics and adjusted OR (95%CI) for factors associated to the adherence to micronutrient supplementation among Chinese women in Shaanxi, 2010-2013[a]

Characteristics	n	FA		Iron		Calcium		MMN	
		Adhered use (%) [b]	Adjusted OR (95%CI)	Adhered use (%)	Adjusted OR (95%CI)	Adhered use (%)	Adjusted OR (95%CI)	Adhered use (%)	Adjusted OR (95%CI)
Sociodemographic characteristics (Model 1) [c]									
Age (years)									
<25	9458	5.3	Ref	0.4	Ref	11.2	Ref	1.7	Ref
25-34	16764	8.7	**1.30 (1.11, 1.52) ***	0.7	**1.49 (1.18, 1.88) ***	12.4	1.03 (0.94, 1.12)	3.3	**1.38 (1.12, 1.71) ***
≥35	2456	6.3	1.22 (0.98, 1.51)	0.6	1.54 (0.80, 2.99)	8.6	**0.71 (0.62, 0.81) ***	2.3	1.24 (0.84, 1.84)
Education									
Junior high school or below	17724	4.9	Ref	0.4	Ref	9.9	Ref	1.6	Ref
Senior high school	5741	7.3	**1.38 (1.18, 1.61) ***	0.9	**2.00 (1.36, 2.96) ***	13.8	**1.32 (1.22, 1.42) ***	2.8	**1.51 (1.21, 1.88) ***
College or above	5213	15.9	**2.59 (2.21, 3.05) ***	1.2	**1.69 (1.12, 2.54) ***	15.5	**1.45 (1.31, 1.60) ***	6.2	**2.65 (2.14, 3.28) ***
Residence									
Rural	19301	5.9	Ref	0.4	Ref	10.6	Ref	2.1	Ref

Urban	9377	10.4	**1.72 (1.08, 2.72) ***	1.1	**1.88 (1.17, 3.01) ***	14.0	1.21 (0.90, 1.62)	3.9	1.30 (0.82, 2.06)
Per capita annual household income (RMB)									
Low	9689	5.0	Ref	0.4	Ref	10.6	Ref	1.8	Ref
Medium	9402	6.4	1.07 (0.94, 1.23)	0.5	1.06 (0.74, 1.54)	11.7	1.08 (0.99, 1.19)	2.2	1.18 (0.96, 1.45)
High	9538	10.7	**1.27 (1.11, 1.45) ***	1.0	**1.56 (1.05, 2.32) ***	12.8	1.09 (0.96, 1.24)	4.0	**1.39 (1.11, 1.76) ***
Birth history and antenatal care information (Model 2) [d]									
Parity									
Primiparous	16803	9.2	Ref	0.7	Ref	12.8	Ref	3.2	Ref
Multiparous	11875	4.8	**0.70 (0.58, 0.84) ***	0.5	0.90 (0.61, 1.34)	10.1	1.02 (0.94, 1.11)	1.9	0.88 (0.72, 1.07)
pregnancy consultation									
No	21385	5.6	Ref	0.5	Ref	10.7	Ref	2.3	Ref
Yes	7293	12.6	**1.91 (1.71, 2.14) ***	1.0	**1.40 (1.21, 1.96) ***	14.7	**1.22 (1.10, 1.34) ***	3.8	**1.40 (1.17, 1.67) ***
The number of antenatal visits									

<5	8608	3.8	Ref	0.3	Ref	7.6	Ref	15.4	Ref
≥5	20070	8.9	**1.59 (1.35, 1.87) ***	0.8	**1.66 (1.18, 2.34) ***	13.4	**1.41 (1.25, 1.60) ***	26.4	**1.33 (1.09, 1.62) ***
Type of hospitals for antenatal visits									
Township hospitals	3405	5.9	Ref	0.5	Ref	9.6	Ref	1.7	Ref
County hospitals or above	25273	7.6	1.14 (0.94, 1.37)	0.6	1.26 (0.79, 2.01)	12.0	1.10 (0.94, 1.29)	2.8	1.14 (0.90, 1.46)

FA, folic acid; MMN, multiple-micronutrients; OR, odds ratio; CI, confident interval.

[a] N=28678. The number of missing values for supplementation of FA, iron, calcium and MMN were 49, 34, 130 and 50. Adjusted OR and 95% CI were derived from multivariable GEE models with random effects at county level.

[b] Adhered to FA supplementation was defined as initiated from the periconceptional period with ≥ 180 days of use; adhered to iron supplementation was considered as initiated from the first trimester with ≥ 90 days of use; adhered to calcium supplementation was considered as initiated from the second trimester with ≥ 90 days of use; adhered to MMS was defined as initiated from the first trimester with ≥ 90 days of use.

[c] Model 1 adjusted for the sociodemographic characteristics including maternal age, education, residence and income, and the OR and 95% CI of these characteristics was derived from model 1.

[d] Model 2 adjusted for all variables in model 1 plus parity and antenatal care characteristics, and the OR and 95% CI of parity and antenatal care characteristics was derived from model 2.

