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Original Article

Association between Iron Supplementation, Dietary Iron Intake and Risk of Moderate Preterm Birth: A Birth Cohort Study in China

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Abstract

Background: To evaluate the independent and collective effects of maternal iron supplementation and dietary iron intake upon the risk of moderate preterm birth and its subtypes.

Methods: In this birth cohort study, 1019 pregnant women with moderate preterm birth and 9160 women with term birth were recruited at Gansu Provincial Maternity and Child Care Hospital from 2010-2012 in China. Unconditional logistic regression models were utilized to evaluate the association between maternal iron supplementation, dietary iron intake, and the risk of moderate preterm birth and its subtypes.

Results: Compared with non-users, iron supplement users exerted a protective effect upon the overall (OR=0.54, 95%CI=0.40-0.72) and spontaneous moderate preterm birth (OR=0.39, 95%CI=0.33-0.83). Compared with the 25th quartiles of dietary iron intake, either before or during pregnancy, it exerted a significantly protective effect upon those who had the highest quartiles of dietary iron intake (OR=0.87, 95%CI=0.82-0.95 for the highest quartiles of dietary iron intake before pregnancy OR=0.85, 95%CI=0.79-0.91). Positive association was observed between the additive scale and multiplicative scale for preterm birth, spontaneous preterm rather than medically indicated preterm.

Conclusion: Iron supplements (60 mg/day) and high-iron intake (>25.86 mg/day before pregnancy, >30.46 mg/day during pregnancy) reduced the risk of moderate preterm birth. Positive correlation is found between the additive scale and multiplicative scale for preterm birth, spontaneous preterm birth.

Keywords: Iron supplementation; Dietary iron intake; Moderate preterm birth

Introduction

In 2010, the statistics demonstrated that the global quantity of preterm birth was estimated up to 15 million (1), and there were the 3.1 million of neonatal death due to preterm birth-related complications (2).

Iron deficiency is the most common nutrition deficiency disorder in pregnant women (3), which estimated from 25% to 80% in preterm birth (4) and caused approximately half of the anemia during pregnancy(5). Scholl et al (6) found that the odds of a preterm delivery increased fivefold for iron-deficiency anemia and doubled for other types of anemia, lower iron status yield higher rate of preterm delivery (7). According to the WHO recommendations, daily iron supplementation with 30-60 mg during pregnancy contributed to prevent the incidence of maternal anemia and preterm birth (8).

However, previous studies yielded conflicting results on the doses and time of maternal iron supplementation and the risk of preterm birth. Supplement of iron intake for 28-36 weeks exerted independent positive effect upon preterm birth (10), whereas the highest supplement of iron intake (37.8 to 41.5 mg/d) yielded a lower birth weight and shorter duration of gestation in South India pregnancy women (10). Regular iron supplement with 60 mg had no significant difference in the incidence of preterm birth (10, 11). Ethnicity distribution probably has different iron status before pregnancy and different dietary habits may contribute to the inconsistency among these results.

Rarely studies about the potential collective effects of iron supplementation and iron intake were reported in previous investigations. Consequently, we conducted a birth cohort to investigate the independent and collective effects of maternal iron intake and iron supplement upon the risk of moderate preterm birth in northwestern China.

Materials and Methods

Study population

A birth cohort study was carried out from 2010 to 2012 at Gansu Maternity and Child Care Hospital, which was the largest hospital in Lanzhou, China. The study population has been described in our previous studies (13-15).

A standardized and structured questionnaire was distributed to participation for collecting demographic factors, reproductive and medical history, smoking and alcohol consumption, occupational and residential history, physical activity and diet. Data on pregnancy-related complications and birth outcomes were extracted from medical records. A total of 14359 eligible women were approached for participation, and 10542 (73.4%) women were interviewed in-person, with 10179 women having singleton live birth.

Moderate Preterm birth

Moderate preterm is defined as babies born alive during 32 to 36 weeks of pregnancy according to the WHO proposals (16), which was further classified as medically indicated preterm birth and spontaneous preterm birth (17). A medically indicated preterm birth occurs when a placental, uterine, fetal, or maternal condition exists prompting the medical team to proceed with delivery after the risks and benefits of continuing pregnancy versus early delivery are weighed.

