Impact of maternal iron and zinc intake on low birth weight risk: a nested case—control study

Liping Yang[1,2,*], Zifu Wang[2,*], Lei Cao[2], Yuqing Li[2], Jingyan Wang[2], Shuyu Ding[2] and Baohong Mao[3]

[1] Department of Public Health and Infection Management, Gansu Provincial Hospital of Traditional Chinese Medicine, Gansu, Lanzhou, China
[2] School of Public Health, Gansu University of Chinese Medicine, Gansu, Lanzhou, China
[3] Department of Medical Education, Gansu Provincial Maternity and Child-care Hospital, Gansu, Lanzhou, China
[*] These authors contributed equally to this work.

ABSTRACT

Background. The association between maternal iron/zinc intake and the risk of low birth weight (LBW) in infants is still unclear. This study aimed to investigate the effects of iron and zinc daily intake preconception and during pregnancy on the risk of delivering LBW babies and to assess whether there is an interaction between iron and zinc intake on the risk of LBW.

Methods. A nested case–control study was performed, including 565 cases and 7,510 controls in Lanzhou City, China. Eligible participants were interviewed about their diets and characteristics during pregnancy. Unconditional logistic regression was used to determine the association between dietary iron/zinc intake and the risk of LBW and its clinical subtypes. Multivariate-adjusted restricted cubic spline (RCS) models were applied to explore the nonlinear association between dietary iron/zinc intake levels and the risk of LBW.

Results. Lower intake of iron/zinc preconception and during pregnancy was associated with a higher risk of LBW and some subtypes, and there was a nonlinear trend between iron/zinc intake and the occurrence risk of LBW ($P_{Nonlinear} < 0.05$). Moreover, the synergistic effects of low iron and low zinc intake on the risk of LBW were found.

Conclusion. Efforts to promote iron and zinc intake preconception and during pregnancy need to be strengthened to reduce the local incidence of LBW.

Subjects Gynecology and Obstetrics, Nutrition, Pediatrics, Public Health, Healthcare Services
Keywords Maternal, Iron, Zinc, Intake, Low-birth-weight, Risk

INTRODUCTION

According to the World Health Organization (WHO) criterion (*De Costa et al., 2021*), low-birth-weight (LBW) infants are defined as newborns weighing less than 2,500 g in the first hour after birth, independent of gestational age. Because of immature development and many complications, LBW is closely related to neonatal death, developmental delays, and long-term chronic diseases in offspring (*Shinzawa et al., 2019*). Studies have shown that LBW accounts for 15–20% of all live births and more than 80% of all neonatal deaths

worldwide; it is still an important public health indicator for assessing the health of infants and young children (*Blencowe et al., 2019*). The overall prevalence of LBW of Chinese children younger than 6 years was 5.15% in 2013, with 4.57% in boys and 5.68% in girls (*Shen et al., 2021*). However, the potential mechanisms for LBW remain unclear. Therefore, identifying modifiable risk factors to provide evidence for the primary prevention of LBW is particularly meaningful.

Maternal nutritional status during pregnancy is an important modifiable factor associated with their health and affects the next generation's growth and development. Adequate nutrition particularly important for the growth, development, and maintenance of normal physiological functions in LBW infants is mainly obtained from the diet. Micronutrient deficiency occurs if the body has insufficient reserves preconception and insufficient supplies after pregnancy. The main function of trace element iron is to transport oxygen and carbon dioxide, participate in tissue respiration, and promote biological redox reactions (*Berggren et al., 2015*; *Tussing-Humphreys et al., 2012*). Zinc is the second most abundant trace element in the body after iron; it is especially abundant in the liver, kidney, retina, bone, and muscle tissue and fluid, and is involved in the regulation of cell function and vitamin A metabolism in the body (*Dusek, Jankovic & Le, 2012*). Zinc deficiency in fetuses can lead to growth restriction and sexual organ dysfunction (*Khoushabi et al., 2016*).

In recent years, the scientific community has been widely concerned about the biological effects of various trace elements during pregnancy and their relationship with the origin of life, heredity, growth and development, congenital disabilities, and other maternal and infant health outcomes. However, available studies on the relationship between iron or zinc intake during pregnancy and LBW have not systematically covered the period preconception and the entire pregnancy (*Chang, Li & Xu, 2018*; *Siyoum & Melese, 2019*; *Palma et al., 2008*; *Yadav et al., 2020*; *Imdad & Bhutta, 2012*; *Haider et al., 2013*; *Cogswell et al., 2003*; *Peña Rosas et al., 2015*; *Bánhidy et al., 2011*; *Negandhi et al., 2014*; *Iannotti et al., 2008*; *Xie, Chen & Pan, 2001*; *Goldenberg et al., 1995*; *Zahiri Sorouri, Sadeghi & Pourmarzi, 2016*; *Osendarp et al., 2000*; *Carducci, Keats & Bhutta, 2021*; *Warthon-Medina et al., 2015*). Some of the studies that have assessed total iron/zinc intake did not separately model the relationships between iron/zinc from food and that from dietary supplements. Moreover, previous studies have not considered the synergistic effects of iron and zinc intake on the risk of LBW. Therefore, this study aimed to investigate the effects of iron and zinc daily intake preconception and during pregnancy on the risk of delivering LBW babies and to assess whether there is an interaction between iron and zinc intake on the risk of LBW.

MATERIALS & METHODS

Study population

A birth cohort study was conducted from January 2018 to June 2019 at Gansu Provincial Maternity and Child Care Hospital, the largest hospital of its kind in Lanzhou City, China. Eligible study participants were pregnant women with no history of mental illness, 18 years old or older, and those who had regular prenatal care. Written informed consent was obtained from all participants. A total of 8,879 eligible women were approached for

participation. After removing the missing information on neonatal weight and dietary survey during pregnancy, stillbirth, and multiple births, a total of 8,673 pregnant women with single live births were finally included. Among them, 7,510 women had normal-birth-weight (NBW) infants, 565 had LBW infants, and 598 had macrosomic infants. The Institutional Review Board of Gansu Provincial Maternity and Child Care Hospital approved this study [No. 2018(029)].

Dietary surveys, iron, and zinc daily intake

Daily surveys and dietary iron and zinc intake were collected through a face-to-face semiquantitative food frequency questionnaire (FFQ) (*Liu et al., 2016*). The survey included sociological characteristics, disease history, physiological fertility, and dietary survey. The dietary status was investigated by a 24-h dietary recall survey administered by trained medical staff. The types and quantities of all kinds of food consumed in three consecutive days were investigated, which mainly included 12 categories of cereals, oils and fats, vegetables, fruits, poultry, livestock meat and its products, eggs, aquatic products, beans and soy products, milk and milk products, fungi and algae, snacks and drinks, and other 59 kinds of common food.

This study is a nested case-control study based on the previous birth cohort. The dietary nutrition survey for each research subject was conducted four times. The first time was during the preconception consultation and health check-up within 3 months preconception, after obtaining informed consent, a preconception dietary nutrition survey was conducted. The second time was during the first trimester ($\leq$ 13 weeks of gestation) when going for prenatal check-ups at the hospital. The third and fourth times were during the second trimester (14–27 weeks of gestation) and the third trimester ($\geq$ 28 weeks of gestation) when going for prenatal check-ups at the hospital again, respectively. After completing all dietary surveys, the daily intake of dietary vitamins and trace elements of each pregnant woman during different pregnancies was calculated following the second edition of the Chinese Food Composition Table 2009 (*Yang, Wang & Pan, 2009*). Daily vitamin and trace element intakes in different pregnancies were divided into groups based on the recommended nutrient intake (RNI) of Chinese residents (*National Health Commission of the People's Republic of China, 2017*) for statistical analysis. The RNI is the amount of a nutrient that is enough to ensure that the needs of 97.5% of the population are met. Data on pregnancy-related complications and birth outcomes were extracted from medical records.

LBW

LBW infants (*World Health Organization, 2004*), defined as newborns weighing less than 2,500 g in the first hour after birth, were included in the case group, while infants with body weight greater than or equal to 2,500 g and lower than 4,000 g were defined as NBW infants and were included in the control group for analyses. LBW infants were further classified as preterm LBW infants (defined as newborns weighing less than 2,500 g in the first hour after birth and gestational age below 37 weeks) and term LBW infants (defined as newborns weighing less than 2,500 g in the first hour after birth and gestational age of more than or equal to 37 weeks).

Body mass index and gestational weight gain

Preconception weight was self-reported during the first prenatal care visit. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m), and then subcategorized in accordance with the Working Group of Obesity in China as follows: underweight (BMI <18.5 kg/m^2), normal weight (18.5 kg/m$^2 \leq$ BMI <24 kg/m^2), overweight (24 kg/m$^2 \leq$ BMI <28 kg/m^2), and obesity (BMI $\geq$ 28 kg/m^2). Gestational weight gain in kg was calculated by subtracting preconception weight from maternal weight at delivery, which was categorized based on the US Institute of Medicine (IOM) GWG Guidelines 2009 (*Rasmussen, Yaktine & Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines, 2009*).