* Refers to P <0.05.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	None
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	None
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 3-4
Outcome data	15*	Report numbers of outcome events or summary measures	Table 1-4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1, Table 4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	None
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	None
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Maternal adherence to micronutrient supplementation before and during pregnancy in Northwest China: a large-scale population-based cross-sectional survey

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Complete List of Authors:	Liu, Danmeng; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Cheng, Yue; Xi'an Jiaotong University Health Science Center, Department of Nutrition Dang, Shaonong; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Wang, Duolao; Liverpool University, Liverpool School of Tropical Medicine Zhao, Yaling; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Li, Chao; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Li, Shanshan; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Lei, Fangliang; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Qu, Pengfei; Northwest women's and children's Hospital, Translational Medicine Center Mi, Baibing; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Zhang, Ruo; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Li, Jiamei; Department of Emergency Medicine, the Second Affiliated Hospital, Xi'an Jiaotong University, Department of Emergency Medicine Zeng, L; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics Yan, H; Xi'an Jiaotong University Health Science Center, Department of Epidemiology and Health Statistics; Nutrition and Food Safety Engineering Research Center of Shaanxi Province
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Maternal adherence to micronutrient supplementation before and during pregnancy in Northwest China: a large-scale population-based cross-sectional survey

Danmeng Liu[1], Yue Cheng[2], Shaonong Dang[1], Duolao Wang[3], Yaling Zhao[1], Chao Li[1], Shanshan Li[1], Fangliang Lei[1], Pengfei Qu[4], Baibing Mi[1], Ruo Zhang[1], Jiamei Li[5], Lingxia Zeng[1] *, Hong Yan[1 6 7] *

[1]Department of Epidemiology and Health Statistics, School of Public Health, Xi'an Jiaotong University Health Science Center, No. 76 Yanta West Road, Xi'an, Shaanxi, 710061, China

[2]Department of Nutrition, School of Public Health, Xi'an Jiaotong University Health Science Center, No. 76 Yanta West Road, Xi'an, Shaanxi, 710061, China

[3]Liverpool School of Tropical Medicine, Liverpool University, Pembroke Place, Liverpool, L3 5QA, UK

[4]Translational Medicine Center, Northwest women's and children's Hospital, No. 1616 Yanxiang Road, Xi'an, Shaanxi, 710061, China

[5]Department of Emergency Medicine, The Second Affiliated Hospital of Xi'an Jiaotong University, No. 157 West Fifth Road, Xi'an, Shaanxi, 710004, China

[6]Nutrition and Food Safety Engineering Research Center of Shaanxi Province, Xi'an, Shaanxi, 710061, China

[7]Key Laboratory of Environment and Genes Related to Diseases, Xi'an Jiaotong University, Ministry of Education, Xi'an, Shaanxi, 710061, China

*Corresponding author:

Lingxia Zeng, Health Science Center, Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, China. Fax +86 29 82655104, email tjzlx@mail.xjtu.edu.cn

Hong Yan, Health Science Center, Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, China. Fax +86 29 82655104, email xjtu_yh.paper@aliyun.com

Abstract

Objectives: To report the situation of maternal micronutrient supplementation before and during pregnancy in Northwest China and to examine the rates of and factors related to the adherence to micronutrient supplementation among pregnant women in this region, where dietary micronutrient intake is commonly insufficient.

Design: A large-scale population-based cross-sectional survey.

Setting: Twenty counties and ten districts of Shaanxi Province.

Participants: A sample of 30,027 women were selected using a stratified multistage random sampling method. A total of 28,678 women were chosen for the final analysis after excluding those who did not provide clear information about nutritional supplementation before and during pregnancy.

Main outcome measures: Maternal adherence to micronutrient supplementation (high and low) were the outcomes. They were determined by the start time and duration of use according to Chinese guidelines (for folic acid [FA] supplements) and WHO recommendations (for iron, calcium, and multiple-micronutrient [MMN] supplements).

Results: In total, 83.9% of women took at least one kind of micronutrient supplement before or during pregnancy. FA (67.6%) and calcium (57.5%) were the primarily used micronutrient supplements; few participants used MMN (14.0%) or iron (5.4%). Adherence to supplementation of all micronutrients

was low (7.4% for FA, 0.8% for iron, 23.2% for calcium and 3.2% for MMN). Higher educational levels, higher income levels, urban residence, and better antenatal care (including pregnancy consultation and a higher frequency of antenatal visits) were associated with high adherence to micronutrient supplementation.

Conclusion: Maternal micronutrient supplementation before and during pregnancy in Northwest China was way below standards recommended by the Chinese guidelines or WHO. Targeted health education and future nutritional guidelines are suggested to improve this situation, especially in pregnant women with disadvantaged sociodemographic conditions.

Keywords: Micronutrient supplementation; Pregnancy; Adherence; Associated factors

Running Head: Adherence to maternal micronutrient supplementation

Word count: 4192

Strengths and limitations of this study

- This is the first large-scale and representative study that vividly described maternal adherence to micronutrient supplementation before and during pregnancy in Northwest China.
- Sample representativeness in Shaanxi was guaranteed by a large sample of 28,678 women that were recruited using a stratified multistage random sampling method.
- The results could be generalized in Northwest China and may also reflect the universality of the problem in China, and could serve as a basis for developing health education strategies in the future.
- Recall bias was ineluctable because the information was self-reported by retrospection.

- The study does not provide an insight into the dosage of specific micronutrient supplementation due to the uncertain specifications of some reported supplements.

Introduction

Pregnancy is a state in which macro- and micronutrient requirements increase due to maternal physiological changes and fetal growth [1]. During pregnancy, adequate micronutrient intake is difficult to achieve from daily diet [2], and maternal micronutrient deficiencies could cause severe adverse outcomes, including stillbirth, low birth weight (LBW), and birth defects [3]. Micronutrient supplementation is an alternative, in addition to the adjustment of diet pattern and quality, to fulfill the increased nutrition demands during pregnancy [4]. In recent decades, maternal micronutrient supplementation during pregnancy has attracted much attention, as growing evidence has shown that it has significant benefits in the improvement of maternal health status as well as birth outcomes [5-8]. As a result, some micronutrients that greatly contribute to maternal and fetal health are highly recommended for routine use during pregnancy. Many countries have implemented periconceptional folic acid (FA) supplementation to protect against neural tube defects (NTDs) [9,10]. WHO has also provided several guidelines for micronutrient supplementation for pregnant women [11]. Daily use of FA (400 μg), starting from 2 months before the planned pregnancy to 12 weeks of pregnancy is recommended for the prevention of NTDs [12]; daily oral FA combined with iron supplementation (400 μg FA and 30-60 mg iron) throughout pregnancy is recommended to reduce the risk of LBW, maternal anemia and iron deficiency [13]; daily oral calcium supplementation (1.5-2.0 g) in the second half of pregnancy is recommended for pregnant women in the area of low dietary calcium intake, to

reduce the risk of pre-eclampsia [14].

