PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Maternal adherence to micronutrient supplementation before and during pregnancy in Northwest China: a large-scale population-based cross-sectional survey
AUTHORS	Liu, Danmeng; Cheng, Yue; Dang, Shaonong; Wang, Duolao; Zhao, Yaling; Li, Chao; Li, Shanshan; Lei, Fangliang; Qu, Pengfei; Mi, Baibing; Zhang, Ruo; Li, Jiamei; Zeng, L; Yan, H

VERSION 1 – REVIEW

REVIEWER	Zhiwen Li Peking University, China
REVIEW RETURNED	21-Jan-2019

GENERAL COMMENTS	Periconceptional micronutrient supplementations is an effective compensation for pregnant women who could not obtain sufficient nutrition from diet, and which would contribute to healthy pregnancy outcomes. In this manuscript, the authors described the rates of and associated factors for micronutrient supplements consumption among pregnant women in Northwest China, where the micronutrition status among pregnant women is poor. The topic is interesting and meaningful. There are some points to be addressed which would improve the clarity and accuracy of the manuscript. Abstract P2, Lines 18-24: “The prevalence and factors related to rational micronutrient supplementations” should be changed to “the rate of and factors related to rational micronutrient supplementations”. The word “prevalence” should be changed to “rate” in such context, similarly hereinafter. P2, Line 24: “background of lack of dietary intake in this region1”: It is unnecessary to cite reference in the abstract. P2, Lines 36-47: The Outcomes section should be revised. For example, the sentence “Generalized estimating equation (GEE) models were performed to analyze the factors associated with rational micronutrient supplementations” was the statement of statistical method, not outcomes. P3, Lines 23-26: The keywords, such as “initiation time of use, total use days, associated-factors” were too trivial. The authors should try to extract some more appropriate keywords.

	Method P7, Lines 24-29, “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”: The expression is long-winded and unclear. Please simplify the sentences. P7, Line 55, “antenatal”: The author should capitalize the initial letter of the sentence. P9, Lines 30-37, “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”: The statement was not clear. OR and 95% CI is for associated factors of rational use of main micronutrient supplementations. Results P10, Line 34, “Prevalence of overall and rational micronutrient supplementations among participants”: “prevalence” should be “rates” (similarly hereinafter). P11, Line 26, “associated with the increased rational micronutrient supplementations”: It is better to replace “increased” with “high”. P13, Line 26-29, “What was worse, unreasonable supplementations of iron exist in our population as well”: What is the meaning of “unreasonable supplementations of iron”? It should be explained or defined in the context. Tables “Prevalence” in Tables 2, 3, 4 should be “rate”. Table 3: It is better to show the figures in the tables are “n (%)” at the head of the column or row. Table 4: The title of the table, “Prevalence and adjusted OR (95%CI) of rational use of main micronutrient supplements among Chinese women in Shaanxi, 2010-2013a”, was not exact and clear. “Prevalence” should be “Rate”. ORs (95%CIs) are for associated factors. Figures Figure 1, Line 32: “were missing” or “were missed”? Figure 2 should add heads for coordinate axes.

REVIEWER	Parul Christian Bill & Melinda Gates Foundation, Seattle, WA, USA
REVIEW RETURNED	13-Feb-2019