Covariates

The study covariates were as follows: maternal age, preconception BMI (kg/m^2), weight gain during pregnancy (kg), father's BMI (kg/m^2), total energy intake (kcal/d), dietary iron intake (mg/d), dietary zinc intake (mg/d), maternal ethnicity (Han/Minority), monthly income (<3,000 RMB per capita/$\geq$3,000 RMB per capita), maternal education level (college or above/below college), smoking include passive and active (passive smoking exposure was operationally defined as inhaling secondhand smoke from others' tobacco products for a minimum of 15 min daily) (Yes/No), maternal employ (Yes/No), multivitamin supplement (Yes/No), gestational hypertension (Yes/No), history of premature birth (Yes/No), reproductive history (Yes/No).

Statistical analysis

Portions of this text were previously published as part of a preprint (*Huang et al., 2024*). Comparisons of the selected characteristics between women with LBW and NBW were evaluated using the chi-square test or Fisher's exact test. The differences in measurement data between the two groups were analyzed by independent-sample t test, and the variables that did not meet the normal distribution were compared between groups by the Wilcoxon rank-sum test. Unconditional logistic regression was used to determine the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between dietary iron and zinc intake and the risk of LBW and its clinical subtypes (preterm LBW and term LBW). Confounding factors, including weight gain during pregnancy, father's BMI, total energy intake, monthly income per capita, maternal education level, smoking, maternal employment, multivitamin supplementation, gestational hypertension, history of premature birth, and reproductive history, were adjusted for in the unconditional logistic regression models. Dietary iron and zinc intake were categorized into quartiles, and the dose–response relationship (*P* for trend) was calculated based on those categorical levels. The association between dietary iron/zinc intake levels and the risk of LBW may result in a nonlinear correlation. Multivariate-adjusted restricted cubic spline (RCS) models with three knots were applied to explore the nonlinear association. The number of knots was determined by comparing the criteria between Bayesian and Akaike information. The RCS models were adjusted for the potential confounding factors listed above. The multiplicative interaction parameters (OR = OR11/(OR01× OR10)) and 95% CI were also estimated

by including the abovementioned variables. The interactions on the additive scale were assessed using relative excess risk due to interaction ($RERI = RR11 - RR10 - RR01 + 1$), attributable proportion ($AP = RERI/RR11$), and synergy index [$S = (RR11 - 1)/[(RR01 - 1) + (RR10 - 1)$] (*Andersson et al., 2005*). We estimated 95% CI for each of these measures; the null values of relative excess risk due to interaction (RERI) and attributable proportion (AP) were 0, whereas the null value for S was 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 'Hmisc', 'rms', and 'survival').

RESULTS

Basic characteristics of the study population

A total of 8,673 women were eligible for the final analysis. Among them, 565 had LBW infants, comprising 126 term LBW and 439 preterm LBW infants. As illustrated in Table 1, compared with women who had NBW infants, mothers of LBW infants were more likely to have lower monthly income, lower education level, less maternal employment, higher proportion of gestational hypertension, history of premature birth, and reproductive history. Moreover, case mothers had a significantly lower weight gain during pregnancy, lower total energy intake, fewer multivitamin supplements, and lower dietary iron and zinc intake. Distribution of the maternal ethnicity, drinking during pregnancy, gestational diabetes, anemia during pregnancy, and history of miscarriage did not significantly differ between the two groups.

Associations of maternal dietary iron intake with the odds of LBW

As shown in Table 2, demonstrates a dose–response relationship between prepregnancy dietary iron intake and low birth weight (LBW) odds. Compared with quartile 4 (highest intake reference group), the adjusted odds ratios (95% confidence intervals) for LBW were: 1.33 (0.98−1.79) for quartile 3, 1.20 (1.03−1.41) for quartile 2 and 1.14 (1.02−1.27) for quartile 1 (lowest intake group), and the test for trend was significant ($P = 0.006$). Quartile 1 and quartile 2 of iron intake showed a significantly higher risk of preterm LBW compared with the highest quartile, and the test for trend was significant ($P = 0.007$). After stratifying by periods of pregnancy, an increased risk of LBW was observed for quartile 1 and quartile 2 compared with quartile 4, first trimester 1.16 (1.01−1.32) and 1.21 (1.02−1.41), Second trimester 1.18 (1.03−1.37) and 1.21 (1.03−1.44), Third trimester 1.17 (1.02−1.34) and 1.28 (1.08−1.52), and the test for trend was significant ($P_{\text{first trimester}} = 0.007$, $P_{\text{second trimester}} = 0.004$, and $P_{\text{third trimester}} = 0.007$). Similarly, the increased risk of preterm LBW was observed for quartile 1 and quartile 2 compared with quartile four preconception and stratifying by periods of the trimester of pregnancy. In addition, an increased risk of term LBW was only observed for quartile 1 compared with quartile four during the second trimester.

Mothers with iron intake below RNI had a significantly higher risk of LBW and preterm LBW preconception, during pregnancy, during the first trimester, and during the second trimester. Specifically, the adjusted OR for LBW was 1.26 (1.03–1.54), 1.13 (1.01–1.27), 1.25 (1.02–1.55), and 1.29 (1.04–1.60), while that for preterm LBW was 1.35 (1.08–1.69),

Table 1 Distributions of selected characteristics of the study population.

Characteristics	NBW ($n = 7,510$)	LBW ($n = 565$)	P-value
Maternal age	28.55 ± 4.20	28.53 ± 5.26	0.944
Preconception BMI (kg/m^2)	20.57 ± 2.65	20.80 ± 3.01	0.084
Weight gain during pregnancy (kg)	17.08 ± 5.29	13.55 ± 5.93	<0.001
Father's BMI (kg/m^2)	23.84 ± 3.08	23.33 ± 3.16	<0.001
Total energy intake (kcal/d)	1,686 (1,440, 1,970)	1,537 (1,240, 1,843)	<0.001
Dietary iron intake (mg/d)	24.24 (19.59, 30.46)	21.74 (17.29, 27.19)	<0.001
Dietary zinc intake (mg/d)	8.40 (6.71, 10.39)	7.17 (5.19, 9.37)	<0.001
Maternal ethnicity			0.051
Han	6,914 (92.06)	507 (89.73)	
Minority	596 (7.94)	58 (10.27)	
Monthly income (RMB per capita)	$2,996 \pm 1,372$	$2,433 \pm 1,334$	<0.001
Maternal education level			<0.001
<College	4,512 (60.08)	447 (79.11)	
$\geq$ College	2,998 (39.92)	118 (20.89)	
Smoking (passive and active)			0.002
No	6,013 (80.07)	421 (74.51)	
Yes	1,497 (19.93)	144 (25.49)	
Drink during pregnancy			0.235[*]
No	7,499 (99.85)	563 (99.64)	
Yes	11 (0.15)	2 (0.36)	
Maternal employ			<0.001
No	3,348 (44.58)	332 (58.76)	
Yes	4,162 (55.42)	233 (41.24)	
Multivitamin supplement			<0.001
No	1,436 (19.12)	191 (33.80)	
Yes	6,074 (80.88)	374 (66.20)	
Gestational diabetes			0.503[*]
No	7,451 (99.21)	562 (99.47)	
Yes	59 (0.79)	3 (0.53)	
Gestational hypertension			<0.001
No	7,241 (96.42)	444 (78.58)	
Yes	269 (3.58)	121 (21.42)	
Anemia during pregnancy			0.803
No	6,698 (89.19)	502 (88.85)	
Yes	812 (10.81)	63 (11.15)	
History of miscarriage			0.535
No	6,477 (86.24)	482 (85.31)	
Yes	1,033 (13.76)	83 (14.69)	
History of premature birth			<0.001
No	7,473 (99.51)	537 (95.04)	
Yes	37 (0.49)	28 (4.96)	

Table 1 (*continued*)

Characteristics	NBW ($n = 7,510$)	LBW ($n = 565$)	P-value
Reproductive history			<0.001
Primipara	5,632 (74.99)	343 (60.71)	
Multiparous	1,878 (25.01)	222 (39.29)	
Newborn's sex			0.053
Male	3,893 (51.84)	269 (47.61)	
Female	3,617 (48.16)	296 (52.39)	

Notes.
*Fisher exact test.

1.14 (1.01–1.30), 1.27 (1.00–1.60), 1.28 (1.01–1.64), and 1.35 (1.02–1.80), respectively. However, no significant associations of iron intake below RNI with LBW and term LBW were observed for the third trimester (Table 3).

Figure 1 shows the RCS curves for the associations between iron intake and the risk of LBW preconception and during pregnancy. As the daily dietary iron intake increases, the risk of LBW decreases rapidly and then gradually increases. In the third trimester, when the intake is below 24.27 mg/d, the risk of LBW increases. When the intake is between 24.27 mg/d and 61.68 mg/d, iron intake is a protective factor for LBW occurrence. When the intake is greater than 61.68 mg/d, the risk of LBW increases. Similar results were obtained in preconception, first trimester and second trimester. respectively ($P_{\text{Nonlinear}}$ <0.05).