China is the most populated developing country with a considerable incidence of adverse pregnancy outcomes, including maternal anemia [15], LBW [16], and small for gestational age [8]. However, the implementation of FA supplementation project (take daily FA (400 μg), start from 3 months before pregnancy to the end of the first trimester) to prevent NTDs, especially in rural areas, is the only nutritional intervention promoted by the Chinese Health Ministry (now the Chinese National Health Commission) for pregnant women and women planning to be pregnant [17,18]. Also, the only routine antenatal micronutrient supplementation recommended by the Chinese Nutrition Society (CNS) for women of childbearing age is the daily use of FA (400 μg), starting from 3 months before the planned pregnancy until the end of pregnancy [19]. No more guidelines for routine supplementation of other micronutrients exist, so that the use of micronutrient supplements during pregnancy varied in Chinese geographic areas and socioeconomic groups [4,20].

All health policies and recommendations of micronutrient supplementation for pregnant women emphasize the timing, dosage, sustainability of use, as well as the target population. Evidence showed that low compliance was a major reason for the low effectiveness of micronutrient supplementation during pregnancy [8,21], and thus the exploration of the determinants of the adherence is important for guiding the appropriate use to guarantee the efficacy. Many factors were reported in relation to maternal adherence to micronutrient supplementation before and during pregnancy, including maternal age, educational background, occupation, and antenatal care. Previous studies have reported on the compliance of maternal micronutrient supplementation in Western countries like the United States of American and Norway [22,23], as well as in Africa countries like Ethiopia and Kenya [24,25]. Few of the studies focused on maternal adherence to micronutrient supplementation before and during

pregnancy in China.

Shaanxi Province is a developing area in Northwest China where most of the micronutrients derived from diet among pregnant women were lower than the Chinese recommended nutrient intake (RNI) [26,27], especially the intake of folate and calcium [26,27]. Although dietary iron intake was close to the RNI for the first and second trimester, most iron from diet were the non-heme iron, which is not efficiently absorbed and utilized by the human body [28]. Additionally, about 40% of women of childbearing age in the region suffered anemia [29], and the incidence of adverse birth outcomes, including LBW and preterm birth, were high in this region [30]. Therefore, maternal micronutrient supplementation seems to be a relatively inexpensive and low risk method for compensating for inadequate dietary intake during pregnancy and improving the health status of local mothers and fetus. However, a representative data from a large-scale study on the maternal micronutrient supplementation before and during pregnancy in this region is not available. Accordingly, this article aims to investigate the condition of maternal micronutrient supplementation before and during pregnancy in Shaanxi, focusing on analyzing the rates and associated factors of maternal adherence to supplement consumptions according to existing recommendations, and to provide evidence for future evaluation of health policy effectiveness and development of health education strategies.

Methods

Data source and participants

The study used data from a large-scale population-based cross-sectional survey, which was conducted between August to November 2013 in the Shaanxi province with the purpose of investigating the prevalence and risk factors of birth defects among newborns, along with maternal

dietary conditions and nutritional supplements use. The target population was women aged from 16 to 49 years, who were pregnant between 2010 to 2013 and had specific pregnancy outcomes before the survey. The sample was acquired from 20 counties and 10 districts of Shaanxi by applying a stratified multistage random sampling method [27,31]. Firstly, 20 counties and 10 districts were randomly selected from the 80 rural counties and 24 urban districts in Shaanxi Province according to the difference in size, distribution and fertility rates of population between rural and urban areas. Subsequently, in the rural area, 6 townships, 6 villages, and 30 eligible women were randomly selected from each sampled county, selected township, and selected village, respectively. In the urban areas, 3 streets, 6 communities, and 60 eligible women were randomly selected from each sampled district, selected street, and selected community, respectively. Data collection was completed with structured-questionnaires via in-person surveys by trained interviewers. Information gathered included maternal sociodemographic characteristics, lifestyle, health condition, health care utilization, and supplement consumption. A strict quality control process was utilized to guarantee data integrity and accuracy [27].

A total of 30,027 women were enrolled in the survey after they signed the informed consent, and women with limited cognitive capacity had been excluded. In order to obtain more accurate analysis results, we further excluded 1,349 women who did not provide clear information about maternal nutritional supplementation (among them, 761 women had no live birth babies in this pregnancy and refused to provide detailed information). In total, 28,678 women were chosen for the final analysis.

Maternal sociodemographic characteristics, parity, and antenatal care information

Maternal age at delivery was divided into 3 categories (<25, 25-34 and ≥35 years), as well as

educational level (Junior high school or below, Senior high school and College and beyond), geographical area (Southern Shaanxi, Central Shaanxi and Northern Shaanxi) and per capita annual household income (Low: <8800, Medium: 8800-15200 and High: ≥ 15200 Yuan, where 1 Yuan=$0·149 on 17 Mar 2019). Residence (urban and rural) and parity (primiparous and multiparous) were classified into 2 categories each. We also investigated the antenatal care information, including the number of antenatal visits (<5 and ≥5), the type of hospitals for antenatal visit (hospitals below the county level and county level hospitals or above), and pregnancy consultation (yes and no, referred to the participation of health counseling that related to maternal health care and fetal development before or during pregnancy).