GENERAL COMMENTS	This is a descriptive paper on the use of micronutrient supplements during pregnancy using large-scale survey data form northern China. The use of the terminology of “rational” seems unconventional and needs defining. In reading the manuscript it appears that the authors are using this word for “according to existing recommendations or guidelines”. This may be a better descriptor. The manuscript needs editing for English in a few sections and for succinctness. “Supplementations” should be changed to singular throughout the manuscript. The following issues need to be addressed. In the introduction, there are statements on guidelines for micronutrient supplement use by the WHO. There are only some nutrients recommended by the WHO (see ANC guidelines 2016). Please provide these specifically with the reference as well as whether the policy is equivalent in China. It would be good to know what the Chinese recommendation is for both timing and doses of nutrients (at least for folic acid, iron, micronutrients and calcium) and if these are matched with what WHO currently recommends. The word “rational” again seems inappropriate if WHO’s recommends is not aligned with what is recommended in China. I am also missing any description of the levels of burden of micronutrient deficiencies, anemia, and adverse birth outcomes which would provide the context of why this specific aspect of antenatal care should be the focus of study. Given that iron-folic acid is the most common of micronutrient recommendations, was this two-nutrient formulation not included in the questionnaire? Also, how was multiple micronutrients defined? It is not clear how were the questions posed – more details are needed. There appears to be no information on specific dosages or amounts consumed or how women procured the supplement. While definitions of the preconception period etc. are useful, how questions were posed to be able to determine use during different times in pregnancy and length of time needs to be described. Aristogenesis is not a commonly used word – suggest replacing it with something more appropriate. Figure 1 is not critical and can just be described briefly in the text, in interest of space. Table 1 may be better to show first, and Table 3 can be consolidated with 1. It would be helpful to have a clear definition of what you are calling “rational” and provide % here. Figure 2 is somewhat hard to understand. The difference between the left and right panel and legend are not clear. Are the 5 categories mutually exclusive – the legend would indicate not and yet the figure describes 100%. Other than folic acid, which supplementation is recommended preconceptionally? The yellow and grey areas should be combined for iron and MNs as there is no current recommendation for pre/periconceptional supplementation. Also, even for Ca, the WHO recommendation is to start at 20 weeks of gestation. It appears that the results shown in Table 4 come from a multivariable model. If so, this should be reflected in the description in the Results. Here the definition of “rational” appears clearly in the footnote and is useful. Perhaps a table of existing recommendations

	by nutrient would help and can be incorporated in the earlier tables (1 and 3). In addition to the above, the entire discussion on iron recommendations and benefits is quite confusing. There is no preconception/periconception iron supplementation recommended and the evidence for benefit is only demonstrated for pregnancy. Please re-work this entire section referencing the appropriate guidelines and evidence from systematic reviews. Also, include the dosage recommended in China. The WHO recommendation is for 30-60 mg of iron daily in pregnancy. For calcium, again the WHO does not recommend preconception and yet this seems to be the criteria applied. The risk factors analysis provides interesting findings, but the background on whether these supplements are commonly recommended by physicians, available during visits at health care facilities, as well as how their use is promoted would be of interest to better understand the existing context. The shortcomings of the analysis are well acknowledged including reporting bias especially on the total days of use and lack of information on dosage.

VERSION 1 – AUTHOR RESPONSE

To reviewer 1:
Periconceptional micronutrient supplementations is an effective compensation for pregnant women who could not obtain sufficient nutrition from diet, and which would contribute to healthy pregnancy outcomes. In this manuscript, the authors described the rates of and associated factors for micronutrient supplements consumption among pregnant women in Northwest China, where the micronutrition status among pregnant women is poor. The topic is interesting and meaningful. There are some points to be addressed which would improve the clarity and accuracy of the manuscript.

Response: Thank you for your comments and suggestions, which are greatly appreciated. We would like to reply the following questions:

Abstract
1. P2, Lines 18-24: “The prevalence and factors related to rational micronutrient supplementations” should be changed to “the rate of and factors related to rational micronutrient supplementations”. The word “prevalence” should be changed to “rate” in such context, similarly hereinafter.

Response: Thank you for your suggestion, and we replaced the word “prevalence” to “rates” in the context as you recommended.

2. P2, Line 24: “background of lack of dietary intake in this region1”: It is unnecessary to cite reference in the abstract.

Response: Thank you for your suggestion, and we deleted this reference in the abstract.

3. P2, Lines 36-47: The Outcomes section should be revised. For example, the sentence “Generalized

estimating equation (GEE) models were performed to analyze the factors associated with rational micronutrient supplementations" was the statement of statistical method, not outcomes.

Response: Thank you for your advice. We revised this part as "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."

4. P3, Lines 23-26: The keywords, such as "initiation time of use, total use days, associated-factors" were too trivial. The authors should try to extract some more appropriate keywords.

Response: Thank you for your advice. We changed the keywords as "Micronutrient supplementation; Pregnancy; Adherence; Associated-factors"

Method

1. P7, Lines 24-29, "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": The expression is long-winded and unclear. Please simplify the sentences.

Response: Thank you for your correction. We reorganized the sentences as "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)."

