Original Article

Maternal iron and zinc and preterm labor risk: A nested case-control study based on the Lanzhou Birth Cohort Study (BBCS) in China

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Background and Objectives: The aim of this study was to investigate the effect of dietary iron and zinc intake on the risk of preterm labor before and during different trimesters, and to assess whether there is an interaction between iron and zinc intake and the risk of preterm labor. **Methods and Study Design:** The study was a nested case-control study of 880 cases and 8017 controls in Lanzhou City, northwest China. Unconditional logistic regression was used to determine the association between dietary iron/zinc intake and the risk of preterm labor and its clinical subtypes. Multivariable-adjusted restricted cubic spline (RCS) modeling was used to explore the non-linear relationship between dietary iron/zinc intake levels and the risk of preterm birth. Lower iron/zinc intake before and during pregnancy was associated with a higher risk of preterm labor and some of its subtypes, and there was a non-linear trend between iron/zinc intake and risk of preterm labor ($p_{\text{non-linear}}<0.05$). A synergistic effect of low iron and zinc intake on the risk of preterm labor was also observed. **Results:** We observed a significant increase in the risk of preterm labor in women with low dietary zinc intake before and during pregnancy, with a dose-response relationship. Similarly, there was a significant negative association between lower dietary iron intake during pregnancy and preterm labor. In addition, there was a multiplicative interaction between low dietary iron and zinc intake and preterm delivery before pregnancy and during three different periods of pregnancy. **Conclusions:** Higher dietary intake of iron and zinc before and during pregnancy may reduce the risk of preterm labor. Low intakes of iron and zinc during pregnancy appear to have a synergistic effect on the risk of preterm labor.

Key Words: iron, zinc, preterm, interaction, pregnancy

INTRODUCTION

The World Health Organization (WHO) defines a premature baby as one born before 37 weeks of gestation, or less than 259 days from the first date of a woman's last menstrual period (LMP) to delivery.[1] Preterm birth is strongly associated with a significant increase in neonatal morbidity, mortality, and distant complications, and is a major cause of its occurrence.[2] Studies have shown that the worldwide incidence of preterm birth is about 10.60% and the incidence of preterm birth in China is about 6.70%.[3,4] However, the underlying mechanisms of preterm birth remain unclear. Therefore, it is important to identify modifiable risk factors to provide evidence for the primary prevention of preterm birth.

The nutritional needs of pregnant women increase gradually during pregnancy in order to maintain maternal metabolism and tissue growth, as well as to support the growth and development of the fetus.[5] Nutrition during pregnancy is an important modifiable factor, not only related to the health of the pregnant woman herself, but also crucial for the growth and development of the fetus.[6]

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Adequacy of the micronutrient iron during pregnancy is essential for fetal growth and to support the increased oxygen consumption requirements of the body during pregnancy.[7] Iron deficiency during pregnancy is associated with serious adverse pregnancy outcomes, including preterm delivery.[8,9] An adequate supply of zinc in the pregnant woman's body during pregnancy is important for fetal growth. One major role of zinc is related to the regulation of chromatin structure and function in the body, and to the expression of genes essential for embryogenesis.[10] Therefore, zinc deficiency during embryogenesis may affect the final phenotype of all organs leading to fetal growth restriction.[11]

Daily diet and dietary supplements are the main sources of zinc and iron in pregnant women. The biological effects of various micronutrients required by pregnant women during pregnancy and their relationship with offspring health outcomes related to fetal growth and development, genetic disorders and birth defects have been an important area of interest. However, according to current studies, the relationship between iron and zinc intakes and preterm birth is not well covered comprehensively before and throughout pregnancy,[12-25] as well as some studies on total iron/zinc intake assessment did not model the relationship between iron/zinc in food and dietary supplements separately, and previous studies did not consider the synergistic effect of iron and zinc intakes on the risk of preterm birth. Therefore, the aim of this study was to investigate the effect of daily intake of iron and zinc on the risk of delivering preterm infants in pregnant women in the Northwest before and during pregnancy, and also to explore the interaction between iron and zinc intake on the risk of preterm birth before and during pregnancy.

METHODS

Study design and participants

From January 2018 to June 2019, we conducted a birth cohort study in the largest hospital of its kind in Lanzhou City, Gansu Province. Details of the study design have been published previously.[26-28] Eligible study participants were residents of northwestern China, resided in Lanzhou, China, during pregnancy, were all pregnant women with no history of psychiatric disorders, were 18 years of age or older, had regular prenatal care, and obtained written informed consent from all participants. After removing missing information and dietary investigations of serious adverse pregnancy outcomes such as stillbirths, multiple births, and other serious adverse pregnancy outcomes during pregnancy, a total of 8,897 eligible women participated in the study, including 880 pregnant women delivering preterm infants and 8,017 infants with normal deliveries.

The study was approved by the Institutional Review Board of Gansu Maternal and Child Health Hospital [2018 (029)]. Participants provided written informed consent.

Dietary assessment

Dietary surveys and dietary iron and zinc intakes were collected via a face-to-face semi-quantitative food frequency questionnaire (FFQ).[29] The survey included sociologic characteristics, medical history, physical reproductive history and dietary survey. Dietary profile was investigated using 24-hour dietary recall method to continuously investigate the types and quantities of various food items consumed over a 3-day period by a trained healthcare professional. The dietary survey consisted of 59 common food items including 12 types of grains, fats and oils, vegetables, fruits, poultry and livestock and their products, eggs, aquatic products, pulses and legumes, milk and milk products, mushrooms and algae, snacks and beverages. The questionnaire were conducted by the first trimester (1-13 weeks), the second trimester (14-27 weeks) and the third trimester (> 27weeks) respectively. After completing all dietary surveys, the daily intake of dietary vitamins and trace elements of each pregnant woman during different trimesters was calculated according to the second edition of Chinese Food Composition Table in 2009.[30,31] The present study was based on the data obtained from the above survey, which was analysed by statistical software for the cut-off values of daily intake of iron and zinc elements before pregnancy and during different trimesters, which were divided into groups for statistical analysis. Data on pregnancy-related complications and delivery outcomes were obtained from medical records.