Associations of maternal dietary zinc intake with the odds of LBW

As shown in Table 4, there was a positive relationship between zinc intake and the risk of LBW. Compared with quartile 4 (highest) and quartile 1 (lowest) of dietary zinc intake during pregnancy and at the third trimester, the adjusted OR for LBW was 1.22 (1.01–1.46) and 1.20 (1.01–1.43), respectively, and the test for trend was significant for both ($P < 0.001$). Additionally, in quartile 1 of zinc intake during pregnancy, the second and third trimesters showed a significantly higher preterm LBW risk than in quartile 4, and the trend test was significant. However, no significant association was observed between zinc intake and term LBW either preconception or when stratifying by the trimesters of pregnancy. There was no relationship between zinc intake below RNI and the risk of LBW, preterm LBW, and term LBW (Table 5).

Figure 2 depicts the RCS curves for the associations between zinc intake and the risk of LBW preconception and during pregnancy. As the daily dietary zinc intake increases, the risk of LBW decreases rapidly and gradually levels off. In the third trimester, when the intake is less than 8.37 mg/d, the risk of LBW increases. When the intake is between 8.37 mg/d and 41.63 mg/d, zinc intake is a protective factor for LBW. When the intake is greater than 41.63 mg/d, the risk of LBW increases. Similar results were obtained in preconception, the first trimester, and the second trimester. respectively ($P_{\text{Nonlinear}}$ <0.05).

Interaction effects of maternal dietary iron and zinc intake on the odds of LBW

We further analyzed the interaction effects of maternal dietary iron and zinc intake on the risk of LBW. An additive interaction between low iron and zinc dietary intake and LBW

Table 2 Associations of maternal dietary iron intake with the odds of LBW.

Dietary iron intake (mg/d)	NBW (7,510)	LBW (n = 565)					Term-LBW (37≥weeks)			Preterm-LBW (<37 weeks)		
		Cases	OR[a] (95% CI)	P-value	OR[b] (95% CI)	P-value	Cases	OR[b] (95% CI)	P-value	Cases	OR[b] (95% CI)	P-value
Preconception												
Q1 <15.98	1,878	182	1.21 (1.12–1.32)	<0.001[**]	1.14 (1.02–1.27)	0.019[*]	37	1.01 (0.81–1.26)	0.930	145	1.15 (1.02–1.30)	0.024[*]
Q2 15.98–20.16	1,877	154	1.23 (1.08–1.40)	<0.001[**]	1.20 (1.03–1.41)	0.023[*]	33	1.11 (0.82–1.50)	0.498	121	1.23 (1.04–1.47)	0.019[*]
Q3 20.16–25.77	1,878	127	1.24 (0.95–1.63)	0.110	1.33 (0.98–1.79)	0.064	32	1.42 (0.79–2.52)	0.236	95	1.27 (0.90–1.79)	0.177
Q4 ≥25.77	1,877	102	Ref.		Ref.		24	Ref.		78	Ref.	
P for trend			<0.001		0.006			0.785			0.007	
During pregnancy												
Q1 <19.59	1,878	213	1.28 (1.18–1.40)	<0.001[**]	1.20 (1.05–1.37)	0.007[**]	46	1.26 (0.97–1.64)	0.084	167	1.18 (1.01–1.37)	0.033[*]
Q2 19.59–24.24	1,877	140	1.18 (1.05–1.33)	0.009[**]	1.18 (1.00–1.40)	0.054	34	1.18 (0.86–1.62)	0.305	106	1.20 (0.99–1.45)	0.061
Q3 24.24–30.46	1,877	114	1.17 (0.90–1.52)	0.284	1.21 (0.88–1.66)	0.239	22	0.96 (0.51–1.81)	0.899	92	1.28 (0.90–1.83)	0.173
Q4 ≥ 30.46	1,878	98	Ref.		Ref.		24	Ref.		74	Ref.	
P for trend			<0.001		0.003			0.166			0.005	
First trimester												
Q1 <18.94	1,878	205	1.27 (1.17–1.38)	<0.001[**]	1.16 (1.01–1.32)	0.030[*]	46	1.24 (0.92–1.67)	0.157	159	1.15 (1.01–1.33)	0.046[*]
Q2 18.94–23.64	1,877	150	1.22 (1.07–1.39)	0.003[**]	1.21 (1.02–1.41)	0.021[*]	38	1.16 (0.91–1.48)	0.232	112	1.21 (1.00–1.45)	0.044[*]
Q3 23.64–29.52	1,877	109	1.08 (0.82–1.43)	0.589	1.07 (0.78–1.46)	0.423	17	0.70 (0.36-1.37)	0.295	92	1.19 (0.84–1.69)	0.330
Q4 ≥29.52	1,878	101	Ref.		Ref.		25	Ref.		76	Ref.	
P for trend			<0.001		0.007			0.086			0.017	
Second trimester												
Q1 <19.67	1,878	209	1.30 (1.19–1.41)	<0.001[**]	1.18 (1.03–1.37)	0.024[*]	45	1.35 (1.02–1.77)[*]	0.033[*]	164	1.19 (1.02–1.38)	0.024[*]
Q2 19.67–24.46	1,877	143	1.23 (1.07–1.40)	0.003[**]	1.21 (1.03–1.44)	0.026[*]	34	1.27 (0.91–1.76)	0.156	109	1.21 (1.01–1.47)	0.046[*]
Q3 24.46–30.79	1,877	118	1.24 (0.94–1.64)	0.125	1.23 (0.90–1.71)	0.206	26	1.35 (0.72-2.55)	0.352	92	1.20 (0.85–1.72)	0.310
Q4 ≥30.79	1,878	95	Ref.		Ref.		21	Ref.		74	Ref.	
P for trend			<0.001		0.004			0.141			0.006	
Third trimester												
Q1 <19.78	1,877	218	1.32 (1.22–1.44)	<0.001[**]	1.17 (1.02–1.34)	0.024[*]	44	1.26 (0.97–1.64)	0.084	174	1.19 (1.02–1.38)	0.024[*]
Q2 19.78–24.54	1,878	137	1.21 (1.05–1.38)	0.006[**]	1.28 (1.08–1.52)	0.005[**]	38	1.34 (0.98–1.84)	0.069	99	1.27 (1.05–1.55)	0.016[*]
Q3 24.54–30.91	1,878	116	1.23 (0.93–1.63)	0.141	1.27 (0.92–1.74)	0.142	21	0.94 (0.49–1.81)	0.853	95	1.38 (0.97–1.97)	0.075
Q4 ≥30.91	1,877	94	Ref.		Ref.		23	Ref.		71	Ref.	
P for trend			<0.001		<0.001			0.136			0.001	

Notes.
[a]OR[a] univariate analyses.
[b]OR[b] adjusted for weight gain during pregnancy, father's BMI, total energy intake, monthly income per capita, maternal education level, smoking, maternal employ, multivitamin supplement, gestational hypertension, history of premature birth, reproductive history and dietary zinc intake.
[**]P-value < 0.01.
[*]P-value < 0.05.

during pregnancy was observed. The synergy index was 2.11 ($S = 2.11$; 95% CI [1.12–3.95]) during pregnancy; the relative excess risk ratio attributable to additive interaction was 0.97 ($RERI = 0.97$; 95% CI [0.34–1.60]); and 34% ($AP = 0.34$; 95% CI [0.14–0.54]) of the LBW risk was attributable to the interaction of low maternal dietary iron and zinc intake. At the same time, there was a multiplicative interaction between low dietary iron intake and low dietary zinc intake during pregnancy ($OR = 1.82$; 95% CI [1.45–2.29]). Similar findings were obtained after stratifying by the trimesters of pregnancy (Table 6).

Table 3 Maternal dietary iron intake categorized by RNIs and the odds of LBW.