2. P7, Line 55, "antenatal": The author should capitalize the initial letter of the sentence.
Response: Thank you for finding this problem. We corrected the word to "Antenatal".

3. P9, Lines 30-37, "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": The statement was not clear. OR and 95% CI is for associated factors of rational use of main micronutrient supplementations.

Response: Thank you for pointing out this problem. We revised the sentence as "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".

Results

1. P10, Line 34, “Prevalence of overall and rational micronutrient supplementations among participants”: “prevalence” should be “rates” (similarly hereinafter).

Response: Thank you for your suggestion, and we replaced the word “prevalence” to “rates” in the context as you recommended.

2. P11, Line 26, “associated with the increased rational micronutrient supplementations”: It is better to replace “increased” with “high”.

Response: Thank you for this correction. We replaced the “rational micronutrient supplementations” to “adhere to the micronutrient supplementations”, and thus this sentence was revised as “associated with the adhered micronutrient supplementation”.

3. P13, Line 26-29, “What was worse, unreasonable supplementations of iron exist in our population as well”: What is the meaning of “unreasonable supplementations of iron”? It should be explained or defined in the context.

Response: Thank you for your concern. This sentence we revised to “the proportion of women who had compliant iron supplementation was very low in our population”.

Tables

1.“Prevalence” in Tables 2, 3, 4 should be “rate”.

Response: Thank you for your suggestion, and we replaced the word “prevalence” to “rates” in the context as you recommended.

2. Table 3: It is better to show the figures in the tables are “n (%)” at the head of the column or row.

Response: Thank you for this suggestion. Combining the advice of the two reviewers, we reorganized the Table3 and Figure 2 in one table, which is presented as Table 3. We showed “n (%)” at the head of each sub-title.

3. Table 4: The title of the table, “Prevalence and adjusted OR (95%CI) of rational use of main micronutrient supplements among Chinese women in Shaanxi, 2010-2013a”, was not exact and clear. “Prevalence” should be “Rate”. ORs (95%CIs) are for associated factors.

Response: Thank you for this suggestion. We modified the title as “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”.

Figures

1. Figure 1, Line 32: “were missing” or “were missed”?

Response: Thank you for your correction. In interest of space, we deleted Figure 1 and described the content of it in the section of Methods as “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".

2. Figure 2 should add heads for coordinate axes.
Response: Thank you for your suggestion. The content of Figure 2 was integrated into Table 3.

To reviewer 2:
1. This is a descriptive paper on the use of micronutrient supplements during pregnancy using large-scale survey data from northern China. The use of the terminology of "rational" seems unconventional and needs defining. In reading the manuscript it appears that the authors are using this word for "according to existing recommendations or guidelines". This may be a better descriptor. The manuscript needs editing for English in a few sections and for succinctness. "Supplementations" should be changed to singular throughout the manuscript.

Response: Thank you for your suggestion and correction. We replaced "rational" to "adhere to / high adherence to / adhered use", which are commonly used in published literature, and "Supplementations" in the manuscript was changed to singular. We also made revisions in some sections for succinctness.

The following issues need to be addressed.
2. In the introduction, there are statements on guidelines for micronutrient supplement use by the WHO. There are only some nutrients recommended by the WHO (see ANC guidelines 2016). Please provide these specifically with the reference as well as whether the policy is equivalent in China. It would be good to know what the Chinese recommendation is for both timing and doses of nutrients (at least for folic acid, iron, micronutrients and calcium) and if these are matched with what WHO currently recommends. The word "rational" again seems inappropriate if WHO's recommends is not aligned with what is recommended in China. I am also missing any description of the levels of burden of micronutrient deficiencies, anemia, and adverse birth outcomes which would provide the context of why this specific aspect of antenatal care should be the focus of study.