Covariates

Study covariates included (1) socio-demographic characteristics: mother's age, maternal country (Han/ ethnic minority), monthly income (<2000/ 2000 - 4000/ ≥4000 RMB (Renminbi) per capita), maternal education (college or above/ under college), smoking during pregnancy (passive and active), passive smoking was defined as exposure to tobacco smoke from another person for more than 15 min/day. Alcohol consumption during pregnancy (No/ Yes) Maternal employment (No/ Yes) History of maternal miscarriage (No/ Yes), maternal childbirth history (No/ Yes) (2) Maternal health-related factors: multivitamin supplementation (No/ Yes), anemia diagnosed by physician using the criteria of hemoglobin concentration below 110 g/L Gestational diabetes (No/ Yes), gestational hypertension (No/ Yes).

Statistical analysis

First, the data obtained from 8897 cases were analyzed using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA) with the corresponding ROC analysis to determine the optimal cut-off values for the different variables. Cut-off values are the thresholds at which data can be categorized according to specific conditions in data analysis. Data comparisons in the selected characteristics between women with premature labor and term birth were evaluated using Chi-square test or Fisher’s exact test if necessary. The differences of measurement data between the two groups were compared by independent sample t-test, and the variables that did not meet the normal distribution were compared between groups by Wilcoxon rank sum test. Unconditional logistic regression was utilized to determine the odds ratios (OR) and 95% confidence intervals (CI) for the association between dietary iron and zinc intake and the risk of premature labor and its clinical subtypes. Confounding factors including maternal age, pre-pregnancy BMI, weight gain during pregnancy, total

energy intake, reproductive history, history of premature birth, maternal nation, maternal education level, monthly income RNB per capita, maternal employment, smoking, multivitamin supplement, gestational diabetes, gestational hypertension were adjusted in the unconditional logistic regression models. Dietary iron and zinc intake were categorized to quartiles, and dose-response relationship ($p_{\text{for trend}}$) was calculated based on those categorical levels. The association between dietary iron/zinc intake levels and the risk of premature labor may result in a non-linear correlation, multivariable adjusted restricted cubic splines (RCS) models with three knots were applied to explore the non-linear association. The determination of knots number was ascertained by comparing the criterions between Bayesian and Akaike information. The RCS models were adjusted by the potential confounding factors listed above.

Biological interaction is a qualitative concept about the biological mechanisms of pathogenesis of multiple risk factors, which refers to the interconnectedness of the biological mechanisms of pathogenesis, including synergistic and antagonistic interactions, provided that both factors are etiological. The effect of two factors when they are present at the same time is not equal to the sum (additive interaction) or the product (multiplicative interaction) of the individual effects of the two factors. For additive interactions, three indicators are usually required to quantitatively evaluate additive interactions between exposure factors and between exposure factors and genes in epidemiological studies, namely relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and the synergy index (S).[32, 33] The multiplicative interaction parameters [OR = OR11 / (OR01 * OR10)] and 95% CI were also estimated by including variables listed above, the interactions on the additive scale were assessed with relative excess risk due to interaction (RERI = OR11 - OR10 - OR01 + 1), attributable proportion (AP = RERI/ Risk Ratio (RR)11), and synergy index [S = (OR11 - 1) / [(OR01 - 1) + (OR10 - 1)],[33] we estimated 95% CI for each of these measures, the null values of RERI and AP are 0,whereas the null value for S is 1. All statistical tests were two-sided. Analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA). The RCS models were performed by R software, version 4.1.3 (package 'foreign' , 'rms').

RESULTS

Basic characteristics of the study population

The study population has been described previously.[26-29] A total of 8897 women were eligible for the final analysis, of which 880 were diagnosed with preterm birth and the remaining 8017 were normal birth infants. As shown in Tables 1 and 2, mothers of preterm infants had lower monthly income, lower educational attainment, and lower rates of maternal employment, and higher gestational hypertension, gestational diabetes, history of preterm delivery, and childbirth history compared to women who delivered normal infants. In addition, mothers in the case group had reduced weight gain during pregnancy, lower total energy intake, lower multivitamin supplements, and lower dietary iron and zinc intake before pregnancy as well as during different trimesters ($p<0.05$). There were no significant differences in the distribution of maternal alcohol consumption during pregnancy, pregnancy anemia, or history of miscarriage between the two groups ($p>0.05$).

Relationship between dietary iron intake and risk of preterm birth during pregnancy

Compared to the lowest quartile (Q1) of pre-pregnancy dietary iron intake, the adjusted odds ratios (ORs) for preterm birth in quartiles 2, 3, and 4 were 1.11 (95% CI: 1.01–1.22), 1.18 (95% CI: 1.03–1.34), and 1.29 (95% CI: 1.01–1.65), respectively, with a statistically significant trend across quartiles ($p_{\text{for trend}} < 0.05$) (Table 3). When stratified by trimester, the risk of preterm labor was increased in quartiles 1-3 compared to quartile 4 in the middle of pregnancy, in late pregnancy, and for the whole pregnancy, with a significant test of trend ($p_{\text{second trimester}} = 0.03$, $p_{\text{third trimester}} = 0.008$, and $p_{\text{during pregnancy}} = 0.02$). After stratifying preterm births by gestational age, it was observed that moderate preterm births were significantly more likely to occur in women within quartile 1 of iron intake during the second and third trimesters, compared to those in quartile 4, with a significant trend across quartiles ($p_{\text{for trend}} = 0.03$ in the second trimester; $p = 0.02$ in the third trimester). Additionally, an increased risk of late preterm birth was found among women in quartiles 1 and 2 of pre-pregnancy iron intake during mid-pregnancy, and in quartile 1 across the entire pregnancy period, with significant trends observed ($p_{\text{for trend}} = 0.008$ pre-pregnancy; $p = 0.03$ second trimester; $p = 0.04$ during pregnancy).

Mothers in the low iron intake group had a significantly higher risk of preterm birth before, during, during, and during the third trimester, with adjusted ORC of 1.26 (1.07-1.48), 1.30 (1.09-1.56), 1.21 (1.02-1.44), and 1.33 (1.12-1.58). The third trimester of moderate preterm infants was 1.58 (1.10 -2.27). Late preterm infants were 1.33 (1.09-1.63), 1.44 (1.16-1.79) and 1.28 (1.03-1.58) before, during and during the first and second trimesters, respectively. However, the low iron intake group was not significantly associated with early preterm birth (Table 4).