Iron supplementation and dietary iron intake

Information of iron supplementation was collected by preconception (12 months before pregnancy), the first trimester (1-13 weeks), the second trimester (14-27 weeks) and the third trimester (>27 weeks) respectively. Iron supplement users were defined as those who took iron supplements during preconception and /or pregnancy (the most pregnant women using iron sulfate as oral iron supplementation, and iron content of each element was 60 mg). Non-users were defined as those who never took iron supplements alone and /or iron-containing multivitamins during preconception and pregnancy. Dietary data was collected via a semi-quantitative food frequency questionnaire. Daily dietary iron intake was estimated from the frequency of consumption and portion size of food items using Chinese Standard Tables of Food Consumption (18) for each period.

Statistical analysis

Data comparisons in the selected characteristics between women with preterm and term birth were evaluated using Chi-square test or Fisher's exact test if necessary. Unconditional logistic regression was utilized to determine the odds ratios (OR) and 95% confidence intervals (CI) for the association among iron supplement, dietary iron intake and the risk of premature birth (PB). Confounding factors including maternal age, maternal employment during pregnancy, monthly household income, maternal education level, parity, twin status, newborn gender, and family history of hypertension were adjusted in the unconditional logistic regression models. Iron supplementation was classified into two levels by the midpoint of using duration, and dietary iron intake was categorized to quartiles, and dose-response relationship (*P* for trend) was calculated based on those categorical levels. The collective association among iron supplements, dietary iron intake and preterm birth were estimated by using the relative excess risk due to interaction (RERI) with 95% CIs. The RERI was calculated using an additive model. The additive model, assessed their influence on disease risk, was adopted to test the biological interaction relating risk factors (19, 20). All statistical tests were two-sided. Analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC, USA).

Ethical approval

The project was approved by the Human Investigation Committees at the Gansu Provincial Maternity and Child Care Hospital as well as Yale University. All participants signed the written informed consents for participation and the use of data in research.

Results

A total of 10179 women were eligible for the final analysis, and of whom 1108 were administered with iron supplementation and 1019 were diagnosed with moderate preterm birth. As illustrated in Table 1, compared with iron supplementation non-users, iron supplementation users were more likely to have a higher education level, be employed during pregnancy, pre-pregnancy BMI less than 24, gain more than 15 kg during pregnancy, be primipara and be preterm. Women who had higher dietary iron intake comparatively were more likely to be older than 25 yr of age, have higher than college education, gain > 3000 RMB monthly per capita, be employed during pregnancy, gain more than 15 kg during pregnancy, have abortion history, be primipara and not preterm.

Table 1: Distributions of selected characteristics for iron supplementation and dietary iron intake

Characteristics	***Total sample (%) n=10179***	***Iron supplementation***		***P value****	***Dietary iron intake (mg/day)***				***P value****
		Users (%) n=1108	Non-users n=9071		Q1 <18.39 n=2545	Q2 18.39-23.04 n=2545	Q3 23.04-29.22 n=2545	Q4 ≥29.22 n=2544	
Maternal age(yr)									
< 25	1634	152(9.30)	1482(90.70)	0.080	557(34.09)	414(25.34)	341(20.87)	322(19.71)	<0.001
25-29	4855	545(11.23)	4310(88.77)		1077(22.18)	1237(25.48)	1298(26.74)	1243(25.60)	
≥30	3690	411(11.14)	3279(88.86)		911(24.69)	894(24.23)	906(24.55)	979(26.53)	
Highest education level									
< College	3998	383(9.58)	3615(90.42)	<0.001	1255(31.39)	975(24.39)	902(22.56)	866(21.66)	<0.001
≥ College	5996	711(11.86)	5285(88.14)		1189(19.83)	1545(25.77)	1615(26.93)	1647(27.47)	
Missing	185	14(7.57)	171(92.43)		101(54.59)	25(13.51)	28(15.14)	31(16.76)	
Monthly income per capita(RMB)									