Response: Thank you for this comprehensive opinion. In the introduction part, we added more details about the WHO guidelines for the supplementation of folic acid, iron and calcium, and also provided specific information about the Chinese recommendation. Daily 400 μg FA supplement intake start at 3-month before pregnancy to the end of pregnancy is the only routine antenatal micronutrient supplementation recommended by the Chinese Nutrition Society (CNS), which is similar to the WHO recommendation for FA supplementation, and thus we examined the rate of women adhere to the FA supplementation using Chinese recommendation. There are no more guidelines for routine supplementation of other micronutrients in China, and thus we evaluated the adherence to supplementation of iron and calcium according to the WHO guidelines. WHO did not universally recommend multiple-micronutrient supplementation (MMS) for pregnant women, but 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. The definition of the adherence to the supplementation of FA, iron, calcium, and MMS is shown in the section of methods as "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".
Also, we described the situations of commonly micronutrient deficiencies, high prevalence of anemia and adverse birth outcomes in the Shaanxi of Northwestern China, and addressed that micronutrient supplementation may be a relatively inexpensive and low-risk method to improve maternal and fetal health in this region, but representative data from large-scale study on the maternal micronutrient supplementation in this region is not available, and that's why we focused on this part of antenatal care in the present study, we expect to provide evidence for future evaluation of health policy effectiveness and development of health education strategies.

3. 1) Given that iron-folic acid is the most common of micronutrient recommendations, was this two-nutrient formulation not included in the questionnaire? 2) Also, how was multiple micronutrients defined? It is not clear how were the questions posed – more details are needed. 3) There appears to be no information on specific dosages or amounts consumed or how women procured the supplement. 4) While definitions of the preconception period etc. are useful, how questions were posed to be able to determine use during different times in pregnancy and length of time needs to be described.

Response: Thank you for pointing out the questions. We gave more information about question 1) and 2) in methods section under the sub-heading of "Micronutrient supplementation" as "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". Question 3) was explained in the section of methods and the limitation part in the last paragraph of discussion. We applied total days of use instead of the total amounts because most of our investigated supplements were taken one tablet per day. But we did not provide the dosage as stated in the limitation "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". Further, we did not design the question about the access that women procured the supplements, and thus this information was not shown in the results.

4. Aristogenesis is not a commonly used word – suggest replacing it with something more appropriate.
Response: Thank you for this suggestion. We replaced “Aristogenesis consultation” to “pregnancy consultation”.

5. Figure 1 is not critical and can just be described briefly in the text, in interest of space. Table 1 may be better to show first, and Table 3 can be consolidated with 1. It would be helpful to have a clear definition of what you are calling “rational” and provide % here.
6. Figure 2 is somewhat hard to understand. The difference between the left and right panel and legend are not clear. Are the 5 categories mutually exclusive – the legend would indicate not and yet the figure describes 100%. Other than folic acid, which supplementation is recommended preconceptionally? The yellow and grey areas should be combined for iron and MNs as there is no current recommendation for pre/periconceptional supplementation. Also, even for Ca, the WHO recommendation is to start at 20 weeks of gestation.

Response: This is the response for Q5-Q6. Thank you for your suggestion and we appreciate your correction. As recommended, we deleted Figure 1 and described the content of it in the “data source and participants” part of the methods section. We kept Table 1 for presenting the overall rates of micronutrient supplementation in our population according to the maternal characteristics. Further, we deleted Figure 2 and consolidated Figure 2 with Table 3, and added the content of recommendations of WHO and CNS in the Table 3. We corrected the mistakes in the classification of adhered supplementation of iron, calcium, and MMN, and re-estimated the rates of the adherence to each micronutrient supplementation. The definition of the adherence was displayed in the footnote of Table 3 as showing below:

Table 3 Maternal micronutrient supplementation recommendations from WHO and CNS; rate 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

7. 1) It appears that the results shown in Table 4 come from a multivariable model. If so, this should be reflected in the description in the Results. Here the definition of “rational” appears clearly in the footnote and is useful. 2) Perhaps a table of existing recommendations by nutrient would help and can be incorporated in the earlier tables (1 and 3).

Response: 1) Table 4 shows the results of multivariable two-level analysis by GEE models. We described this method in the statistical analysis part in the methods section, and thus just mentioned it in the results section as “Multivariable two-level analysis was used to identify factors related to the adherence to micronutrient supplementation”.
2) We added the content of recommendations of WHO and CNS in the Table 3 as shown above.

8. In addition to the above, the entire discussion on iron recommendations and benefits is quite confusing. There is no preconception/periconception iron supplementation recommended and the evidence for benefit is only demonstrated for pregnancy. Please re-work this entire section referencing the appropriate guidelines and evidence from systematic reviews. Also, include the dosage recommended in China. The WHO recommendation is for 30-60 mg of iron daily in pregnancy. For calcium, again the WHO does not recommend preconception and yet this seems to be the criteria applied.