Micronutrient supplementation

Information about micronutrient supplements in tablet and capsule forms were mainly collected. We asked the participants to choose the supplements they used before or during pregnancy from a list of brands of supplements that were commonly provided in the local hospital or pharmacy, and to further tell the brand and kind of supplement they consumed, if it was not shown in the list. We did not list iron-FA supplements in the questionnaire, since few supplements on the market were two-nutrient formulations of iron and FA. In the analysis, FA supplements referred to those that only contained FA; iron supplements referred to those that only contained iron; calcium supplements referred to those that contained calcium or calcium with another micronutrient (including calcium-vitamin D and calcium-zinc); multiple-micronutrient (MMN) supplements referred to those that contained FA, iron, and other micronutrients. Women who consumed any micronutrient supplement before or during pregnancy were considered as micronutrient supplement users; otherwise, were

regarded as non-users.

We further obtained the time and duration of use of each supplement they reported. The participants were required to select the time of supplement use from the 4 pregnancy periods (3 months before the last menstrual period, the first trimester, the second trimester, and the third trimester) and report the duration of supplementation for each supplement they used. The 3 months before the last menstrual period was defined as the pre-conceptional period; the time from the 3 months before the last menstrual period to the end of first trimester was defined as the periconceptional period; the time of the second and third trimester was defined as the after-periconceptional period.

Adherence to micronutrient supplementation before and during pregnancy was determined by the start time and duration of use according to Chinese guidelines (for FA) and WHO recommendations (for iron, calcium, and MMN). Although WHO did not universally recommend MMN supplementation (MMS) for pregnant women, due to its components of iron and FA, we still examined the compliance of MMS by referencing the WHO recommendation for iron and FA supplementation. We considered the duration of use instead of the total amounts, because most of the supplements of interest were taken as 1 tablet daily. In the present study, the thresholds used to define the adhered duration of use were 180 days for FA and 90 days for others. Therefore, high adherence to FA supplementation was defined as starting from the periconceptional period with ≥ 180 days of use; otherwise, was regarded as low adherence. High adherence to iron supplementation was considered as starting from the first trimester with ≥ 90 days of use; otherwise, was regarded as low adherence. For calcium supplementation, 20 weeks of gestation was the start time recommended by WHO. Since we did not collect the specific weeks of gestation of micronutrient supplementation,

high adherence to calcium supplementation was considered as starting from the second trimester with ≥ 90 days of use; otherwise, was regarded as low adherence. High adherence to MMS was defined as one starting from the first trimester with ≥ 90 days of use; otherwise, was considered as low adherence.

Statistical analysis

Dataset was established using Epidata 3.1 (The Epidata Association, Odense, Denmark) with double entry. Multiple imputation was used to attribute values for the missing variables, including income level (n=5830), maternal age group (n=434), and the type of hospital for antenatal visits (n=327), taking education level, geographic area, residence, parity, the number of antenatal visits, and pregnancy consultation as covariates with 5 imputed data sets [32]. Numbers and percentages (n [%]) were estimated for reporting the rate of micronutrient supplementation in different groups and for presenting the adherence to micronutrient supplementation. Comparisons between groups were completed by either the Chi-square test or Fisher's exact test.

Because of the hierarchical structure of the data derived from the stratified multistage random sampling design, multivariable generalized estimating equation (GEE) models [33] with random effect at county level were applied to estimate adjusted odds ratio (OR) and 95% confidence interval (CI) for factors associated with maternal adherence to micronutrient supplementation before and during pregnancy. Maternal characteristics including age, education, residence, income, parity, pregnancy consultation, number of antenatal visits, and type of hospital for antenatal visits were the fixed effects in the GEE models. Binomial distribution, logit link function, and an exchangeable covariance structure were used in the GEE analysis. Model 1 analyzed the relationship between the adherence to micronutrient supplementation and the sociodemographic characteristics including age, education,

residence, and income. Model 2 analyzed the relationship between the adherence to micronutrient supplementation and sociodemographic characteristics (all the variables in model 1), as well as parity and antenatal care characteristics. The criteria for statistical significance was $P < 0.05$. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Patient and public involvement

No patients were involved in developing the research question, outcome measure and design of the study. We were unable to disseminate the results of the research directly to study participants, and we informed the results to the local health authorities.

Results

Maternal characteristics according to micronutrient supplementation before and during pregnancy

Significant differences existed in aspects of maternal sociodemographic conditions, birth history, and antenatal care characteristics between users and non-users of micronutrient supplements before and during pregnancy (**Table 1**). Users of micronutrient supplements were more likely to be aged from 25 to 34 years, be better educated, have higher income level, live in central Shaanxi live, be rural residents, be primiparous, and have better antenatal care (including pregnancy consultations, higher-level hospital for antenatal visits, and a higher frequency of antenatal visits).

Rates of and the adherence to micronutrient supplementation before and during pregnancy

In total, 83.9% of women took at least one kind of micronutrient supplement before or during

their last pregnancy. The main supplements used by participants were folic acid (FA) (67.6%), calcium (57.5%), MMN (14.0%), and iron (5.4%) (**Table 2**). Although FA had a relatively higher rate of use during the periconceptional period (64.5%), only 7.4% of women continued usage from the periconceptional period for longer than 180 days. Most of the users started taking calcium supplements during the second trimester (39%), but only 11.7% met the recommended standards after taking the duration of use into consideration. Comparing to the rates of those who began to use iron or MMN in the after-periconceptional period (3.7% for iron, and 8.2% for MMN), smaller proportion of women commenced consumption from the first trimester (1.7% for iron, and 5.8% for MMN), and few of them adhered to use of iron or MMN in more than 90 days (0.6% for iron, and 2.7% for MMN). (**Table 3**). We also found that very few women (0.2%) consumed FA and iron starting from the first trimester with more than 90 days of use (not shown in table). We further examined the adherence to supplementation of FA, iron, and FA with iron by taking the contribution of MMS into consideration. Still, the rates of compliant use were low (8.5% for FA, 3.2% for iron, and 2.9% for FA with iron, not shown in table).