< 3000	5137	563(10.96)	4574(89.04)	0.316	1393(27.12)	1336(26.01)	1281(24.94)	1127(21.94)	<0.001
≥ 3000	4069	473(11.62)	3596(88.38)		885(21.75)	1033(25.39)	1078(26.49)	1073(26.37)	
Missing	973	72(7.40)	901(92.60)		267(27.44)	176(18.09)	186(19.12)	344(35.35)	
Maternal employ									
No	3340	349(10.45)	2991(89.55)	<0.001	996(29.82)	848(25.39)	762(22.81)	734(21.98)	<0.001
Yes	6839	759(11.10)	6080(88.90)		1549(22.65)	1697(24.81)	1783(26.07)	1810(26.47)	
Smoking (passive and active)									
No	8188	891(10.88)	7297(89.12)	0.982	1994(24.35)	2034(24.84)	2024(24.72)	2136(26.09)	<0.001
Yes	1991	217(10.90)	1774(89.10)		551(27.67)	511(25.67)	521(26.17)	408(20.49)	
Drink during pregnancy									
No	10159	1107(10.90)	9052(89.10)	0.717#	2540(25.00)	2542(25.02)	2540(25.00)	2537(24.97)	0.658
Yes	20	1(5.00)	19(95.00)		5(25.00)	3(15.00)	5(25.00)	7(35.00)	
Pre-pregnancy BMI (kg/m²)									
< 18.5	2074	248(11.96)	1826(88.04)	0.003	488(23.53)	516(24.88)	516(24.88)	554(26.71)	0.697
18.5-23.9	6676	757(11.34)	5919(88.66)		1597(23.92)	1716(25.07)	1710(25.61)	1653(24.76)	
≥24.0	1080	88(8.15)	992(91.85)		263(24.35)	264(24.44)	279(25.83)	274(25.37)	
Missing	349	15(4.30)	334(95.70)		197(56.45)	49(14.04)	40(11.46)	63(18.05)	
Weight gain during pregnancy (kg)									
< 15	3112	306(9.83)	2806(90.17)	0.013	907(29.15)	811(26.06)	704(22.62)	690(22.17)	<0.001
15-18.5	3107	372(11.97)	2735(88.03)		689(22.18)	800(25.75)	826(26.59)	792(25.49)	
> 18.5	3533	414(11.72)	3119(88.28)		720(20.38)	863(24.43)	962(27.23)	988(27.96)	
Missing	427	16(3.75)	411(96.25)		229(53.63)	71(16.63)	53(12.41)	74(17.33)	
Gestational diabetes									
No	10076	1102(10.94)	8974(89.06)	0.098	2521(25.02)	2515(24.96)	2524(25.05)	2516(24.97)	0.590
Yes	103	6(5.83)	97(94.17)		24(23.30)	30(29.13)	21(20.39)	28(27.18)	
Abortion history									
No	8851	966(10.91)	7885(89.09)	0.809	2257(25.50)	2203(24.89)	2177(24.60)	2214(25.01)	0.009
Yes	1328	142(10.69)	1186(89.31)		288(21.69)	342(25.75)	368(27.71)	330(24.85)	
Parity									
Primipara	7349	859(11.69)	6490(88.31)	<0.001	1706(23.21)	1924(26.18)	1928(26.23)	1791(24.37)	<0.001

Multipara	2830	249(8.80)	2581(91.20)		839(29.65)	621(21.94)	617(21.80)	753(26.61)	
Preeclampsia									
No	9833	1089(11.07)	8744(88.93)	0.001	2429(24.70)	2473(25.15)	2465(25.07)	2466(25.08)	0.003
Yes	346	19(5.49)	327(94.51)		116(33.53)	72(20.81)	80(23.12)	78(22.54)	
History of preterm									
No	10105	1101(10.90)	9004(89.10)	0.693	2524(24.98)	2527(25.01)	2533(25.07)	2521(24.95)	0.289
Yes	74	7(9.46)	67(90.54)		21(28.38)	18(24.32)	12(16.22)	23(31.08)	
Caesarean section									
No	6206	706(11.38)	5500(88.62)	0.105	1542(24.85)	1594(25.68)	1557(25.09)	1513(24.38)	0.262
Yes	3860	399(10.34)	3461(89.66)		976(25.28)	932(24.15)	962(24.92)	990(25.65)	
Missing	113	3(2.65)	110(97.35)		27(23.89)	19(16.81)	26(23.01)	41(36.28)	
Vitamin supplement									
No	7955	817(10.27)	7138(89.73)	<0.001	2058(25.87)	1942(24.41)	1904(23.93)	2051(25.78)	<0.001
Yes	2224	291(13.08)	1933(86.92)		487(21.90)	603(27.11)	641(28.82)	493(22.17)	
Gender									
Male	5358	596(11.12)	4762(88.88)	0.467	1335(24.92)	1336(24.93)	1335 (24.92)	1352(25.23)	0.950
Female	4788	511(10.67)	4277(89.33)		1200(25.06)	1200(25.06)	1204(25.15)	1184(24.73)	
Missing	33	1(3.03)	32(96.97)		10(30.30)	9(27.27)	6(18.18)	8(24.24)	
Moderate preterm birth									
No	9160	1051(11.47)	8109(88.53)	<0.001	2183(23.83)	2301(25.12)	2316(25.28)	2360(25.76)	<0.001
Yes	1019	57(5.59)	962(94.41)		362(35.53)	244(23.95)	229(22.47)	184(18.06)	