Dietary iron intake (mg/d)	NBW (7,510)	LBW (n = 565)					Term-LBW (37≥weeks)			Preterm-LBW (<37 weeks)		
		Cases	OR[a] (95% CI)	P-value	OR[b] (95% CI)	P-value	Cases	OR[b] (95% CI)	P-value	Cases	OR[b] (95% CI)	P-value
Preconception												
Met the RNI	3,829	233	Ref.		Ref.		57	Ref.		176	Ref.	
Below the RNI	3,681	332	1.48 (1.25–1.76)	<0.001**	1.26 (1.03–1.54)	0.024*	69	1.06 (0.72–1.57)	0.770	263	1.35 (1.08–1.69)	0.009**
During pregnancy												
Met all the RNI	2,199	118	Ref.		Ref.		29	Ref.		89	Ref.	
Below 1 trimester	1,697	99	1.09 (0.83–1.43)	0.535	1.08 (0.79–1.47)	0.627	19	0.87 (0.45–1.66)	0.676	80	1.22 (0.86–1.73)	0.263
Below 2 trimester	1,428	114	1.22 (1.07–1.39)	0.003**	1.19 (1.01–1.41)	0.041*	23	1.12 (0.81–1.55)	0.497	91	1.23 (1.02–1.48)	0.029*
Below 3 trimester	2,186	234	1.26 (1.17–1.36)	<0.001**	1.13 (1.01–1.27)	0.037*	55	1.16 (0.93–1.45)	0.190	179	1.14 (1.01–1.30)	0.041*
First trimester												
Met the RNI	5,203	320	Ref.		Ref.		69	Ref.		251	Ref.	
Below the RNI	2,307	245	1.73 (1.45–2.05)	<0.001**	1.25 (1.02–1.55)	0.037*	57	1.44 (0.96–2.17)	0.078	188	1.27 (1.00–1.60)	0.047*
Second trimester												
Met the RNI	3,937	226	Ref.		Ref.		49	Ref.		177	Ref.	
Below the RNI	3,573	339	1.65 (1.39–1.97)	<0.001**	1.29 (1.04–1.60)	0.020*	77	1.40 (0.92–2.14)	0.118	262	1.28 (1.01–1.64)	0.046*
Third trimester												
Met the RNI	2,279	120	Ref.		Ref.		30	Ref.		90	Ref.	
Below the RNI	5,231	445	1.62 (1.32–1.99)	<0.001**	1.27 (0.98–1.63)	0.066	96	1.09 (0.67–1.78)	0.729	349	1.35 (1.02–1.80)	0.038*

Notes.

[a] OR[a] univariate analyses.

[b] OR[b] adjusted for weight gain during pregnancy, father's BMI, total energy intake, monthly income per capita, maternal education level, smoking, maternal employ, multivitamin supplement, gestational hypertension, history of premature birth, reproductive history and dietary zinc intake.

** P-value < 0.01.

* P-value < 0.05.

DISCUSSION

Pregnancy is a critical period for both the short- and long-term health effects of mothers and infants. To meet the needs of their own and fetal growth and development during pregnancy, pregnant women have an increased demand for various nutrients. However, in developing countries, women tend to pay more attention to the intake of macronutrients such as protein during pregnancy than some trace elements, increasing the risk of LBW (*Haider & Bhutta, 2017*; *Parodi et al., 2018*). It has been shown (*Guilbert, 2003*; *Prasad, 2003*) that more than 2 billion people worldwide are iron-deficient, and billions more are exposed to zinc deficiency, the vast majority of which occur in developing countries. Causes of micronutrient deficiencies include inadequate intake, poor absorption, impaired utilization, excessive loss, increased physiological requirements, or a combination of these factors. Inadequate intake could be the main cause of deficiency in developing countries (*Gibson, 2006*). A nutritional survey of pregnant women in western China implied (*Mao et al., 2020*) that the deficiency ratio of dietary iron, zinc, iodine, copper, and selenium was higher during pregnancy (*P* < 0.05). Iron plays a critical role in energy metabolism, regulation of DNA synthesis, cell proliferation and differentiation, and oxygen transport. Nearly half of pregnant women in the second and third trimesters consume less than their average dietary iron requirements (estimated average requirement, EAR). Iron
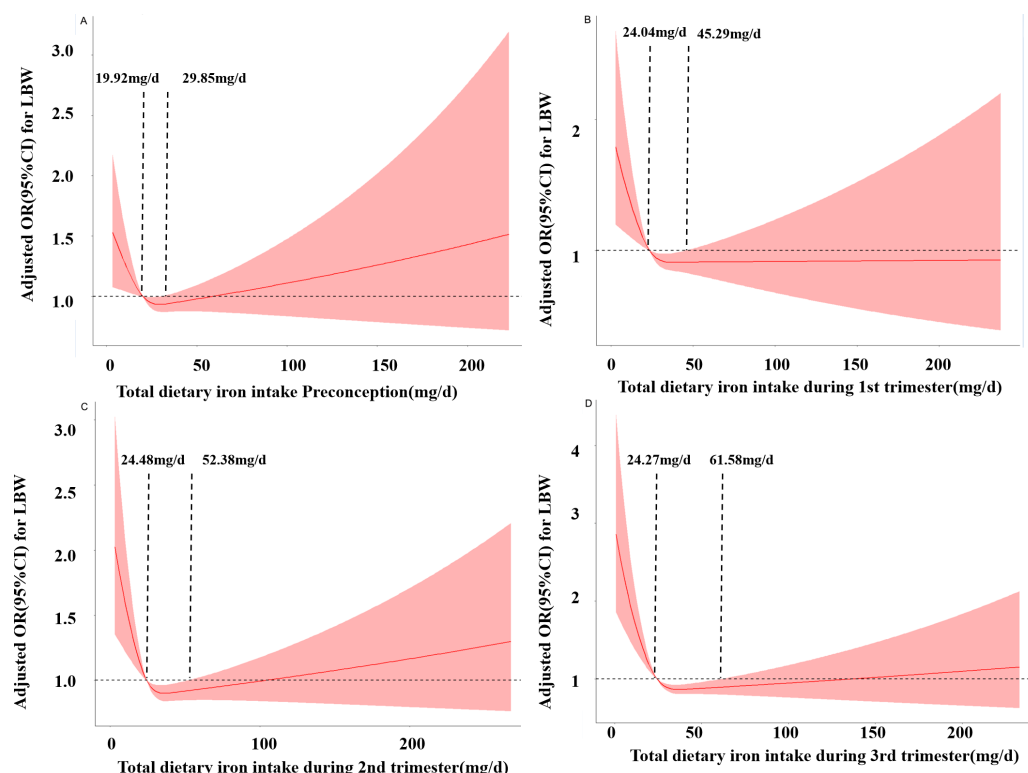
Figure 1 Restricted cubic spline models of LBW odds associated with iron intake preconception (A), at the first trimester (B), at the second trimester (C), and at the third trimester (D).

Full-size 🖼 DOI: 10.7717/peerj.19896/fig-1

absorption during pregnancy is a complex process and generally increases with the increase of gestational age. The incidence of iron deficiency anemia is high in women during pregnancy, with the highest prevalence in the second and third trimesters. Therefore, the WHO recommends iron supplementation during pregnancy to prevent birth related adverse outcomes in the future (*Rahman et al., 2021*). While prenatal iron supplementation has a beneficial effect on women with anemia, it has a controversial effect on women without anemia (*Ribot et al., 2012*); namely, in women with normal hemoglobin levels during pregnancy, daily iron supplementation may be harmful to fetal growth (*Aranda et al., 2013*). A cohort study (*Shastri et al., 2015*) revealed that women with the highest dose (>39.2 mg/day) of supplemental iron intake had an increased risk of term LBW compared with those with the lowest dose (≤36.6 mg/day) (RR = 1.89; 95% CI [1.26–2.83]). Pregnant women should not take iron supplementation if their hemoglobin levels exceed 110 g/L during the first and third trimesters and 105 g/L during the second trimester. Excessive or insufficient dietary iron in mothers can both increase the risk of low birth weight. Excessive iron can lead to endocrine disorders, such as hypothyroidism, elevated HbA1c levels and decreased adrenocorticotropic hormone levels, thereby affecting bone health (*Chen et al., 2024*; *Yang et al., 2020*). In plant-based diets, iron exists in the form of inorganic non-haem iron, which is less bioavailable than haem iron from animal foods sources, and this results in lower total iron absorption from vegetarian diets (*Hurrell & Egli, 2010*). Studies have

Table 4 Associations of maternal dietary zinc intake with the odds of LBW.