Figure 1 shows a restricted cubic spline curve of the relationship between iron intake before and during pregnancy and the risk of preterm birth. As iron intake increased, the risk of preterm birth decreased at 20.2 mg/d during the first trimester, Iron intake in the early, middle and third trimesters of pregnancy decreased the risk of preterm birth in the range of (23.9-53.8) mg/d, (24.2 - 45.7) mg/d and (24.2 - 84.7) mg/d, respectively, while the rest were associated with an increased risk of preterm birth ($p_{\text{non-linear}} <0.05$).

Relationship between dietary zinc intake and preterm birth risk

As shown in Table 5, the adjusted ORs for preterm babies in pregnancy and three different trimesters of dietary zinc intake in quartile 2 were 1.15 (1.07-1.47), 1.16 (0.99-1.35), 1.17 (1.00-1.36), and 1.22 (1.04-1.42), respectively, as compared to quartile 4 (the highest), and the tests for trend were all significant ($p_{\text{during pregnancy}}= 0.001$, $p_{\text{first trimester}} = 0.04$, $p_{\text{second trimester}} = 0.008$, $p_{\text{third trimester}} = 0.001$). After stratification of preterm babies by different gesta-

Table 1. Distributions of selected characteristics of the study population

Characteristics	Term (n=8017)	Preterm (n=880)	Chi-square	*p* value
Maternal age			68.7	<0.001
<25	1168 (85.6)	197 (14.4)		
25~	3981 (92.6)	318 (7.4)		
≥30	2868 (88.7)	365 (11.3)		
Pre-pregnancy BMI (kg/m^2)			7.7	0.021
<18.5	1709 (90.7)	176 (9.3)		
18.5~	5450 (90.3)	583 (9.7)		
≥24	858 (87.6)	121 (12.4)		
Weight gain during pregnancy (kg)			261	<0.001[†]
<15	2323 (83.0)	476 (17.0)		
15~18.5	2615 (92.9)	201 (7.1)		
>18.5	3026 (94.6)	172 (5.4)		
Missing	53 (63.1)	31 (36.9)		
Total energy intake(kcal/d)	1685 (1435,1972)	1548 (1244,1831)	88.2	<0.001
Reproductive history			60.9	<0.001
Primipara	5983 (91.6)	549 (8.4)		
Multiparous	2034 (86.0)	331 (14.0)		
History of miscarriage			0.9	0.331
No	6919 (90.2)	749 (9.8)		
Yes	1098 (89.3)	131 (10.7)		
History of premature birth			139	<0.001
No	7910 (90.6)	818 (9.4)		
Yes	107 (63.3)	62 (36.7)		
Maternal nation			8.4	0.004
Han	7518 (90.4)	803 (9.6)		
Minority	499 (86.6)	77 (13.4)		
Maternal education level			190	<0.001
<Middle school	352 (76.0)	111 (24.0)		
Middle school~	2603 (86.9)	391 (13.1)		
≥Junior college	5062 (93.1)	378 (6.9)		
Monthly income (RMB per capita)			96.5	<0.001
<2000	1945 (85.1)	340 (14.9)		
2000~4000	4187 (91.0)	412 (9.0)		
≥4000	1885 (93.6)	128 (6.4)		
Maternal employment			43.6	<0.001
No	2384 (87.0)	357 (13.0)		
Yes	5633 (91.5)	523 (8.5)		
Smoking (passive and active)			7.9	0.005
No	6433 (90.6)	671 (9.4)		
Yes	1584 (88.3)	209 (11.7)		
Drink during pregnancy			-	0.189[‡]
No	8005 (90.1)	877 (9.9)		
Yes	12 (80.0)	3 (20.0)		
Multivitamin supplement			48.3	
No	1569 (85.8)	260 (14.2)		
Yes	6448 (91.2)	620 (8.8)		
Gestational diabetes			4.9	0.027
No	7943 (90.2)	865 (9.8)		
Yes	74 (83.2)	15 (16.8)		
Gestational hypertension			268	<0.001
No	7726 (91.3)	738 (8.7)		
Yes	291 (67.2)	142 (32.8)		
Anemia during pregnancy			0.9	0.351
No	7123 (90.0)	791 (10.0)		
Yes	894 (90.9)	89 (9.1)		
Pre-eclampsia			291	<0.001
No	7841 (91.1)	766 (8.9)		
Yes	176 (60.7)	114 (39.3)		

BMI, body mass index; RMB, Renminbi.
[†]The *p* value was obtained by Fisher exact test in chi-square test.
[‡]The *p* value is the one that does not contain missing values.

tional weeks, it was observed that early preterm babies were at increased risk throughout the entire gestation as well as across different trimesters in quartile 2 as compared to quartile 4, and the test for trend was significant ($p_{\text{during pregnancy}} < 0.001$, $p_{\text{first trimester}} = 0.008$, $p_{\text{second trimester}} = 0.03$, $p_{\text{third trimester}} = 0.001$). In addition, moderately preterm infants had an increased risk of developing quartile 1 in the second trimester, in the second trimester, and

Table 2. Comparison of dietary zinc and iron intake between different pregnancy groups [P50 (P25, P75), mg/d]

Dietary nutrients	Term (n=8017)			Preterm (n=880)			Z	*p* value
	P_{25}	P_{50}	P_{75}	P_{25}	P_{50}	P_{75}		
Dietary iron intake (mg/d)								
Before pregnancy	15.9	20.1	25.7	15.1	18.8	23.5	28.3	<0.001
Iron intake during first trimester	18.8	23.5	29.5	16.8	21.6	27.5	43.9	<0.001
Iron intake during second trimester	19.5	24.4	30.7	17.5	22.5	27.8	45.7	<0.001
Iron intake during third trimester	19.6	24.4	30.9	17.1	22.2	27.8	64.3	<0.001
Dietary zinc intake (mg/d)								
Before pregnancy	5.3	6.8	8.5	4.5	5.9	7.8	76.5	<0.001
Iron intake during first trimester	6.4	8.1	10.1	5.2	7.2	9.1	98.7	<0.001
Iron intake during second trimester	6.7	8.5	10.6	5.4	7.4	9.6	99.8	<0.001
Iron intake during third trimester	6.7	8.5	10.6	5.2	7.3	9.4	123	<0.001

P, percentage.