*Estimated by Pearson's Chi-square test and without accounting for missing data
Fisher exact test

The independent effect of iron supplement and dietary iron intake was shown in Table 2. Compared with non-users, iron supplement users exerted a protective effect upon the overall moderate preterm birth (OR=0.54, 95%CI=0.40-0.72) with a significant dose dependence response (P<0.01). After stratified by the time periods, a significant association was observed for users of iron supplementation during the third trimester (OR=0.48, 95%CI=0.34-0.68). Compared with the lowest quartiles (25^{th}) of dietary iron intake, either before or during pregnancy, protective effect was observed for those who had the highest quartiles of dietary iron intake (OR=0.87, 95%CI=0.82-0.95 for the highest quartiles of dietary iron intake before pregnancy OR=0.85, 95%CI=0.79-0.91) for the duration of use (P=0.025).

Table 2: Independent effect of iron supplement and dietary iron intake on the risk of moderate preterm births

Iron intake	*Term Births (n=9160)*	*Moderate Preterm Birth(n=1019)*	
		Cases	OR[a] (*95% CI*)
Iron supplement			
Nonusers	8109	962	1.00
Users	1051	57	0.54(0.40～0.72)
< 4 weeks	504	27	0.49(0.33～0.74)
≥ 4 weeks	547	30	0.76(0.63～0.92)
P for trend			<0.001
Before pregnancy user	28	2	0.95(0.22～4.17)
During the first trimester user	39	2	0.34(0.07～1.68)
During the second trimester user	332	23	0.75(0.48～1.17)
< 4 weeks	138	7	0.55(0.25～1.19)
≥ 4 weeks	194	16	0.90(0.53～1.54)
P for trend			0.261
During the third trimester user	718	36	0.48(0.34～0.68)
< 4 weeks	357	19	0.46(0.28～0.76)
≥ 4 weeks	361	17	0.49(0.30～0.82)
P for trend			<0.001
Dietary iron intake(mg/day)			
Before pregnancy			
Q1 <15.68	2229	313	1.00
Q2 15.68-19.94	2284	267	0.98(0.81～1.20)
Q3 19.94-25.86	2299	244	0.96(0.87～1.07)
Q4 ≥25.86	2348	195	0.87(0.82～0.95)
P for trend			<0.001
During pregnancy			
Q1 <18.97	2183	362	1.00
Q2 18.97-23.95	2301	244	0.82(0.67～1.00)
Q3 23.95-30.45	2316	229	0.90(0.82～1.00)
Q4 ≥30.46	2360	184	0.85(0.79～0.91)
P for trend			<0.001

[a] Adjusted for maternal age, employment, monthly income per capita, education level, smoking, pre-pregnancy BMI, weight gain during pregnancy, parity, preeclampsia, history of preterm, maternal diabetes, caesarean section, vitamin supplement, total energy intake, dietary iron intake or iron supplement

The data separately for medically indicated and spontaneous preterm births were analyzed in Table 3. Compared with non-users, a significant association was observed between iron supplementation and spontaneous preterm rather than for medically preterm births. Compared with the lowest quartiles of dietary iron intake, the highest quartiles of dietary iron intake exerted significant protective effect upon the medically indicated overall preterm and spontaneous preterm birth.

The collective effects of iron supplementation and dietary iron intake by subtype of preterm were evaluated (Table 4). Compared with iron supplementation non-users with adequate dietary iron intake (<23.04 mg), women using iron supplementation with adequate dietary iron intake (<23.04 mg) had a lower risk of preterm birth (OR=0.51, 95%CI=0.35-0.76). Due to interaction between iron supplement and dietary iron intake, the relative protection on the incidence of preterm birth was 0.29 (OR for RERI=0.29, 95%CI=0.07-0.51), and an identical association was observed for spontaneous preterm births (OR for RERI=0.30, 95%CI=0.04-0.57)

Table 3: Associations between iron supplementation, iron intake and risk of moderate preterm birth and subtypes