Dietary zinc intake (mg/d)	NBW (7,510)	LBW (n = 565)					Term-LBW (37≥weeks)			Preterm-LBW (<37 weeks)		
		Cases	OR[a] (95% CI)	P-value	OR[c] (95% CI)	P-value	Cases	OR[c] (95% CI)	P-value	Cases	OR[c] (95% CI)	P-value
Preconception												
Q1 <5.34	1,878	232	1.29 (1.20–1.40)	<0.001[**]	1.05 (0.95–1.17)	0.360	47	0.93 (0.76–1.14)	0.483	185	1.08 (0.96–1.22)	0.208
Q2 5.34–6.79	1,877	123	1.07 (0.94–1.23)	0.306	0.96 (0.82–1.13)	0.617	31	0.81 (0.60–1.08)	0.160	92	0.98 (0.82–1.17)	0.824
Q3 6.79–8.52	1,878	103	0.96 (0.73–1.27)	0.785	0.98 (0.72–1.33)	0.900	19	0.64 (0.35–1.17)	0.147	84	1.02 (0.73–1.43)	0.115
Q4 ≥ 8.52	1,877	107	Ref.		Ref.		29	Ref.		78	Ref.	
P for trend			<0.001		0.019			0.975			0.005	
During pregnancy												
Q1 <6.71	1,877	243	1.39 (1.27–1.51)	<0.001[**]	1.22 (1.01–1.46)	0.034[*]	51	0.92 (0.64–1.33)	0.654	192	1.34 (1.09–1.63)	0.004[**]
Q2 6.71–8.40	1,878	140	1.15 (1.05–1.26)	0.002[**]	1.10 (0.91–1.32)	0.315	29	0.81 (0.52–1.24)	0.342	111	1.09 (0.88–1.34)	0.442
Q3 8.40–10.39	1,877	90	0.88 (0.79–1.02)	0.888	0.93 (0.67–1.28)	0.661	22	0.88 (0.47–1.65)	0.689	68	0.94 (0.65–1.36)	0.742
Q4 ≥ 10.39	1,878	92	Ref.		Ref.		24	Ref.		68	Ref.	
P for trend			<0.001		<0.001			0.658			<0.001	
First trimester												
Q1 <6.46	1,877	231	1.34 (1.23–1.45)	<0.001[**]	1.02 (0.85–1.17)	0.808	47	0.81 (0.59–1.10)	0.185	184	1.21 (0.99–1.48)	0.063
Q2 6.46–8.13	1,878	137	1.19 (1.04–1.36)	0.012[*]	1.11 (0.93–1.33)	0.253	31	0.80 (0.55–1.19)	0.257	106	1.07 (0.89–1.27)	0.456
Q3 8.13–10.09	1,878	100	1.03 (0.77–1.37)	0.838	0.91 (0.67–1.24)	0.547	23	0.83 (0.44–1.54)	0.56	77	0.94 (0.66–1.34)	0.732
Q4 ≥ 10.09	1,877	97	Ref.		Ref.		25	Ref.		72	Ref.	
P for trend			<0.001		0.055			0.855			0.002	
Second trimester												
Q1 <6.76	1,877	244	1.38 (1.27–1.49)	<0.001[**]	1.14 (0.95–1.37)	0.160	50	0.95 (0.67–1.34)	0.772	194	1.24 (1.01–1.51)	0.036[*]
Q2 6.76–8.50	1,878	135	1.20 (1.05–1.37)	0.009[**]	1.07 (0.90–1.28)	0.451	28	0.82 (0.54–1.25)	0.354	107	1.12 (0.92–1.37)	0.264
Q3 8.50–10.57	1,877	92	0.98 (0.73–1.32)	0.889	0.93 (0.68–1.29)	0.656	24	0.91 (0.49–1.69)	0.764	68	0.94 (0.65–1.35)	0.740
Q4 ≥ 10.57	1,878	94	Ref.		Ref.		24	Ref.		70	Ref.	
P for trend			<0.001		0.002			0.866			<0.001	
Third trimester												
Q1 <6.74	1,877	243	1.38 (1.27–1.50)	<0.001[**]	1.20 (1.01–1.43)	0.040[*]	50	0.99 (0.71–1.38)	0.952	193	1.28 (1.05–1.55)	0.013[*]
Q2 6.74–8.49	1,878	146	1.25 (1.10–1.43)	0.001[**]	1.15 (0.98–1.36)	0.094	31	0.92 (0.62–1.36)	0.678	115	1.21 (1.00–1.45)	0.044[*]
Q3 8.49–10.56	1,878	83	0.89 (0.66–1.21)	0.459	0.88 (0.64–1.23)	0.443	22	0.94 (0.50–1.75)	0.846	61	0.87 (0.60–1.26)	0.462
Q4 ≥ 10.56	1,877	93	Ref.		Ref.		23	Ref.		70	Ref.	
P for trend			<0.001		<0.001			0.511			<0.001	

Notes.

[a] OR[a] univariate analyses.

[c] OR[c] adjusted for weight gain during pregnancy, father's BMI, total energy intake, monthly income per capita, maternal education level, smoking, maternal employ, multivitamin supplement, gestational hypertension, history of premature birth, reproductive history and dietary iron intake.

[**] P-value < 0.01.

[*] P-value < 0.05.

shown that the bioavailability of iron can be enhanced by taking iron supplements orally, adjusting the diet, including increasing the intake of iron-rich foods such as meat, as well as through techniques like sprouting and fermentation (*Abbaspour, Hurrell & Kelishadi, 2014*).

Zinc is an essential trace element and is very important for the normal development of the fetus during pregnancy. Zinc deficiency has become a major nutritional and health problem worldwide (*Roohani et al., 2013*). Considering the differences in ethnicity, living

Yang et al. (2025), *PeerJ*, DOI 10.7717/peerj.19896

11/23

Table 5 Maternal dietary zinc intake categorized by RNIs and the odds of LBW.

Dietary zinc intake (mg/d)	NBW (7,510)	LBW (n = 565)					Term-LBW (37≥weeks)			Preterm-LBW (<37 weeks)		
		Cases	OR[a] (95% CI)	p-value	OR[c] (95% CI)	p-value	Cases	OR[c] (95% CI)	p-value	Cases	OR[c] (95% CI)	p-value
Preconception												
Met the RNI	2,818	158	Ref.		Ref.		37	Ref.		121	Ref.	
Below the RNI	4,692	407	1.44 (1.12–1.86)	<0.001[**]	1.11 (0.89–1.39)	0.362	89	0.97 (0.62–1.51)	0.382	318	1.20 (0.93–1.55)	0.162
During pregnancy												
Met all the RNI	2,120	110	Ref.		Ref.		28	Ref.		82	Ref.	
Below 1 trimester	519	30	1.11 (0.74–1.69)	0.624	1.00 (0.64–1.57)	1.000	8	0.94 (0.41–2.18)	0.884	22	1.02 (0.61–1.70)	0.940
Below 2 trimester	388	21	1.02 (0.80–1.30)	0.873	0.93 (0.71–1.22)	0.600	4	0.75 (0.42–1.34)	0.331	17	0.99 (0.73–1.33)	0.948
Below 3 trimester	4,483	404	1.20 (1.12–1.29)	<0.001[**]	1.01 (0.91–1.12)	0.850	86	0.85 (0.69–1.04)	0.121	318	1.08 (0.97–1.20)	0.156
First trimester												
Met the RNI	2,329	121	Ref.		Ref.		30	Ref.		91	Ref.	
Below the RNI	5,181	444	1.65 (1.34–2.03)	<0.001[**]	1.01 (0.77–1.32)	0.942	96	0.74 (0.43–1.27)	0.276	348	1.11 (0.82–1.51)	0.503
Second trimester												
Met the RNI	2,725	147	Ref.		Ref.		37	Ref.		110	Ref.	
Below the RNI	4,785	418	1.62 (1.33–1.96)	<0.001[**]	0.97 (0.74–1.27)	0.824	89	0.65 (0.39–1.12)	0.109	329	1.09 (0.81–1.47)	0.570
Third trimester												
Met the RNI	2,732	143	Ref.		Ref.		37	Ref.		106	Ref.	
Below the RNI	4,778	422	1.69 (1.39–2.05)	<0.001[**]	1.04 (0.80–1.36)	0.773	89	0.69 (0.41–1.16)	0.162	333	1.18 (0.88–1.59)	0.272

Notes.
[a]OR[a] univariate analyses.
[c]OR[c] adjusted for weight gain during pregnancy, father's BMI, total energy intake, monthly income per capita, maternal education level, smoking, maternal employ, multivitamin supplement, gestational hypertension, history of premature birth, reproductive history and dietary iron intake.
[**]P-value < 0.01.
[*]P-value < 0.05.