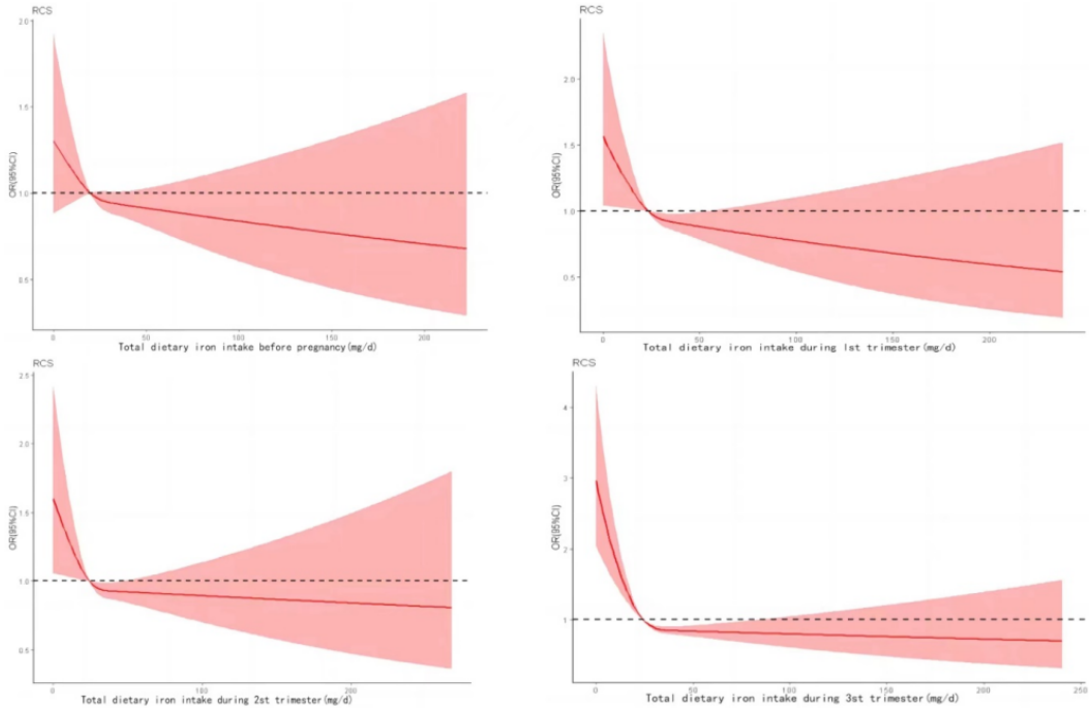

Figure 1. Restricted cubic spline models of preterm risk associated with iron intake (A) before pregnancy, (B) first trimester, (C) second trimester, and (D) third trimester. RCS, restricted cubic spline; OR, odds ratio; CI, confidence interval

throughout the entire pregnancy, and the test for trend was significant ($p_{\text{second trimester}} = 0.005$, $p_{\text{third trimester}} = 0.003$, $p_{\text{during pregnancy}} = 0.02$).

Mothers in the low zinc intake group had a significantly higher risk of preterm birth before, during early, mid and late pregnancy, with adjusted OR of 1.35 (1.13-1.61), 1.32 (1.10-1.59), 1.25 (1.03-1.51) and 1.71 (1.41-2.08). Mothers in the low zinc intake group had a significantly higher risk of delivering early preterm infants with an OR of 1.52 (1.03-2.25), 1.60 (1.08-2.39), 1.66 (1.08-2.56) and 2.58 (1.71-3.90). Moderate preterm births were 1.51 (1.00-2.28) and 1.76 (1.19-2.62) in mid- and late gestation, respectively. The OR of late preterm infants was 1.30 (1.05-1.61), 1.25 (1.00-1.57) and 1.42 (1.11-1.80) in preterm, early and late gestation, respectively (Table 6).

Figure 2 shows the restricted cubic spline curves of the relationship between zinc intake and risk of preterm birth before and during pregnancy. With increasing zinc intake, the risk of preterm delivery decreases in the range of (6.66-14.5) mg/d, (8.12-15.6) mg/d, (8.34-20.5) mg/d and (8.41-31.7) mg/d for pre-, early-, mid- and late pregnancy, respectively, while the rest have an increased risk for the occurrence of preterm delivery ($p_{\text{non-linear}} < 0.05$).

Interaction effects of maternal dietary iron and zinc intake on the risk of preterm

We further stratified the interaction of maternal dietary iron and zinc intakes on the risk of preterm birth. An additional interaction between low dietary iron and zinc intake during pregnancy and preterm birth was observed. The synergy index was 2.60 (S = 2.60,95% CI: 1.37-4.91), the relative additional risk ratio for additive interaction during pregnancy was 1.40 (RERI = 1.40,95% CI: 0.70-2.11), and 43% (AP = 0.43,95% CI: 0.25-0.61) was attributable to low maternal dietary iron and zinc intake The interaction of low maternal dietary iron and zinc intakes There was also a multiplicative interaction between low dietary iron intake and low dietary zinc intake during pregnancy (OR = 1.62, 95% CI: 1.34-1.96). Similar