Factors associated with the adherence to micronutrient supplementation before and during pregnancy

Table 4 shows the results of multivariable GEE models. Higher educational levels (for example: FA: Senior high school vs. Junior high school or below: OR 1.38, 95% CI 1.18, 1.61; College and beyond *vs.* Junior high school or below: OR 2.59, 95% CI 2.21, 3.05), higher income levels (for example: FA: High *vs.* Low: OR 1.27, 95% CI 1.11, 1.45), urban residence (for example: FA: Urban *vs.* Rural: OR 1.72, 95% CI 1.08, 2.72), and better antenatal care (including pregnancy consultation

[for example: FA: Yes *vs.* No: OR 1.91, 95% CI 1.71, 2.14] and a higher frequency of antenatal visits [for example: FA: ≥5 times *vs.* < 5 times: OR 1.59, 95% CI 1.35, 1.87]) were associated with high adherence to micronutrient supplementation before and during pregnancy. Compared with women below 25 years, women aged from 25 to 34 years were more likely to have high adherence to the supplementation of FA (OR 1.30, 95% CI 1.11, 1.52), iron (OR 1.49 95% CI 1.18, 1.88), and MMN (OR 1.38, 95% CI 1.12, 1.71). Women above 35 years were associated with a lower probability of high adherence to calcium supplementation (OR 0.71, 95% CI 0.62, 0.81). Being multipara was less likely related to high adherence to FA supplementation (OR 0.70, 95% CI 0.58, 0.84). The type of hospital for antenatal visits was not linked to the adherence to micronutrient supplementation.

Discussion

In this large-scale cross-sectional study, we observed that micronutrient supplements were not used as commonly as expected before and during pregnancy, and maternal adherence to micronutrient supplementation among our population, particularly in women with sociodemographic-disadvantages, were low based on the CNS and WHO recommendations. Totally, the prevalence of maternal micronutrient supplementation before and during pregnancy in Shaanxi from 2010 to 2013 was 83.9%. Compared with other countries, our overall use rate was higher than that of United States from 1999 to 2006 (77.6%) [2], but lower than those of Sydney, Australia in 2014 (93.8%) [34] and Seoul, Korea in 2012 (88%) [35]. Compared with the domestic data, it was similar to that of Sichuan Province (81.8%) in 2010 [4] and higher than the overall prevalence of 8 Provinces of China in 2009 (66.4%) [20]. FA, calcium, MMN, and iron were the four supplements primarily used by participants.

Maternal FA supplementation is associated with the prevention of NTDs as well as the reduced

risk of preterm delivery and small for gestational age (SGA) births [36]. Both WHO and CNS developed guidelines for promoting daily FA supplementation before and during pregnancy [13,19], and the Chinese government also implemented the periconceptional FA supplementation to prevent NTDs since 2009. In our population, FA was the most popularly used supplement before and during pregnancy, but more than 30% of women still did not take it. Additionally, most of the users started to take FA supplements after they became pregnant, and only few took FA supplements to prepare for pregnancy, which may indicate the high frequency of unplanned pregnancies or the lack of knowledge about pre-conceptional FA supplementation. The more serious reality was that less than 10% of women adhered to FA supplementation periconceptionally in more than 180 days. Therefore, the use of FA supplements failed to reach the recommended standards among pregnant women in Northwest China, even when maternal routine FA supplementation was strongly promoted in China.

China has a high prevalence of pregnancy anemia, which is commonly caused by iron deficiency during pregnancy [15,37]. Reviews stated that daily iron supplementation in pregnancy could be useful in improving iron status and birth outcomes [6,38]. Only 5.4% of the participants consumed iron supplements during pregnancy, and the low rate of iron supplementation was possibly attributed to the lack of routine maternal iron supplementation guidelines in China and the popular use of anti-anemic Chinese patent medicines among pregnant women in this region [39]. The proportion of women who had compliant iron supplementation was very low in our population (0.6% for iron and 3.2% for iron and iron-containing MMS), which is much lower than that of Western Amhara of Ethiopia (20.4% for FA-iron) [21]. On the basis of the WHO recommendation, maternal iron supplementation should be started as early as possible during pregnancy [13]. Our participants usually began to use iron supplements after the periconceptional period rather than from the beginning of pregnancy. The

reason may be that most women only took iron supplements under the direction of physicians after the occurrence of iron deficiency or iron deficiency anemia during the second half of pregnancy, but prophylactic supplementation was very rare.

Maternal calcium supplementation has a clear beneficial effect on hypertension-related disorders during pregnancy and is possibly related to the reduction of preterm birth risk [40]. To prevent pre-eclampsia, WHO recommends daily calcium supplementation from 20 weeks of gestation for populations with low dietary calcium intake [14]. From the background of the low dietary calcium intake among pregnant women (512 mg/d) [27] and the high prevalence of preterm birth [41], the WHO guideline may be suitable for widespread implementation in our population. A gap still exists between calcium supplementation among pregnant women in Northwest China and the WHO recommendation, according to the fact that more than 40% of women did not take calcium supplements during pregnancy and only 11.7% of the participants adhered to take calcium right from the start of the second trimester for more than 90 days of use.