environment, eating habits, and economic status, zinc deficiency in mainland China shows regional variability, and zinc deficiency levels in different pregnancies are not all the same (*Liang et al., 2019*). Zinc is involved in maintaining many important physiological functions in the human body, such as promoting growth and development, enhancing immunity, and promoting wound healing. Zinc is involved in many processes, such as cells (*Grzeszczak, Kwiatkowski & Kosik-Bogacka, 2020*). Zinc-binding proteins and zinc transporters are involved in the distribution and transport of zinc in the body, and they regulate and maintain zinc homeostasis in the body through various mechanisms (*Baltaci & Yuce, 2018*). Zinc deficiency can decrease the activity of Cu–Zn superoxide dismutase (SOD) (*Abolbashari et al., 2018*) and increase serum homocysteine levels (*Jing et al., 2015*), which may be the pathological basis for LBW in childbirth. The absorption and bioavailability of zinc are influenced by many factors. The two main factors affecting zinc absorption are dietary zinc intake and phytates, which together account for more than 80% of the variation in zinc absorption (*Hambidge et al., 2010*). Because of the wide range of biological functions of zinc and its importance to human health, the WHO recommends using zinc-rich foods when adequate zinc intake is not possible in the general diet. Zinc can be obtained from various sources, including food, fortified foods and supplements. Taking zinc supplements is a convenient and effective option for treating zinc deficiency and maintaining healthy levels of zinc (*Devarshi et al., 2024*). Iron deficiency and zinc deficiency
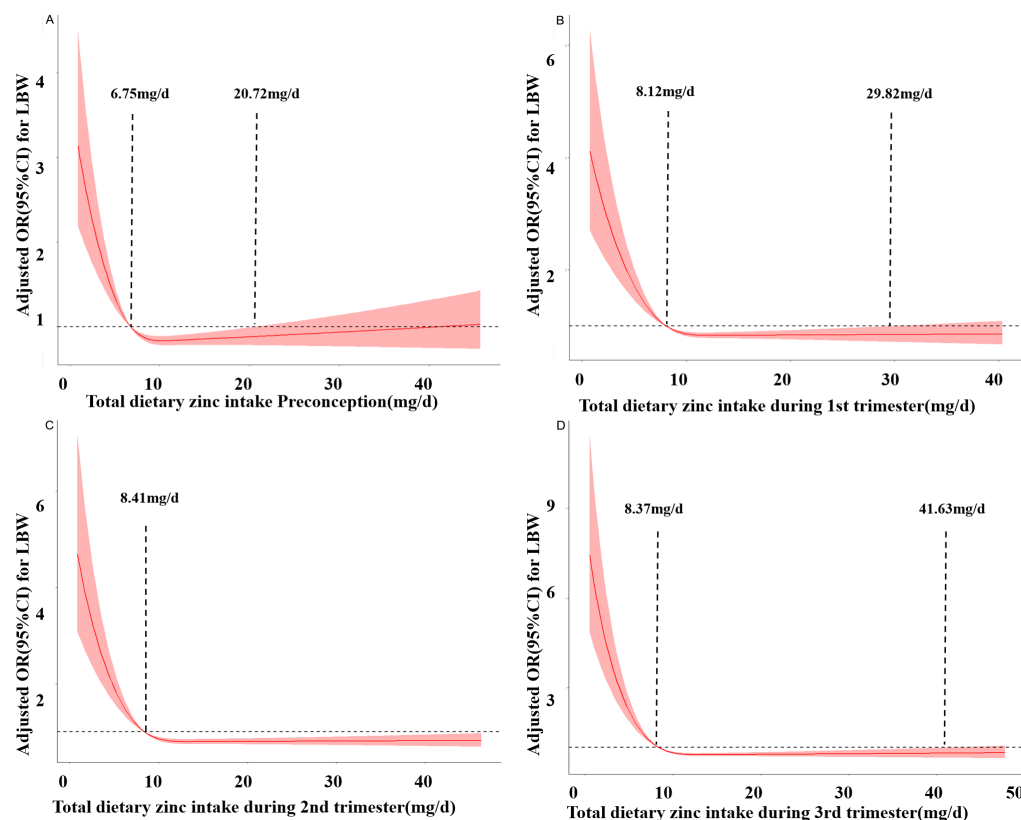
Figure 2 Restricted cubic spline models of LBW odds associated with zinc intake preconception (A), at the first trimester (B), at the second trimester (C), and at the third trimester (D).

Full-size 🖼 DOI: 10.7717/peerj.19896/fig-2

often occur together during pregnancy (*Nishiyama et al., 1999*). Combining iron and zinc supplementation in women with iron deficiency in early pregnancy could have more benefits than iron therapy alone. The recovery of serum ferritin in pregnant women is more effective when iron and zinc are combined 1:1 (*Saaka, Oosthuizen & Beatty, 2009*). The possible reason may be that zinc promotes the formation of IGF-1, which along with erythropoietin, is required for hematopoiesis (*Ten Have, van der Lely & Lamberts, 1997*). Additionally, it has been reported that iron loading reduces divalent metal transport-1 (DMT1) expression, resulting in reduced iron absorption. However, zinc can increase DMT1 mRNA expression (*Yamaji et al., 2001*), which may also be a potential mechanism for the interaction between dietary iron deficiency and zinc deficiency observed in this study. In this nested cohort study, we observed that women with low dietary iron intake preconception and during pregnancy had a significantly increased risk of delivering LBW infants, with a dose–response relationship, especially for preterm LBW infants. Similarly, significant inverse associations with LBW were found for lower dietary zinc intake during pregnancy. Moreover, the positive additive and multiplicative scale interactions between low dietary iron and zinc intake and LBW were observed preconception and during different trimesters of pregnancy. This is the first study that comprehensively examined

Table 6 Interaction effects of maternal dietary iron and zinc intake on the odds of LBW.

Maternal dietary intake	NBW/LBW	OR[a] (95% CI)	OR[d] (95% CI)
Preconception			
High iron and high zinc	4,142/227	Ref.	Ref.
High iron and low zinc	594/61	1.78 (1.29–1.59)	1.26 (0.90–1.77)
Low iron and high zinc	1,806/126	1.13 (1.01–1.26)	1.12 (1.00–1.28)
Low iron and low zinc	968/151	1.42 (1.32–1.53)	1.24 (1.13–1.36)

Multiplicative interaction: OR[d] (95% CI) = 1.72 (1.37–2.16), $P < 0.001$

Additive interaction: RERI (95% CI) = 0.70 (0.03–1.43), AP (95% CI) = 0.34 (0.01∼0.48),

S (95% CI) = 1.61 (0.91–2.84)

Maternal dietary intake	NBW/LBW	OR[a] (95% CI)	OR[d] (95% CI)
During pregnancy			
High iron and high zinc	4,003/204	Ref.	Ref.
High iron and low zinc	1,163/100	1.19 (0.88–1.61)	1.17 (0.85–1.62)
Low iron and high zinc	939/57	1.69 (1.32–2.16)	1.07 (0.90–1.27)
Low iron and low zinc	1,405/204	2.85 (2.33–3.49)	1.22 (1.09–1.37)

Multiplicative interaction: OR[d] (95% CI) = 1.82 (1.45–2.29), $P < 0.001$

Additive interaction: RERI (95% CI) = 0.97 (0.34–1.60), AP (95% CI) = 0.34 (0.14–0.54),

S (95% CI) = 2.11 (1.12–3.95)

Maternal dietary intake	NBW/LBW	OR[a] (95% CI)	OR[d] (95% CI)
First trimester			
High iron and high zinc	3,426/174	Ref.	Ref.
High iron and low zinc	977/78	1.57 (1.19–2.07)	1.06 (0.75–1.49)
Low iron and high zinc	1,234/77	1.11 (0.97–1.27)	1.08 (0.93–1.26)
Low iron and low zinc	1,873/236	1.35 (1.27–1.45)	1.10 (0.99–1.23)

Multiplicative interaction: OR[d] (95% CI) = 1.57 (1.26–1.96), $P < 0.001$

Additive interaction: RERI (95% CI) = 0.68 (0.11–1.25), AP (95% CI) = 0.27 (0.06–0.49),

S (95% CI) = 1.85 (0.94–3.64)

Maternal dietary intake	NBW/LBW	OR[a] (95% CI)	OR[d] (95% CI)
Second trimester			
High iron and high zinc	4,188/221	Ref.	Ref.
High iron and low zinc	1,067/96	1.71 (1.13–2.19)	1.06 (0.78–1.46)
Low iron and high zinc	955/60	1.09 (0.94–1.26)	1.02 (0.87–1.21)
Low iron and low zinc	1,300/188	1.40 (1.31–1.50)	1.20 (1.08–1.34)

Multiplicative interaction: OR[d] (95% CI) = 1.74 (1.39–2.19), $P < 0.001$

Additive interaction: RERI (95% CI) = 0.85 (0.21–1.48), AP (95% CI) = 0.31 (0.10–0.52),

S (95% CI) = 1.94 (1.04–3.62)

Maternal dietary intake	NBW/LBW	OR[a] (95% CI)	OR[d] (95% CI)
Third trimester			
High iron and high zinc	4,191/216	Ref.	Ref.
High iron and low zinc	1,066/95	1.73 (1.27–2.22)	1.15 (0.84–1.59)
Low iron and high zinc	981/59	1.08 (0.93–1.25)	1.04 (0.88–1.23)
Low iron and low zinc	1,272/195	1.44 (1.34–1.54)	1.26 (1.13–1.40)

Multiplicative interaction: OR[d] (95% CI) = 1.92 (1.53–2.42), $P < 0.001$

Additive interaction: RERI (95% CI) = 1.08 (0.43–1.73), AP (95% CI) = 0.36 (0.17–0.56),

S (95% CI) = 2.20 (1.18–4.11)

Notes.

[a] OR[a] univariate analyses.

[d] OR[d] adjusted for weight gain during pregnancy, father's BMI, total energy intake, monthly income per capita, maternal education level, smoking, maternal employ, multivitamin supplement, gestational hypertension, history of premature birth and reproductive history.

the effects of dietary iron and zinc intake on LBW infants from the preconception period through the entire gestational period.