Table 3. Associations of maternal dietary iron intake with the risk of preterm

Dietary iron intake (mg/d)	Term (8017)	Preterm (n=880)			Early preterm births (<32 weeks)		Moderate preterm births (32≤ weeks <34)		Late preterm births (34≤ weeks <37)	
		Cases	OR† (95% *CI*)	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)
Before pregnancy										
Q1 <15.8	1951	274	1.21 (1.13-1.29)	1.11 (1.01-1.22)	51	0.96 (0.78-1.18)	52	1.12 (0.91-1.38)	171	1.13 (1.01-1.26)
Q2 15.8-19.9	1994	230	1.20 (1.08-1.34)	1.18 (1.03-1.34)	39	0.96 (0.71-1.29)	49	1.34 (1.01-1.77)	142	1.19 (1.02-1.39)
Q3 19.9-25.5	2011	212	1.33 (1.07-1.64)	1.29 (1.01-1.65)	40	0.93 (0.53-1.62)	41	1.43 (0.84-2.43)	131	1.28 (0.96-1.72)
Q4 ≥25.5	2061	164	1.00	1.00	32	1.00	28	1.00	104	1.00
p for trend			<0.001	0.031		0.426		0.263		0.008
First trimester										
Q1 <18.6	1922	303	1.25 (1.17-1.33)	1.09 (0.99-1.21)	55	0.94 (0.75-1.17)	63	1.20 (0.96-1.50)	185	1.11 (0.99-1.25)
Q2 18.6-23.3	2018	206	1.12 (1.01-1.24)	1.07 (0.93-1.22)	44	0.95 (0.71-1.27)	42	1.23 (0.91-1.67)	120	1.04 (0.88-1.22)
Q3 23.3-29.3	2021	203	1.23 (0.99-1.52)	1.14 (0.89-1.45)	32	0.74 (0.41-1.32)	39	1.30 (0.76-2.24)	132	1.16 (0.87-1.54)
Q4 ≥29.3	2056	168	1.00	1.00	31	1.00	26	1.00	111	1.00
p for trend			<0.001	0.092		0.429		0.115		0.049
Second trimester										
Q1 < 19.3	1921	303	1.26 (1.18-1.35)	1.14 (1.02-1.26)	53	1.00 (0.78-1.28)	69	1.40 (1.11-1.77)	181	1.11 (0.97-1.26)
Q2 19.3-24.2	2012	212	1.16 (1.04-1.28)	1.09 (0.95-1.25)	43	1.08 (0.80-1.46)	33	1.14 (0.83-1.57)	136	1.05 (0.90-1.23)
Q3 24.2-30.4	2022	202	1.26 (1.02-1.57)	1.16 (0.91-1.48)	39	0.95 (0.53-1.69)	44	1.54 (0.90-2.65)	119	1.07 (0.80-1.44)
Q4 ≥ 30.4	2062	163	1.00	1.00	27	1.00	24	1.00	112	1.00
p for trend			<0.001	0.034		0.383		0.029		0.029
Third trimester										
Q1 < 19.3	1909	315	1.29 (1.21-1.38)	1.11 (1.00-1.24)	73	0.96 (0.76-1.21)	69	1.34 (1.07-1.69)	173	1.07 (0.94-1.22)
Q2 19.3-24.2	2014	210	1.16 (1.05-1.30)	1.17 (1.02-1.34)	36	1.16 (0.84-1.59)	35	1.21 (0.89-1.65)	139	1.14 (0.97-1.34)
Q3 24.2-30.6	2029	196	1.26 (1.01-1.56)	1.19 (0.92-1.52)	27	0.82 (0.44-1.53)	41	1.42 (0.83-2.46)	128	1.15 (0.86-1.54)
Q4 ≥ 30.6	2065	159	1.00	1.00	26	1.00	25	1.00	108	1.00
p for trend			<0.001	0.008		0.644		0.023		0.072
During pregnancy										
Q1 < 19.2	1907	317	1.28 (1.20-1.37)	1.12 (1.01-1.24)	68	1.01 (0.80-1.28)	67	1.29 (1.02-1.62)	182	1.10 (0.97-1.25)
Q2 19.2-24.0	2020	204	1.13 (1.02-1.26)	1.07 (0.94-1.23)	41	1.04 (0.77-1.42)	34	1.11 (0.81-1.53)	129	1.06 (0.90-1.24)
Q3 24.0-30.1	2029	196	1.22 (0.98-1.51)	1.18 (0.92-1.52)	26	0.83 (0.44-1.54)	44	1.64 (0.96-2.81)	126	1.12 (0.83-1.50)
Q4 ≥ 30.1	2061	163	1.00	1.00	27	1.00	25	1.00	111	1.00
p for trend			<0.001	0.022		0.660		0.080		0.041

Q, quartile; OR, odds ratio.

†univariate analyses.

‡adjusted for maternal age, pre-pregnancy BMI, weight gain during pregnancy, total energy intake, reproductive history, history of premature birth, maternal nation, maternal education level, monthly income RNB per capita, maternal employment, smoking, multivitamin supplement, gestational diabetes, gestational hypertension and dietary zinc intake

Table 4. Maternal dietary iron intake categorized by cut-off value and the risk of preterm

Dietary iron intake (mg/d)	Term (8017)	Preterm (n=880)			Early preterm births (<32 weeks)		Moderate preterm births (32≤ weeks <34)		Late preterm births (34≤ weeks <37)	
		Cases	OR† (95% *CI*)	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)
Before pregnancy										
High group	5091	472	1.00	1.00	90	1.00	86	1.00	296	1.00
Low group	2926	408	1.50 (1.31-1.73)	1.26 (1.07-1.48)	72	0.93 (0.65-1.33)	84	1.39 (0.99-1.97)	252	1.33 (1.09-1.63)
First trimester										
High group	6300	595	1.00	1.00	111	1.00	111	1.00	373	1.00
Low group	1717	285	1.76 (1.51-2.04)	1.30 (1.09-1.56)	51	0.91 (0.62-1.35)	59	1.35 (0.93-1.96)	175	1.44 (1.16-1.79)
Second trimester										
High group	5618	519	1.00	1.00	96	1.00	93	1.00	330	1.00
Low group	2399	361	1.63 (1.41-1.88)	1.21 (1.02-1.44)	66	0.88 (0.60-1.28)	77	1.42 (0.99-2.05)	218	1.28 (1.03-1.58)
Third trimester										
High group	5573	497	1.00	1.00	77	1.00	89	1.00	331	1.00
Low group	2444	383	1.76 (1.53-2.02)	1.33 (1.12-1.58)	85	1.28 (0.86-1.88)	81	1.58 (1.10-2.27)	217	1.22 (0.99-1.51)

R, odds ratio.

†univariate analyses

‡adjusted for maternal age, pre-pregnancy BMI, weight gain during pregnancy, total energy intake, reproductive history, history of premature birth, maternal nation, maternal education level, monthly income RNB per capita, maternal employment, smoking, multivitamin supplement, gestational diabetes, gestational hypertension and dietary zinc intake.