Iron intake	***Term Births (n=9160)***	***Medically indicated preterm(n=338)***		***Spontaneous preterm(n=681)***	
		Cases	*OR*[a] *(95% CI)*	Cases	*OR*[a] *(95% CI)*
Iron supplement					
Nonusers	8109	318	1.00	644	1.00
Users	1051	20	0.72(0.43～1.18)	37	0.48(0.34～0.68)
< 4 weeks	504	10	0.67(0.33～1.35)	17	0.43(0.26～0.71)
≥ 4 weeks	547	10	0.75(0.38～1.48)	20	0.52(0.33～0.83)
P for trend			0.179		<0.001
During the second trimester user	332	6	0.91(0.39～2.11)	17	0.76(0.46～1.26)
During the third trimester user	718	15	0.72(0.40～1.27)	21	0.39(0.24～0.61)
Dietary iron intake(mg/day)					
Before pregnancy					
Q1 <15.68	2229	102	1.00	211	1.00
Q2 15.68-19.94	2284	95	1.10(0.77～1.58)	172	0.91(0.72～1.15)
Q3 19.94-25.86	2299	81	0.98(0.81～1.18)	163	0.96(0.85～1.08)
Q4 ≥25.86	2348	60	0.85(0.74～0.97)	135	0.90(0.83～0.98)
P for trend			0.003		0.003
During pregnancy					
Q1 <18.97	2183	130	1.00	232	1.00
Q2 18.97-23.95	2301	77	0.75(0.52～1.07)	167	0.84(0.66～1.06)
Q3 23.95-30.45	2316	70	0.85(0.71～1.03)	159	0.93(0.83～1.05)
Q4 ≥30.46	2360	61	0.80(0.70～0.91)	123	0.87(0.80～0.94)
P for trend			<0.001		<0.001

[a] Adjusted for maternal age, employment, monthly income per capita, education level, smoking, pre-pregnancy BMI, weight gain during pregnancy, parity, preeclampsia, history of preterm, maternal diabetes, caesarean section, vitamin supplement, total energy intake, dietary iron intake or iron supplement

[b] Preterm premature rupture of membranes

Table 4: Collective effect of iron supplementation and dietary iron intake on the risk of moderate preterm birth and subtypes

Dietary iron intake (mg/day)	Iron supplementation non-users		Iron supplementation users		Multiplicative interaction	P for interaction
	Case/controls	Or[a] (95% CI)	Case/controls	Or[a] (95% CI)		
Moderate preterm birth (n=10179)						
<23.04	574/3942	1.00	32/542	0.51(0.35 ~ 0.76)	0.53(0.35 ~ 0.81)	0.003
≥23.04	388/4167	0.89(0.83 ~ 0.96)	25/509	0.78(0.67 ~ 0.90)		
Additive interaction: RERI (95% CI) =0.29(0.07 ~ 0.51), AP (95% CI) =0.87(0.33 ~ 1.41), S (95% CI)=0.69(0.53 ~ 0.91)						
Medically indicated preterm (n=9498)						
<23.04	195/3942	1.00	12/542	0.70(0.36 ~ 1.35)	0.57(0.26 ~ 1.25)	0.160
≥23.04	123/4167	0.84(0.73 ~ 0.97)	8/509	0.78(0.60 ~ 1.02)		
Additive interaction: RERI (95% CI) =0.27(-0.10 ~ 0.64), AP (95% CI) =0.86(-0.13 ~ 1.85), S (95% CI)=0.71(0.46 ~ 1.11)						
Spontaneous preterm (n=9841)						
<23.04	379/3942	1.00	20/542	0.44(0.27 ~ 0.70)	0.52(0.32 ~ 0.86)	0.012
≥23.04	265/4167	0.91(0.83 ~ 0.99)	17/509	0.78(0.66 ~ 0.93)		
Additive interaction: RERI (95% CI) =0.30(0.04 ~ 0.57), AP (95% CI) =0.87(0.24 ~ 1.50), S (95% CI)=0.68(0.49 ~ 0.95)						

RERI: relative excess risk due to interaction
AP: attributable proportion due to interaction
S: the synergy index
[a]Adjusted for maternal age, employment, monthly income per capita, education level, smoking, pre-pregnancy BMI, weight gain during pregnancy, parity, preeclampsia, history of preterm, maternal diabetes, caesarean section, vitamin supplement, total energy intake