Few previous studies have investigated the effects of dietary iron intake preconception and during pregnancy on LBW. Most of the studies have focused on nutrient supplementation interventions and reported controversial results; thus, the evidence on whether dietary iron intake decreases the risk of LBW is still not established (*Chang, Li & Xu, 2018*). Most studies have reported that iron supplementation could decrease the risk of LBW. One prospective study (*Chang, Li & Xu, 2018*) reported that iron supplementation during the whole period of pregnancy reduced the risk of LBW (OR = 0.60; 95% CI [0.43–0.83]). However, the risk of LBW was 0.90 (95% CI [0.64–1.28]) and 0.77 (95% CI [0.58–1.03]) when iron supplementation was only given in the first trimester and in the middle-to-late pregnancy, respectively. One case–control study (*Siyoum & Melese, 2019*) in Ethiopia demonstrated that the lack of iron supplementation during pregnancy increased the risk of LBW infants (OR = 2.89; 95% CI [1.58–5.29]), and a case–control study in Spain similarly demonstrated (*Palma et al., 2008*) that 80 mg ferrous sulfate supplementation was associated with a lower risk of LBW (OR = 0.58; 95% CI [0.34–0.98]). A matched case–control study (*Yadav et al., 2020*) in Nepal indicated that iron and folic acid consumption less than 60 days before delivery raised the risk of LBW (OR = 5.47; 95% CI [2.73–10.95]). One meta-analysis (*Imdad & Bhutta, 2012*) revealed that routine daily iron supplementation during pregnancy resulted in a significant reduction of 20% in the incidence of LBW in the intervention group compared with the control group (RR = 0.80; 95% CI [0.71–0.90]). Another meta-analysis (*Haider et al., 2013*) indicated that for every 10 mg increase in iron dose/day, up to 66 mg/day, the birth weight increased by 15.1 (6.0 to 24.2) g (*P* for linear trend = 0.005), and the relative risk of LBW decreased by 3% (RR = 0.97; 95% CI [0.95–0.98]) for every 10 mg increase in dose/day (*P* for linear trend <0.001). One randomized controlled trial (*Cogswell et al., 2003*) showed that iron supplementation from enrollment to 28 weeks of gestation led to a significantly higher mean birthweight (206 ± 565 g; *P* = 0.010) and a significantly lower incidence of LBW infants (4% compared with 17%; *P* = 0.003). However, other three studies (*Imdad & Bhutta, 2012*; *Haider et al., 2013*; *Cogswell et al., 2003*; *Peña Rosas et al., 2015*; *Bánhidy et al., 2011*) observed that iron supplementation alone during pregnancy was not associated with LBW (RR = 0.78, 95% CI [0.56–1.02]), and there was no higher rate of LBW in newborns of anemic pregnant women who received iron supplementation. Studies investigating the relationship between dietary zinc intake and the risk of LBW are also conflicting (*Negandhi et al., 2014*; *Iannotti et al., 2008*; *Xie, Chen & Pan, 2001*; *Goldenberg et al., 1995*; *Zahiri Sorouri, Sadeghi & Pourmarzi, 2016*; *Osendarp et al., 2000*; *Carducci, Keats & Bhutta, 2021*; *Warthon-Medina et al., 2015*). Four of the eight studies reported that zinc supplementation reduced the risk of LBW. One case–control study (*Negandhi et al., 2014*) in India reported that low zinc intake (<5.39 mg/dL) showed a significant association with the risk of LBW. One randomized controlled trial in Peru (*Iannotti et al., 2008*) showed that zinc supplementation through pregnancy to 1 month after delivery was associated with greater weight (by 0.58 ± 0.12 kg; *P* < 0.001), but no effect was observed for linear growth. One randomized, double-blind trial (*Xie, Chen & Pan, 2001*) in western China demonstrated that zinc supplementation in

the doses of five and 10 mg/day had no benefit, whereas the 30 mg/day dose resulted in great improvements in the infants' birth weight (283.07 g, $P = 0.016$). Another randomized, double-blind placebo-controlled trial (*Goldenberg et al., 1995*) in USA demonstrated that daily zinc supplementation with 25 mg/day zinc sulfate in women with relatively low plasma zinc concentrations in early pregnancy was associated with greater infant birth weights (126 g, $P = 0.03$). However, other studies found no effect of zinc supplementation on infants' birth weight. Namely, one study reported (*Zahiri Sorouri, Sadeghi & Pourmarzi, 2016*) that 15 mg zinc supplementation daily from 16 weeks of pregnancy until delivery did not improve birth weight (3,262 g *vs.* 3,272 g, $P = 0.780$). In addition, one zinc supplementation trial indicated that no differences were noted in infants birth weight (3,267 ± 461 g *vs.* 3,300 ±498 g) by prenatal supplement type (iron + folate + zinc *vs.* iron + folate; $P > 0.05$), and there were no differences in the rates of LBW. A placebo-controlled trial in Bangladesh (*Osendarp et al., 2000*) demonstrated that supplementation with 30 mg zinc during the last two trimesters of pregnancy did not improve infant birth weights. One meta-analysis (*Carducci, Keats & Bhutta, 2021*) revealed that low or high doses of zinc supplementation during pregnancy were not significantly associated with high birth weight. Similarly, another meta-analysis (*Warthon-Medina et al., 2015*) showed that zinc supplementation during pregnancy (mean dose of 26.8 mg/day) might not attenuate the risk of LBW (RR = 0.76; 95% CI [0.52–1.11]). To the best of our knowledge, few previous studies have addressed the correlation between LBW and iron/zinc dietary intake, and there have been no previous studies of iron and zinc dietary intake interactions on LBW. Our results indicated that the simultaneous low intakes of iron and zinc preconception/during pregnancy might have an additive effect on the risk of LBW. Given the rarity of research on the combined effects of iron and zinc intakes on infant birth weight, further studies are warranted to confirm and interpret these findings. There are several strengths and limitations to be acknowledged in our study. First, information on dietary iron and zinc intake was obtained from participants' self-reports, which may have led to recall bias. Second, quantitative analysis of the interaction between dietary multivitamins and trace elements was not feasible. Thus, there could be potentially confounding effects. Therefore, strict quality control was maintained throughout the process, from questionnaire design to data entry, to minimize recall bias. Detailed information on demographic data, medical history, and lifestyle factors allowed us to adjust and control for the confounding factors. LBW and its subtypes were diagnosed based on the medical records rather than based on self-reports, which minimized the risk of potential disease misclassification; in addition, this is the first large-scale sample study to comprehensively, systematically, and deeply explore the co-effects of dietary zinc and iron intake on LBW, which has important guiding significance for the next stage of research.

CONCLUSIONS

Our study suggests that lower intakes of iron and zinc preconception and during pregnancy may increase the risk for LBW. This study also suggests that low intakes of iron and zinc during pregnancy synergistically affect the LBW risk. These findings imply the importance

of promoting iron and zinc intakes preconception and during pregnancy to reduce the incidence of LBW in Lanzhou City. Future human studies with data on maternal biological markers, mineral intake, and genetics are warranted to confirm these findings and elucidate underlying mechanisms.

ACKNOWLEDGEMENTS

ADDITIONAL INFORMATION AND DECLARATIONS

Competing Interests

The authors declare there are no competing interests.

Author Contributions

- Liping Yang conceived and designed the experiments, performed the experiments, authored or reviewed drafts of the article, and approved the final draft.
- Zifu Wang analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
- Lei Cao analyzed the data, prepared figures and/or tables, and approved the final draft.
- Yuqing Li analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
- Jingyan Wang analyzed the data, prepared figures and/or tables, and approved the final draft.
- Shuyu Ding analyzed the data, prepared figures and/or tables, and approved the final draft.

- Baohong Mao conceived and designed the experiments, performed the experiments, authored or reviewed drafts of the article, and approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (*i.e.*, approving body and any reference numbers):

Approved was provided by the Medical Ethics Committee of Gansu Provincial Maternity and Child-care Hospital ([2018](29)).

Data Availability

The following information was supplied regarding data availability:

Raw data is available in the Supplemental Files.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.19896#supplemental-information.

REFERENCES

Abbaspour N, Hurrell R, Kelishadi R. 2014. Review on iron and its importance for human health. *Journal of Research in Medical Sciences* **19**(**2**):164–174.

Abolbashari S, Darroudi S, Tayefi M, Khashyarmaneh Z, Zamani P, Haghighi HM, Mohammadpour AH, Tavalaei S, Ahmadnezhad M, Esmaily H, Ferns GA, Meshkat Z, Ghayour-Mobarhan M. 2018. Association between serum zinc and copper levels and antioxidant defense in subjects infected with human T-lymphotropic virus type 1. *Journal of Blood Medicine* **10**:29–35 DOI 10.2147/JBM.S184913.

Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A. 2005. Calculating measures of biological interaction. *European Journal of Epidemiology* **20**(**7**):575–579 DOI 10.1007/s10654-005-7835-x.