Table 5. Associations of maternal dietary zinc intake with the risk of preterm

Dietary iron intake (mg/d)	Term (8017)	Preterm (n=880)			Early preterm births (<32 weeks)		Moderate preterm births (32≤ weeks <34)		Late preterm births (34≤ weeks <37)	
		Cases	OR† (95% *CI*)	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)
Before pregnancy										
Q1 <15.8	1894	330	1.30 (1.22-1.39)	1.07 (0.96-1.19)	71	1.01 (0.81-1.26)	69	1.05 (0.84-1.32)	190	1.09 (0.96-1.24)
Q2 15.8-19.9	2018	207	1.14 (1.03-1.27)	1.00 (0.87-1.16)	37	0.98 (0.70-1.36)	42	1.16 (0.84-1.59)	128	0.96 (0.81-1.14)
Q3 19.9-25.5	2043	181	1.13 (0.90-1.41)	1.12 (0.87-1.45)	27	0.94 (0.50-1.77)	31	1.06 (0.58-1.93)	123	1.17 (0.86-1.59)
Q4 ≥25.5	2062	162	1.00	1.00	27	1.00	28	1.00	107	1.00
p for trend			<0.001	0.013		0.094		0.076		0.127
First trimester										
Q1 <18.6	1894	331	1.31 (1.23-1.40)	1.02 (0.90-1.16)	74	1.18 (0.89-1.56)	73	1.09 (0.83-1.43)	184	0.98 (0.84-1.14)
Q2 18.6-23.3	1994	229	1.22 (1.10-1.35)	1.16 (0.99-1.35)	43	1.50 (1.04-2.15)	38	1.12 (0.78-1.60)	148	1.11 (0.93-1.34)
Q3 23.3-29.3	2065	160	1.00 (0.80-1.26)	0.88 (0.67-1.15)	26	0.95 (0.46-1.94)	33	1.10 (0.61-1.97)	101	0.84 (0.61-1.14)
Q4 ≥29.3	2064	160	1.00	1.00	19	1.00	26	1.00	115	1.00
p for trend			<0.001	0.044		0.016		0.136		0.459
Second trimester										
Q1 < 19.3	1888	336	1.34 (1.25-1.43)	1.09 (0.96-1.25)	72	1.15 (0.85-1.55)	78	1.31 (1.00-1.71)	186	1.03 (0.87-1.21)
Q2 19.3-24.2	2000	224	1.22 (1.10-1.36)	1.17 (1.00-1.36)	44	1.74 (1.22-2.49)	41	1.09 (0.77-1.55)	139	1.09 (0.90-1.31)
Q3 24.2-30.4	2059	165	1.07 (0.85-1.34)	1.01 (0.78-1.32)	27	0.95 (0.47-1.91)	24	0.87 (0.47-1.60)	114	1.05 (0.78-1.42)
Q4 ≥ 30.4	2070	155	1.00	1.00	19	1.00	27	1.00	109	1.00
p for trend			<0.001	0.008		0.032		0.005		0.351
Third trimester										
Q1 < 19.3	1878	346	1.36 (1.27-1.46)	1.09 (0.95-1.24)	87	1.06 (0.81-1.40)	79	1.34 (1.03-1.73)	180	0.99 (0.84-1.17)
Q2 19.3-24.2	2001	224	1.24 (1.11-1.38)	1.22 (1.04-1.42)	37	1.61 (1.14-2.28)	42	1.16 (0.82-1.63)	145	1.15 (0.95-1.38)
Q3 24.2-30.6	2064	159	1.06 (0.84-1.33)	1.03 (0.79-1.35)	17	0.60 (0.28-1.29)	23	0.86 (0.45-1.62)	119	1.14 (0.84-1.55)
Q4 ≥ 30.6	2074	151	1.00	1.00	21	1.00	26	1.00	104	1.00
p for trend			<0.001	0.001		0.004		0.003		0.442
During pregnancy										
Q1 < 19.2	1873	352	1.37 (1.28-1.46)	1.05 (0.92-1.21)	86	1.29 (0.95-1.77)	77	1.23 (0.92-1.63)	189	0.96 (0.80-1.14)
Q2 19.2-24.0	2005	219	1.22 (1.10-1.36)	1.15 (1.07-1.47)	39	2.13 (1.47-3.09)	40	1.15 (0.80-1.65)	140	1.14 (0.94-1.38)
Q3 24.0-30.1	2067	157	1.04 (0.82-1.31)	0.92 (0.70-1.20)	21	0.97 (0.45-2.10)	27	0.85 (0.46-1.59)	109	0.91 (0.67-1.24)
Q4 ≥ 30.1	2072	152	1.00	1.00	16	1.00	26	1.00	110	1.00
p for trend			<0.001	0.001		<0.001		0.018		0.279

Q, quartile; OR, odds ratio.

†univariate analyses.

‡adjusted for maternal age, pre-pregnancy BMI, weight gain during pregnancy, total energy intake, reproductive history, history of premature birth, maternal nation, maternal education level, monthly income RNB per capita, maternal employ, smoking, multivitamin supplement, gestational diabetes, gestational hypertension and dietary iron intake.

Table 6. Maternal dietary zinc intake categorized by cut-off value and the risk of preterm

Dietary iron intake (mg/d)	Term (8017)	Preterm (n=880)			Early preterm births (<32 weeks)		Moderate preterm births (32≤ weeks <34)		Late preterm births (34≤ weeks <37)	
		Cases	OR† (95% *CI*)	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)	Cases	OR‡ (*95% CI*)
Before pregnancy										
High group	4828	393	1.00	1.00	63	1.00	71	1.00	259	1.00
Low group	3189	487	1.88 (1.63-2.16)	1.35 (1.13-1.61)	99	1.52 (1.03-2.25)	99	1.44 (0.99-2.11)	289	1.30 (1.05-1.61)
First trimester										
High group	5822	495	1.00	1.00	77	1.00	91	1.00	327	1.00
Low group	2195	385	2.06 (1.79-2.38)	1.32 (1.10-1.59)	85	1.60 (1.08-2.39)	79	1.36 (0.92-2.01)	221	1.25 (1.00-1.57)
Second trimester										
High group	5175	429	1.00	1.00	62	1.00	74	1.00	293	1.00
Low group	2842	451	1.91 (1.66-2.20)	1.25 (1.03-1.51)	100	1.66 (1.08-2.56)	96	1.51 (1.00-2.28)	255	1.10 (0.87-1.39)
Third trimester										
High group	6787	593	1.00	1.00	86	1.00	111	1.00	396	1.00
Low group	1230	287	2.67 (2.29-3.11)	1.71 (1.41-2.08)	76	2.58 (1.71-3.90)	59	1.76 (1.19-2.62)	152	1.42 (1.11-1.80)

R, odds ratio.
†univariate analyses
‡adjusted for maternal age, pre-pregnancy BMI, weight gain during pregnancy, total energy intake, reproductive history, history of premature birth, maternal nation, maternal education level, monthly income RNB per capita, maternal employment, smoking, multivitamin supplement, gestational diabetes, gestational hypertension and dietary iron intake.