Response: Thank you for your correction. We re-worked the analysis of rates of and factors associated with the adherence of supplementation of iron, calcium, and MMN according to WHO recommendation, and the results did not change much (the results were shown in Table 3 and 4). Also, we re-organized the discussion of these three types of micronutrients.

9. The risk factors analysis provides interesting findings, but the background on whether these supplements are commonly recommended by physicians, available during visits at health care facilities, as well as how their use is promoted would be of interest to better understand the existing context.
Response: We added more information to explain the result that in our population, more times of

antenatal visits were associated with higher adherence of micronutrient supplementation. As stated in the discussion part, “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”.

10. The shortcomings of the analysis are well acknowledged including reporting bias especially on the total days of use and lack of information on dosage.

Response: Thank you for this advice. We discussed these limitations of the study in the last paragraph of discussion section as “This study was retrospective and all the information of micronutrient supplementation was self-reported from participants, and therefore the recall bias was ineluctable. In addition, 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”.

VERSION 2 – REVIEW

REVIEWER	Zhiwen Li Peking University
REVIEW RETURNED	08-Apr-2019

GENERAL COMMENTS	Manuscript ID bmjopen-2018-028843.R1 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 Comments: The revised version is much clear than the former. However, there are still some points to be addressed which would improve the clarity and accuracy of the manuscript.

	Title and main text The authors should state clearly the topic of this manuscript was periconcettional maternal (pregnant women's) micronutrient supplementation. The statement used now in the title and main text, "maternal micronutrient supplementation", was imprecise. Abstract P2, Lines 31-37: "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". This sentence was not clear and should be revised. P2, Lines 39-45: The Main Outcome Measures section should be revised. The sentence "Factors associated with the adherence to micronutrient supplementation are analyzed using Generalized Estimating Equation (GEE) models." was the statement of the statistical method, not outcome or outcome measure. The authors should briefly state how to measure the main outcomes. P2, Line 47: "In total, 83.9% of women took micronutrient supplements before or during pregnancy." It is better to add "any" before "micronutrient supplements". P2: Abbreviations such as FA and MMN should be defined (presented full name) at first mention. P3, Line 5: The word "usually" was inappropriate and needless. P5, Line 13: "the National Health Commission (NHC)" might be revised to "the Chinese Health Ministry (now the Chinese National Health Commission (NHC))", that is, using the name when the policy was issued. Result P11 Lines 41-50: "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." Please revise the sentence. P11, Line 57: "In total, 83.9% of women took at least one micronutrient supplement during their last pregnancy." One kind or one tablet？It should be expressed clearly. P12, Lines 49-55: "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." Please revise the sentence. P12 Line 41: It is better to present the ORs of main results in the Factors associated with the Adherence to Micronutrient section. Zhiwen Li 2019-3-31

VERSION 2 – AUTHOR RESPONSE

To reviewer 1:

Comments:

The revised version is much clear than the former. However, there are still some points to be addressed which would improve the clarity and accuracy of the manuscript.

Title and main text

1. The authors should state clearly the topic of this manuscript was periconceptional maternal (pregnant women's) micronutrient supplementation. The statement used now in the title and main text, "maternal micronutrient supplementation", was imprecise.

Response: Thank you so much for this correction. The periconceptional period in this study referred to the period from 3 months before pregnancy to the end of the first trimester, but the time range of interest in this study was from 3 months before pregnancy to the time at delivery. Thus, we added the time range to "maternal micronutrient supplementation" as "maternal micronutrient supplementation before and during pregnancy" to improve the accuracy. The following are the revisions of this problem in the title and main text:

Title:

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

Main text:

1)Abstract

Conclusion section: "Maternal micronutrient supplementation before and during pregnancy in Northwest China was way below standards recommended by the Chinese guidelines or WHO".

2)Strengths and limitations of this study

The first point: "This is the first large-scale and representative study that vividly described maternal adherence to micronutrient supplementation before and during pregnancy in Northwest China".