Evidence demonstrated that periconceptional MMN supplementation with iron and folic acid could promote maternal health status, reduce the risk of LBW, SGA, and congenital abnormalities[42,43], as well as improve the long-term intellectual development of offspring [44]. Developed countries like Australia had a high prevalence of periconceptional MMS (79.2%) [34], but the rate of MMS among our participants was 14.0%. WHO did not universally recommend MMS for pregnant women due to its potential neonatal mortality risks [11], but the recent evidence showed no increased risk of neonatal mortality [43,45]. Moreover, the 2016 WHO guidelines stated that “policy-makers in populations with a high prevalence of nutritional deficiencies might consider the benefits of MMS on maternal health to outweigh the disadvantages, and may choose to give MMS that include iron and folic acid”.

Comprehensively taking the situations of Shaanxi (including high incidence of adverse birth outcomes, low intake of most micronutrients from daily diet as well as from supplements, and disadvantaged sociodemographic conditions among many pregnant women) into consideration, to replace iron and folic acid with MMS for pregnant women in low-income areas might be a useful strategy to improve overall maternal micronutrient intake in this region [43].

When examining the factors associated with maternal adherence to micronutrient supplementation before and during pregnancy, we found that sociodemographic disadvantages and lower antenatal care level were associated with low adherence to micronutrient supplementation. Similar associations between educational level and prenatal health counseling with adherence to micronutrient supplementation were reported in literature [10,24,46]. Our finding that higher age and primiparity were predictors of compliant use of FA was consistent with that of a previous study in Ireland [47]. We did not find any relationship between the type of hospital for antenatal visits and FA supplementation, which may reflect the balanced implementation of national health policy on maternal FA supplementation in the health system of the study region. In our population, higher frequency of antenatal visits was associated with higher adherence to micronutrient supplementation. Aside from routine obstetric examination, women accept the phased health education from the physicians during their antenatal care visits. In addition, women planning to be pregnant or are pregnant (before 12 weeks of gestation) can receive free FA provided by the Chinese government during antenatal care visits and learn to appropriately use them under professional guidance. Iron or calcium supplementation is usually recommended to pregnant women by physicians after the diagnosis of physical or pathological changes related to iron or calcium deficiency. For women with severe pregnancy reactions or multiple-micronutrient deficiency, the physician may recommend

MMS. Thus, higher frequency of antenatal care visits provides more opportunities for women to learn, and increases the possibilities for physicians to know the pregnant women's health condition and to give recommendations in time, which finally promotes the adherence to micronutrient supplementation.

To the best of our knowledge, this is the first large-scale and representative study that investigated maternal micronutrient supplementation before and during pregnancy in Northwest China. To guarantee the representativeness, a large sample was recruited from Shaanxi Province of Northwest China using a stratified multistage random sampling method according to the proportion of rural to urban residents, population size and fertility rate in the region. The results could be generalized to other regions in Northwest China according to the similarities in terms of economy, culture, lifestyle and diet habits existing in these regions, and may also reflect the universality of the low adherence to micronutrient supplementation before and during pregnancy in China. Therefore, it could serve as a basis for developing health education strategies in the future. Nonetheless, several limitations of the present study should be stated. First, this study was retrospective, and all the information of micronutrient supplementation was self-reported from participants, and therefore recall bias was ineluctable. Second, we did not provide an insight into the dosage of use. Although we listed the possible brands of supplements that women might consume, many women could only recall the micronutrient they used without clear commodity information. Except for FA supplements, which usually have specified dosage of 400 μg per pill, the specifications of other supplements vary from each other, and thus it is difficult to calculate the accurate dosage used by our participants. However, what is certain is that some supplements women consumed were not specialized for pregnant women, and thus the content of elemental iron or calcium in one tablet of the supplement is

lower than the WHO recommended dosage, which may indicate the more severe situation of low adherence of micronutrient supplementation in our population. Third, the sources of recommendation regarding the use of supplements, as well as the access that women procured the supplements, were not recorded. Hence, the approach for more appropriate future interventions could not be known. More large-scale, in-depth, and well-designed studies are recommended to explore the effectiveness of supplementation of iron, calcium, and MMN on pregnancy outcomes according to the adherence of use, and further promote the establishment of new nutritional recommendations for pregnancy in China.

Conclusion

In conclusion, maternal micronutrient supplementation before and during pregnancy in Shaanxi failed to meet the Chinese guidelines and WHO recommendation, with respect to start time and duration of use. Improving the adherence to micronutrient supplementation before or during pregnancy is still a dire issue for maternal and child health in Northwest China. Targeted health education and future guidelines of micronutrient supplementation for pregnant women should be implemented, especially for those with disadvantaged sociodemographic conditions.

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Ethics

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Ethic Review Committee and

Academic Committee of Xi'an Jiaotong University Health Science Center (number 2012008). Written informed consent was obtained from all participants.

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Competing interests

None.

Contributions

D.L., Y.C., L.Z., and H.Y. conceived and designed the study; D.L., S.L., F.L., B.M., R.Z., J.L. collected and cleared the data; D.L., D.W., Y.Z., C.L., S.L., F.L., and P.Q. analyzed and interpreted the data; D.L., Y.C., S.D., and L.Z. drafted and revised the manuscript. All authors read and approved the final version of the manuscript.

Data sharing statement

There is no additional data available.