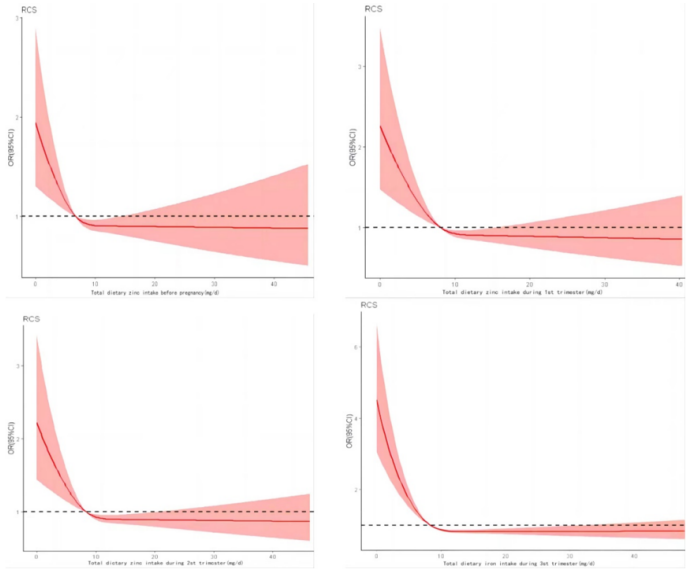

Figure 2. Restricted cubic spline models of preterm risk associated with zinc intake (A) before pregnancy, (B) first trimester, (C) second trimester, and (D) third trimester. RCS, restricted cubic spline; OR, odds ratio; CI, confidence interval

results were obtained when the entire gestation period was stratified by trimester time period (Table 7).

DISCUSSION

In this nested cohort study, we observed a significantly increased risk of preterm delivery among women with lower dietary iron intake before and during pregnancy, demonstrating a clear dose-response relationship. Similarly lower dietary zinc intake before and during pregnancy was also significantly and negatively associated with preterm birth. In addition, positive additive and multiplicative scale interactions between low dietary iron and zinc intakes and preterm birth were observed before and during different gestation periods. To our knowledge, this is the first comprehensive study to examine the effects of dietary iron and zinc intake on preterm infants.

Comparisons with other studies

To date, few studies have examined the effects of zinc and iron on preterm labor before and during different trimesters. Relevant human studies have addressed the status of zinc and iron in serum samples from mothers as well as newborns. However, the findings remain controversial.[33-41] One study reported that higher zinc levels were associated with an increased risk of preterm labor.[34] Low dietary zinc intake during early pregnancy was associated with a more than threefold increase in the risk of very preterm labor (<33 weeks of gestation).[35] Meanwhile, another study showed an increased risk of preterm labor in pregnant women with moderate (RR = 4.35, 95% CI: 1.94-9.74) or low (RR = 4.90, 95% CI: 2.12-11.3) zinc levels compared to those with high zinc levels during pregnancy.[36] However, some studies have shown that pregnant women in the preterm labor group had higher plasma zinc levels at delivery than those in the control group,[37] suggesting that the risk of preterm labor may be increased when zinc levels are too high. Previous studies have confirmed that the risk of preterm labor is significantly higher in iron-deficient pregnant women and that the risk of preterm labor decreases with the duration of iron supplementation.[38,39] In one study, iron levels in preterm infants and their mothers were significantly lower than in the term group.[40] In addition a study reported a decreasing trend in the incidence of preterm labor in pregnant women who did not take iron during pregnancy as well as in those who took three different levels: low,

Table 7. Interaction effects of maternal dietary iron and zinc intake on the risk of preterm

Maternal dietary intake	Term/Preterm	OR† (95% CI)	OR‡ (95% CI)
Before pregnancy			
High iron and high zinc	3724/304	1.00	1.00
High iron and low zinc	1367/168	1.51 (1.24-1.84)	1.13 (0.89-1.43)
Low iron and high zinc	1104/89	0.99 (0.88-1.12)	0.98 (0.78-1.26)
Low iron and low zinc	18222/319	1.19 (1.12-1.26)	1.14 (1.05-1.09)
Multiplicative interaction: OR¶ (95% CI) =1.54 (1.29-1.84), p<0.001			
Additive interaction: RERI (95% CI) =0.65 (0.24-1.06), AP (95% CI) =0.30 (0.12-0.48), S (95% CI) =2.32 (1.06-5.09)			
First trimester			
High iron and high zinc	5130/423	1.00	1.00
High iron and low zinc	1170/172	1.78 (1.48-2.15)	1.16 (0.92-1.47)
Low iron and high zinc	692/72	1.12 (0.99-1.28)	1.06 (0.92-1.22)
Low iron and low zinc	1025/213	1.36 (1.28-1.44)	1.21 (1.11-1.31)
Multiplicative interaction: OR¶ (95% CI) =1.51 (1.24-1.85), p<0.001			
Additive interaction: RERI (95% CI) =0.48 (-0.09-1.04), AP (95% CI) =0.19 (-0.02-0.40), S (95% CI) =1.46 (0.90-2.37)			
Second trimester			
High iron and high zinc	4324/346	1.00	1.00
High iron and low zinc	1294/173	1.37 (1.13-1.65)	1.00 (0.79-1.26)
Low iron and high zinc	851/83	0.89 (0.64-1.23)	0.83 (0.59-1.17)
Low iron and low zinc	1548/278	1.26 (1.18-1.34)	1.12 (1.01-1.25)
Multiplicative interaction: OR¶ (95% CI) =1.36 (1.12-1.64), p<0.05 (p=0.002)			
Additive interaction: RERI (95% CI) =0.36 (-0.13-0.84), AP (95% CI) =0.16 (-0.05-0.37), S (95% CI) =1.40 (0.84-2.33)			
Third trimester			
High iron and high zinc	5158/436	1.00	1.00
High iron and low zinc	415/61	1.74 (1.31-2.32)	1.03 (0.74-1.44)
Low iron and high zinc	1629/157	1.07 (0.97-1.18)	1.02 (0.92-1.14)
Low iron and low zinc	815/226	1.49 (1.40-1.58)	1.29 (1.19-1.40)
Multiplicative interaction: OR¶ (95% CI) =2.14 (1.75-2.63), p<0.001			
Additive interaction: RERI (95% CI) =0.35 (-0.10-0.79), AP (95% CI) =0.18 (-0.05-0.42), S (95% CI) =1.64 (0.70-3.86)			
During pregnancy			
High iron and high zinc	4316/338	1.00	1.00
High iron and low zinc	1498/188	1.60 (1.33-1.93)	1.15 (0.90-1.47)
Low iron and high zinc	704/62	1.06 (0.92-1.22)	1.02 (0.87-1.19)
Low iron and low zinc	1499/292	1.36 (1.28-1.43)	1.18 (1.08-1.30)
Multiplicative interaction: OR¶ (95% CI) =1.62 (1.34-1.96), p<0.001			
Additive interaction: RERI (95% CI) =1.40 (0.70-2.11), AP (95% CI) =0.43 (0.25-0.61), S (95% CI) =2.60 (1.37-4.91)			

OR, odds ratio; CI, confidence interval; RERI, relative excess risk due to interaction; AP, the attributable proportion due to interaction; S, synergy index.