3) Introduction

Paragraph 3, line 5-6: "Many factors were reported in relation to maternal adherence to micronutrient supplementation before and during pregnancy";

Paragraph 3, line 9-11: “Few of the studies focused on maternal adherence to micronutrient supplementation before and during pregnancy in China”;

Paragraph 4, line 10-11: “However, a representative data from a large-scale study on the maternal micronutrient supplementation before and during pregnancy in this region is not available”;

Paragraph 4, line 11-13: “this article aims to investigate the condition of maternal micronutrient supplementation before and during pregnancy in Shaanxi”.

4)Methods

Micronutrient supplementation part, paragraph 3, line 1-2: “Adherence to micronutrient supplementation before and during pregnancy was determined by…”;

Statistical analysis part, paragraph 2, line 4-5: “…for factors associated with maternal adherence to micronutrient supplementation before and during pregnancy”.

5)Results

All subtitles were added the time range “before and during pregnancy” after “micronutrient supplementation”.

Paragraph 1, line 2-3: “…between users and non-users of micronutrient supplements before and during pregnancy”;

Paragraph 3, line 3-4: “…were associated with high adherence to micronutrient supplementation before and during pregnancy”.

6)Discussion

Paragraph 1, line 1-2: “In this large-scale cross-sectional study, we observed that micronutrient supplements were not used as commonly as expected before and during pregnancy”;

Paragraph 1, line 4-6: “Totally, the prevalence of maternal micronutrient supplementation before and during pregnancy in Shaanxi from 2010 to 2013 was 83.9%”;

Paragraph 4, line 6-8: “A gap still exists between calcium supplementation among pregnant women in Northwest China and the WHO recommendation”;

Paragraph 6, line 1-2: “When examining the factors associated with maternal adherence to micronutrient supplementation before and during pregnancy”;

Paragraph 7, line 1-3: “this is the first large-scale and representative study that investigated maternal micronutrient supplementation before and during pregnancy in Northwest China”.

7)Conclusion

Paragraph 6, line 1: “maternal micronutrient supplementation before and during pregnancy in Shaanxi…”.

Abstract

2. P2, Lines 31-37: “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”. This sentence was not clear and should be revised.

Response: Thank you so much for this suggestion. We revised this sentence to “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”.

3. P2, Lines 39-45: The Main Outcome Measures section should be revised. The sentence “Factors associated with the adherence to micronutrient supplementation are analyzed using Generalized Estimating Equation (GEE) models.” was the statement of the statistical method, not outcome or outcome measure. The authors should briefly state how to measure the main outcomes.

Response: Thank you so much for this correction. We revised this part to “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)”.

4. P2, Line 47: “In total, 83.9% of women took micronutrient supplements before or during pregnancy.” It is better to add “any” before “micronutrient supplements”.

Response: Thank you so much for this suggestion. We revised this sentence to “In total, 83.9% of women took at least one kind of micronutrient supplement before or during pregnancy”.

5. P2: Abbreviations such as FA and MMN should be defined (presented full name) at first mention.

Response: Thank you so much for this correction. We presented the full name of FA and MMN in the abstract when the first mention. In the Main Outcome Measures section of the abstract: “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)”.

6. P3, Line 5: The word “usually” was inappropriate and needless.

Response: Thank you so much for this correction. We deleted this word.

7. P5, Line 13: “the National Health Commission (NHC)” might be revised to “the Chinese Health Ministry (now the Chinese National Health Commission (NHC))”, that is, using the name when the policy was issued.

Response: Thank you so much for this correction. We revised it as you recommended.

Result

8. P11 Lines 41-50: “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.” Please revise the sentence.

Response: Thank you so much for this suggestion. We revised the sentence to “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)”.

9. P11, Line 57: “In total, 83.9% of women took at least one micronutrient supplement during their last pregnancy.” One kind or one tablet？It should be expressed clearly.

Response: Thank you so much for this correction. We revised the sentence to “In total, 83.9% of women took at least one kind of micronutrient supplement before or during their last pregnancy”.

10. P12, Lines 49-55: “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.” Please revise the sentence.

Response: Thank you so much for this suggestion. We revised the sentence to “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 before and during pregnancy”.

11. P12 Line 41: It is better to present the ORs of main results in the Factors associated with the Adherence to Micronutrient section.

Response: Thank you so much for this suggestion. We added the OR (95% CI) of main results in this section as “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)".