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Table 1 Maternal characteristics according to micronutrient supplementation before and during pregnancy among Chinese women in Shaanxi, 2010-2013

Characteristics	Micronutrient supplementation				*P* [a]
	Yes (n=24051)		No (n=4627)		
	n	%	*n*	%	
Sociodemographic characteristics					
Age (years)					<0.001
<25	7843	32.6	1615	34.9	
25-34	14299	59.5	2465	53.3	
≥35	1909	7.9	547	11.8	
Education					<0.001
Junior high school or below	14113	58.7	3611	78.0	
Senior high school	5114	21.3	627	13.6	
College and beyond	4824	20.0	389	8.4	
Geographic area					<0.001
Southern Shaanxi	5099	21.2	776	16.8	
Central Shaanxi	13731	57.1	1725	37.3	
Northern Shaanxi	5221	21.7	2126	45.9	
Residence					<0.001
Rural	15846	65.9	3455	74.7	
Urban	8205	34.1	1172	25.3	
Per capita annual household income (RMB)					<0.001
Low	7990	33.2	1714	37.0	
Medium	7819	32.5	1604	34.7	
High	8242	34.3	1309	28.3	
Birth history and antenatal care information					
Parity					<0.001
Primiparous	14651	60.9	2152	46.5	
Multiparous	9400	39.1	2475	53.5	
Pregnancy consultation [b]					<0.001
No	17404	72.4	3981	86.0	
Yes	6647	27.6	646	14.0	
The number of antenatal visits					<0.001
<5	6310	26.2	2298	49.7	
≥5	17741	73.8	2329	50.3	
Type of hospitals for antenatal visits					<0.001
Township hospitals	2783	11.6	622	13.4	
County hospitals or above	21268	88.4	4005	86.6	

[a] *P* values for the differences among groups were derived from either the $\chi 2$ tests or Fisher's exact test.

[b] Referred to the participation of health counselling that related to maternal healthcare and fetal development before or during pregnancy.

Table 2 Rates of maternal micronutrient supplementation before and during pregnancy among Chinese women in Shaanxi, 2010-2013

Micronutrient supplements	n	%
Folic acid	19352	67.6
Calcium	16414	57.5
Multiple micronutrient	4018	14.0
Iron	1547	5.4
Vitamin C	1147	4.0
B Vitamins	814	2.8
Vitamin E	173	0.6
Others [a]	1271	4.4

[a] Including vitamin A, vitamin D and fish oil.

Table 3 Maternal micronutrient supplementation recommendations from WHO and CNS; rates of main micronutrient supplementation by start time and duration of use, and adherence to micronutrient supplementation before and during pregnancy among Chinese women in Shaanxi, 2010-2013

	FA (N=28629)	Iron (N=28644)	Calcium (N=28548)	MMN (N=28628)
Recommendations				
WHO recommendation	1. **Purpose**: NTDs prevention **Settings**: all **Supplementation**: daily use of FA (400 μg) **Duration**: start at 2-month before the planned pregnancy until 12 weeks of pregnancy 2. See recommendation for iron and FA supplementation in the right column	**Purpose**: pregnancy outcome improvement **Settings**: all **Supplementation**: daily use of iron (30-60 mg)-FA (400 μg) **Duration**: throughout pregnancy	**Purpose**: pre-eclampsia prevention **Settings**: areas with low calcium intake **Supplementation**: daily use of calcium (1.5-2.0 g) **Duration**: from 20 weeks' gestation until the end of pregnancy	N/A
CNS recommendation	**Purpose**: NTDs prevention and pregnancy outcome improvement **Settings**: all regions in China **Supplementation**: daily use of FA (400 μg) **Duration**: start at 3-month before the planned pregnancy until the end of pregnancy	No routine iron supplementation is recommended for pregnant women; Pregnant women with severe anemia should appropriately take iron supplements under the guidance of physicians	N/A	N/A
Micronutrient supplementation in our population (n (%))				
Start at periconceptional period	18469 (64.5)	499 (1.7)	5292 (18.5)	1665 (5.8)
Start at 3-month before pregnancy	4966 (17.4)	79 (0.3)	272 (1.0)	212 (0.8)
< 90 days (180 days for FA)	3373 (11.8)	35 (0.1)	104 (0.4)	81 (0.3)
≥ 90 days (180 days for FA)	1593 (5.6)	44 (0.2)	168 (0.6)	131 (0.5)
Start at first trimester	13503 (47.2)	420 (1.5)	5020 (17.6)	1453 (5.1)

< 90 days (180 days for FA)	12992 (45.4)	243 (0.9)	2291 (8.0)	683 (2.4)
≥ 90 days (180 days for FA)	511 (1.8)	177 (0.6)	2729 (9.6)	770 (2.7)
Start at after-periconceptional period	883 (3.1)	1048 (3.7)	11122 (39.0)	2353 (8.2)
Start at second trimester	737 (2.6)	633 (2.2)	8947 (31.4)	1844 (6.4)
< 90 days	524 (1.8)	454 (1.6)	5614 (19.7)	1238 (4.3)
≥ 90 days	213 (0.7)	179 (0.6)	3333 (11.7)	606 (2.1)
Start at third trimester	146 (0.5)	415 (1.5)	2175 (7.6)	508 (1.8)
< 90 days	127 (0.4)	365 (1.3)	1810 (6.3)	435 (1.5)
≥ 90 days	19 (0.1)	50 (0.2)	365 (1.3)	73 (0.3)
Adherence to micronutrient supplementation (n (%)) [a]				
Low adherence	26525 (92.7)	28467 (99.4)	25215 (88.3)	27858 (97.3)
High adherence	2104 (7.4)	177 (0.6)	3333 (11.7)	770 (2.7)

FA, folic acid; MMN, multiple-micronutrients; WHO, World Health Organization; CNS, Chinese Nutrition Society.