†univariate analyses.

‡adjusted for maternal age, pre-pregnancy BMI, weight gain during pregnancy, total energy intake, reproductive history, history of premature birth, maternal nation, maternal education level, monthly income RNB per capita, maternal employment, smoking, multivitamin supplement, gestational diabetes, gestational hypertension.

medium and high.[41] However, some studies have also shown that pregnant women with high iron levels did not have a significantly lower risk of preterm labor compared to those with low dietary iron levels.[42]

This study focused on maternal iron and zinc intake before and during pregnancy. In this nested cohort study, we found that low dietary zinc intake during both periods was significantly associated with an increased risk of preterm labor, demonstrating a clear dose-response relationship. Similarly, there was a significant inverse association between lower dietary iron intake during pregnancy and preterm labor. In addition, there was a multiplicative interaction between low dietary iron and zinc intake and preterm labor across trimesters of preconception and pregnancy. To our knowledge, this is the first study to comprehensively examine the effects of dietary iron and zinc intake on preterm labor from preconception through the entire gestational trimester. There are no previous studies on the interaction between zinc-iron and preterm labor. Although positive additive interactions between nutrient intake of iron and zinc and preterm labor were not observed in our study, the results of categorical variables suggest that low iron or zinc increases the risk of developing preterm labor. Given the paucity of studies on the combined effects of iron and zinc on the occurrence of preterm labor in pregnant women, further studies are needed to confirm and interpret these findings.

Possible mechanisms

Zinc is an essential component of many metalloenzymes and is involved in the maintenance of many important physiological functions in the body, including the promotion of growth and development, participation in protein and carbohydrate metabolism, and nucleic acid synthesis.[43-45] Most steroid hormone (androgen, estrogen, and progesterone) receptors consist of zinc finger proteins, thus allowing zinc to fulfill its multifactorial role in reproduction.[46-49] Zinc binding proteins and zinc transporters are involved in the distribution and transport of zinc in the body and regulate and maintain zinc homeostasis in the body through various mechanisms.[50] Low maternal zinc concentrations during pregnancy are associated with adverse pregnancy outcomes, including preterm labor.[51]

Iron is an essential nutrient and cofactor for the synthesis of hemoglobin and myoglobin and plays an important role in a variety of cellular functions.[43] Iron deficiency is the most common cause of anemia during pregnancy and has been associated with increased risks such as preterm birth.[15,52] Iron deficiency leads to anemia and reduces the ability of hemoglobin to carry oxygen, resulting in chronic hypoxia in both mother and fetus.[53] Iron sufficiency is essential for the delivery of oxygen to the maternal placental-fetal unit to support the increased demand for oxygen consumption during pregnancy.[7] In addition, iron enhances leukocyte resistance and strengthens the fetal immune system.[54] Iron deficiency or anemia during pregnancy due to inadequate iron intake can directly affect fetal growth and development.

In low-income countries, where many women enter pregnancy already malnourished, the increased nutritional demands of pregnancy can further exacerbate micronutrient deficiencies. These deficiencies may have adverse effects on fetal health but can be mitigated through appropriate micronutrient supplementation.[55,56] During pregnancy, maternal iron and zinc deficiencies often occur simultaneously. Alterations in maternal iron and zinc concentrations during pregnancy have a regulatory effect on gene expression of intrauterine iron and zinc transport proteins in the placenta, and simultaneous deficiencies in maternal iron and zinc levels up-regulate gene expression of iron and zinc uptake proteins in the placenta, which can have an impact on the nutritional status of the fetus.[57] Pregnant women with low plasma zinc levels in early pregnancy have an increased incidence of iron deficiency, and simultaneous iron and zinc supplementation is more effective than iron supplementation alone in improving hemoglobin and serum ferritin values in women with iron deficiency in early pregnancy.[58] The possible reason for this is that fetal erythropoiesis requires the active participation of IGF-1, which is synthesized with zinc.59 This may also be a potential mechanism for the interaction between dietary iron deficiency and zinc deficiency in this study.

Strengths and limitations

The present study provides valuable evidence on the relationship between iron and zinc intake and preterm labor in pregnant women before and during different trimesters. However, some limitations should be recognized. First, information on dietary iron and zinc intake was obtained from participants' self-reports, and therefore recall bias is inevitable. Second, Although the inability to quantify interactions between dietary multivitamins and micronutrients may have introduced confounding effects, we implemented strict quality control measures throughout the entire process (from questionnaire design to data entry) to minimize recall bias. It should be noted that this study did not differentiate between the chemical forms of dietary iron (heme and non-heme iron) or account for their differing bioavailability, which may have affected the accurate assessment of iron’s physiological effects. On the other hand, detailed information on demographics, medical history, and lifestyle allowed us to adjust for confounders. Additionally, preterm birth and its subtypes were diagnosed based on medical records rather than self-reporting, minimizing the risk of misclassification. However, we acknowledge that unmeasured confounders may still exist, and true causality cannot be fully established. However, this is the first large-scale study to comprehensively and systematically investigate the synergistic effects of dietary iron and zinc intake on preterm labor, providing important guidance for future research.

Conclusions

Our study suggests that higher dietary intake of iron and zinc before and during pregnancy may reduce the risk of preterm labor. This study also suggests that low intakes of iron and zinc during pregnancy appear to have a synergistic effect on the risk of preterm labor. These results suggest the importance of promoting iron and zinc intake before and during pregnancy to reduce the incidence of preterm labor in Lanzhou City, Gansu Province, Northwest China. Future human studies will require data on maternal mineral intake, biomarkers, genetic and soil fac-

tors to confirm these findings and elucidate the underlying mechanisms.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors declare no conflict of interest.

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