Discussion

In this cohort study, iron supplementation at a dosage of 60 mg/day and iron intake at a dose of >25.86 mg/d before pregnancy, >30.46 mg/d during pregnancy can reduce the risk of moderate preterm birth, which probably varies according to the subtypes of preterm birth. Moreover, the positive interactions between the additive scale and the multiplicative scale were observed for overall preterm and spontaneous preterm birth.
The protective effect was documented for iron supplementation users ≥4 weeks. The risk of preterm birth was decreased along with the duration of use of iron supplementation and the protective effect was increased in spontaneous preterm

birth rather than in medically preterm birth. Either before or during pregnancy, higher level of dietary iron intake reduced the risk of overall moderate preterm birth with a significant dose response, similarly for spontaneous preterm birth. In the collective effect, compared with iron supplementation non-users with adequate dietary iron intake, the iron-supplementation users exerted an effort on decreasing the risk of overall preterm birth and spontaneous preterm births, indicating that the estimated collective effect of iron supplementation and dietary iron intake was higher than the sum of the estimated effect of iron supplementation or dietary iron intake alone. Iron supplementation and dietary iron intake failed to prevent the risk of medically induced preterm birth indicating that this subtype of preterm birth possess specific etiology instead of iron status.

During pregnancy, maternal iron needs are increased because fetus and placenta require iron to maintain growth. In the third trimester, the expansion of maternal blood volume needs more iron (21, 22). The daily requirement for iron is ranged from 1-1.5 mg/day, up to 5.0 mg/day in the second and third trimesters (23). However, the nutrient intake during pregnancy may be inadequate, and pregnant women might consume merely 85% of the recommended dietary allowance for energy and shortfall iron (24). Poor quality diet, inadequate intake combined with increased nutrient requirement led to multiple micronutrient deficiencies (25). Previous studies confirmed that pregnancy women with the iron deficiency had a significantly higher risk of preterm birth and a decreasing risk with the duration of iron supplementation (21, 26, 27). According to an American study (NHANES), pregnant women presented with an increasing prevalence of iron deficiency along with trimester (21). In our study, women, receiving persistent iron supplementation rather than those with iron supplementation before pregnancy or only using during the first and second trimesters, have a lower risk of preterm birth, indicating that the risk of preterm birth decreased along with the duration of iron supplementation.

Iron supplementation has been administered in a variety of doses and regimens (28). Haider BA et al (27) suggested 10 mg of iron supplementation daily reduced the 3% risk of low-birth weight. Prophylactic iron supplementation (30 mg) reduced the risk of preterm birth (29). Sixty eight mg daily supplementation of iron from 17 gestational weeks to 6-week postpartum failed to decrease the risk of preterm birth (30). The incidence of preterm birth was not decreased after administering 30 mg of ferrous sulfate from the enrollment to 28 weeks of gestation (31). The dose of iron supplementation remains debated, since the functional impairment when iron was inadequate and cytotoxicity when excessive (32). Women with high iron supplementation had a greater risk of haemoconcentration at partum (32). In the current investigation, 60 mg of iron supplementation was chosen in accordance with WHO recommendations of the daily dose of oral iron supplementation, and a positive protective effect on moderate preterm birth was observed. However, whether other doses also had the same positive protective effect remain need further elucidated.

Our findings extend previous research by investigating the collective effect of iron supplementation and dietary iron intake upon the incident of moderate preterm birth. We found that pregnant women with iron supplementation and adequate dietary iron intake had a lower risk of moderate preterm delivery than their counterparts with either treatment alone, indicating that the collective effect of the additive scale of iron supplementation and dietary iron intake together is higher than the sum of the estimated effect of either iron supplementation or dietary iron intake alone. Iron absorption is a complex physiological process depending upon physiological demand, iron content and bioavailability. The underlying mechanism of this interaction remains to be validated by subsequent studies.

There were several strengths and limitations to be acknowledged in our study. Detailed information on demographic data, medical history and life-style factors allowed us to adjust and control the confounding factors. The moderate preterm birth and subtypes were diagnosed based on the medical records rather than self-reports, which minimized the risk of potential disease misclassification. Due to the deficiency of serological parameters to evaluate the iron status, the iron status cannot be evaluated. The underlying mechanism of the collective effect should be investigated.

Conclusion

Iron supplementation and dietary iron intake were independently associated with a reduced risk of moderate preterm birth. Adequate dietary iron intake may interact with iron supplementation to further decrease the risk of moderate preterm birth. Therefore, we need the further preventive strategies to confirm the presence of synergy between these two factors and to explore the underlying mechanisms.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors. .

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Conflict of interest

The authors declare that there is no conflict of interest.

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