[a] High adherence to FA supplementation was defined as starting from the periconceptional period with ≥ 180 days of use; otherwise, was regarded as low adherence. High adherence to iron supplementation was considered as starting from the first trimester with ≥ 90 days of use; otherwise, was regarded as low adherence. High adherence to calcium supplementation was considered as starting from the second trimester with ≥ 90 days of use; otherwise, was regarded as low adherence. High adherence to MMS was defined as starting from the first trimester with ≥ 90 days of use; otherwise, was considered as low adherence.

Table 4 Rates of high adherence to micronutrient supplementation before and during pregnancy by maternal characteristics and adjusted OR (95%CI) for factors associated to the high adherence among Chinese women in Shaanxi, 2010-2013[a]

Characteristics	n	FA		Iron		Calcium		MMN	
		High adherence (%) [b]	Adjusted OR (95%CI)	High adherence (%)	Adjusted OR (95%CI)	High adherence (%)	Adjusted OR (95%CI)	High adherence (%)	Adjusted OR (95%CI)
Sociodemographic characteristics (Model 1) [c]									
Age (years)									
<25	9458	5.3	Ref	0.4	Ref	11.2	Ref	1.7	Ref
25-34	16764	8.7	**1.30 (1.11, 1.52) ***	0.7	**1.49 (1.18, 1.88) ***	12.4	1.03 (0.94, 1.12)	3.3	**1.38 (1.12, 1.71) ***
≥35	2456	6.3	1.22 (0.98, 1.51)	0.6	1.54 (0.80, 2.99)	8.6	**0.71 (0.62, 0.81) ***	2.3	1.24 (0.84, 1.84)
Education									
Junior high school or below	17724	4.9	Ref	0.4	Ref	9.9	Ref	1.6	Ref
Senior high school	5741	7.3	**1.38 (1.18, 1.61) ***	0.9	**2.00 (1.36, 2.96) ***	13.8	**1.32 (1.22, 1.42) ***	2.8	**1.51 (1.21, 1.88) ***
College and beyond	5213	15.9	**2.59 (2.21, 3.05) ***	1.2	**1.69 (1.12, 2.54) ***	15.5	**1.45 (1.31, 1.60) ***	6.2	**2.65 (2.14, 3.28) ***
Residence									

Rural	19301	5.9	Ref	0.4	Ref	10.6	Ref	2.1	Ref
Urban	9377	10.4	**1.72 (1.08, 2.72) ***	1.1	**1.88 (1.17, 3.01) ***	14.0	1.21 (0.90, 1.62)	3.9	1.30 (0.82, 2.06)
Per capita annual household income (RMB)									
Low	9689	5.0	Ref	0.4	Ref	10.6	Ref	1.8	Ref
Medium	9402	6.4	1.07 (0.94, 1.23)	0.5	1.06 (0.74, 1.54)	11.7	1.08 (0.99, 1.19)	2.2	1.18 (0.96, 1.45)
High	9538	10.7	**1.27 (1.11, 1.45) ***	1.0	**1.56 (1.05, 2.32) ***	12.8	1.09 (0.96, 1.24)	4.0	**1.39 (1.11, 1.76) ***
Birth history and antenatal care information (Model 2) [d]									
Parity									
Primiparous	16803	9.2	Ref	0.7	Ref	12.8	Ref	3.2	Ref
Multiparous	11875	4.8	**0.70 (0.58, 0.84) ***	0.5	0.90 (0.61, 1.34)	10.1	1.02 (0.94, 1.11)	1.9	0.88 (0.72, 1.07)
pregnancy consultation									
No	21385	5.6	Ref	0.5	Ref	10.7	Ref	2.3	Ref
Yes	7293	12.6	**1.91 (1.71, 2.14) ***	1.0	**1.40 (1.21, 1.96) ***	14.7	**1.22 (1.10, 1.34) ***	3.8	**1.40 (1.17, 1.67) ***

The number of antenatal visits									
<5	8608	3.8	Ref	0.3	Ref	7.6	Ref	15.4	Ref
≥5	20070	8.9	**1.59 (1.35, 1.87) ***	0.8	**1.66 (1.18, 2.34) ***	13.4	**1.41 (1.25, 1.60) ***	26.4	**1.33 (1.09, 1.62) ***
Type of hospitals for antenatal visits									
Township hospitals	3405	5.9	Ref	0.5	Ref	9.6	Ref	1.7	Ref
County hospitals or above	25273	7.6	1.14 (0.94, 1.37)	0.6	1.26 (0.79, 2.01)	12.0	1.10 (0.94, 1.29)	2.8	1.14 (0.90, 1.46)

FA, folic acid; MMN, multiple-micronutrients; OR, odds ratio; CI, confident interval.

[a] N=28678. The number of missing values for supplementation of FA, iron, calcium and MMN were 49, 34, 130 and 50. Adjusted OR and 95% CI were derived from multivariable GEE models with random effects at county level.

[b] High adherence to FA supplementation was defined as starting from the periconceptional period with ≥ 180 days of use; high adherence to iron supplementation was considered as starting from the first trimester with ≥ 90 days of use; high adherence to calcium supplementation was considered as starting from the second trimester with ≥ 90 days of use; high adherence to MMS was defined as starting from the first trimester with ≥ 90 days of use.

[c] Model 1 adjusted for the sociodemographic characteristics including maternal age, education, residence and income, and the OR and 95% CI of these characteristics was derived from model 1.

[d] Model 2 adjusted for all variables in model 1 plus parity and antenatal care characteristics, and the OR and 95% CI of parity and antenatal care characteristics was derived from model 2.

* Refers to P <0.05.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	None
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	None
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 3-4
Outcome data	15*	Report numbers of outcome events or summary measures	Table 1-4
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 4
		(*b*) Report category boundaries when continuous variables were categorized	Table 1, Table 4
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	None
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	None
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.