Aranda N, Ribot B, Viteri F, Cavallé P, Arija V. 2013. Predictors of haemoconcentration at delivery: association with low birth weight. *European Journal Nutrition* **52**(**6**):1631–1639 DOI 10.1007/s00394-012-0468-4.

Baltaci AK, Yuce K. 2018. Zinc transporter proteins. *Neurochemical Research* **43**(**3**):517–530 DOI 10.1007/s11064-017-2454-y.

Bánhidy F, Ács N, Puhó EH, Czeizel AE. 2011. Iron deficiency anemia: pregnancy outcomes with or without iron supplementation. *Nutrition* **27**(**1**):65–72 DOI 10.1016/j.nut.2009.12.005.

Berggren KL, Chen J, Fox J, Miller J, Dodds L, Dugas B, Vargas L, Lothian A, McAllum E, Volitakis I, Roberts B, Bush AI, Fox JH. 2015. Neonatal iron supplementation potentiates oxidative stress, energetic dysfunction and neurodegeneration in the R6/2 mouse model of Huntington's disease. *Redox Biology* **4**:363–374 DOI 10.1016/j.redox.2015.02.002.

Blencowe H, Krasevec J, De Onis M, Black RE, An X, Stevens GA, Borghi E, Hayashi C, Estevez D, Cegolon L, Shiekh S, Ponce Hardy V, Lawn JE, Cousens S. 2019.

National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2,000: a systematic analysis. *Lancet Global Health* **7(7)**:e849–e860 DOI 10.1016/S2214-109X(18)30565-5.

Carducci B, Keats EC, Bhutta ZA. 2021. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database of Systematic Reviews* **3(3)**:CD000230 DOI 10.1002/14651858.CD000230.pub6.

Chang XN, Li RZ, Xu SQ. 2018. Association between dietary supplementation during pregnancy and low birth weight: a prospective study. *Chinese Journal of Preventative Medicine* **52(10)**:1003–1007 (Chinese) DOI 10.3760/cma.j.issn.0253-9624.2018.10.007.

Chen GD, Li PS, Zhou ZX, Wang H-Y, Gou X-Y, Ye S-X, Lin D-X, Fan D-Z, Wang L-J, Liu Z-P. 2024. Associations of maternal serum concentration of iron-related indicators with birth outcomes in Chinese: a pilot prospective cohort study. *Italian Journal of Pediatrics* **50(1)**:39 DOI 10.1186/s13052-024-01621-0.

Cogswell ME, Parvanta I, Ickes L, Yip R, Brittenham GM. 2003. Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. *American Journal of Clinical Nutrition* **78(4)**:773–781 DOI 10.1093/ajcn/78.4.773.

De Costa A, Moller AB, Blencowe H, Johansson EW, Hussain-Alkhateeb L, Ohuma EO, Okwaraji YB, Cresswell J, Requejo JH, Bahl R, Oladapo OT, Lawn JE, Moran AC. 2021. Study protocol for WHO and UNICEF estimates of global, regional, and national preterm birth rates for 2010 to 2019. *PLOS ONE* **16(10)**:e0258751 DOI 10.1371/journal.pone.0258751.

Devarshi PP, Mao Q, Grant RW, Hazels Mitmesser S. 2024. Comparative absorption and bioavailability of various chemical forms of zinc in humans: a narrative review. *Nutrients* **16(24)**:4269 DOI 10.3390/nu16244269.

Dusek P, Jankovic J, Le W. 2012. Iron dysregulation in movement disorders. *Neurobiology of Disease* **46(1)**:1–18 DOI 10.1016/j.nbd.2011.12.054.

Gibson RS. 2006. Zinc: the missing link in combating micronutrient malnutrition in developing countries. *Proceedings of the Nutrition Society* **65(1)**:51–60 DOI 10.1079/pns2005474.

Goldenberg RL, Tamura T, Neggers Y, Copper RL, Johnston KE, DuBard MB, Hauth JC. 1995. The effect of zinc supplementation on pregnancy outcome. *Journal of the American Medical Association* **274(6)**:463–468 DOI 10.1001/jama.1995.03530060037030.

Grzeszczak K, Kwiatkowski S, Kosik-Bogacka D. 2020. The role of Fe, Zn, and Cu in pregnancy. *Biomolecules* **10(8)**:1176 DOI 10.3390/biom10081176.

Guilbert JJ. 2003. The world health report 2002—reducing risks, promoting healthy life. *Education for Health (Abingdon)* **16(2)**:230 DOI 10.1080/1357628031000116808.

Haider BA, Bhutta ZA. 2017. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* **4(4)**:CD004905 DOI 10.1002/14651858.CD004905.pub5.

Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW, Nutrition Impact Model Study Group (anaemia). 2013. Anaemia, prenatal iron use, and risk of

adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ* **346**:f3443 DOI 10.1136/bmj.f3443.

Hambidge KM, Miller LV, Westcott JE, Sheng X, Krebs NF. 2010. Zinc bioavailability and homeostasis. *American Journal of Clinical Nutrition* **91(5)**:1478S–1483S DOI 10.3945/ajcn.2010.28674I.

Huang W, Wang J, Ding S, Li Y, Fang L, Luo W, Li Z, Mao B. 2024. Association between maternal copper/zinc intake and the risk of preterm birth. *Iranian Journal of Pediatrics* **34(4)**:e145250 DOI 10.5812/ijp-145250.

Hurrell R, Egli I. 2010. Iron bioavailability and dietary reference values. *American Journal of Clinical Nutrition* **91(5)**:1461S–1467S DOI 10.3945/ajcn.2010.28674F.

Iannotti LL, Zavaleta N, León Z, Shankar AH, Caulfield LE. 2008. Maternal zinc supplementation and growth in Peruvian infants. *American Journal of Clinical Nutrition* **88(1)**:154–160 DOI 10.1093/ajcn/88.1.154.

Imdad A, Bhutta ZA. 2012. Routine iron/folate supplementation during pregnancy: effect on maternal anaemia and birth outcomes. *Paediatric and Perinatal Epidemiology* **26(Suppl 1)**:168–177 DOI 10.1111/j.1365-3016.2012.01312.x.

Jing M, Rech L, Wu Y, Goltz D, Taylor CG, House JD. 2015. Effects of zinc deficiency and zinc supplementation on homocysteine levels and related enzyme expression in rats. *Journal of Trace Elements in Medicine and Biology* **30**:77–82 DOI 10.1016/j.jtemb.2014.10.013.

Khoushabi F, Shadan MR, Miri A, Sharifi-Rad J. 2016. Determination of maternal serum zinc, iron, calcium and magnesium during pregnancy in pregnant women and umbilical cord blood and their association with outcome of pregnancy. *Materia Socio Medica* **28(2)**:104–107 DOI 10.5455/msm.2016.28.104-107.

Liang CM, Wu XY, Huang K, Yan SQ, Li ZJ, Xia X, Pan WJ, Sheng J, Tao YR, Xiang HY, Hao JH, Wang QN, Tao FB, Tong SL. 2019. Trace element profiles in pregnant women's sera and umbilical cord sera and influencing factors: repeated measurements. *Chemosphere* **218**:869–878 DOI 10.1016/j.chemosphere.2018.11.115.

Liu X, Lv L, Zhang H, Zhao N, Qiu J, He X, Zhou M, Xu X, Cui H, Liu S, Lerro C, Lin X, Zhang C, Zhang H, Xu R, Zhu D, Dang Y, Han X, Bai H, Chen Y, Tang Z, Lin R, Yao T, Su J, Wang W, Wang Y, Ma B, Huang H, Liang J, Qiu W, Liu Q, Zhang Y. 2016. Folic acid supplementation, dietary folate intake and risk of preterm birth in China. *European Journal Nutrition* **55(4)**:1411–1422 DOI 10.1007/s00394-015-0959-1.

Mao B, Wang Y, Li J, Wang W, Wang J, Xu X, Zhou M. 2020. Investigation of the dietary vitamins and trace element intake during pregnancy in Lanzhou city. *Chinese Journal of Women and Children Health* **11(1)**:10–16 (Chinese) DOI 10.19757/j.cnki.issn1674-7763.2020.01.003.

National Health Commission of the People's Republic of China. 2017. *Reference intakes of dietary nutrients for Chinese residents. Part 3: Trace element.* Beijing: National Health Commission of the People's Republic of China, 1–6.

Negandhi PH, Negandhi HN, Zodpey SP, Ughade SN, Biranjan JR. 2014. Risk factors for low birth weight in an Indian urban setting: a nested case control study. *Asia-Pacific Journal of Public Health* **26(5)**:461–469 DOI 10.1177/1010539511431486.

Nishiyama S, Kiwaki K, Miyazaki Y, Hasuda T. 1999. Zinc and IGF-I concentrations in pregnant women with anemia before and after supplementation with iron and/or zinc. *Journal of the American College of Nutrition* **18(3)**:261–267 DOI 10.1080/07315724.1999.10718861.

Osendarp SJ, Van Raaij JM, Arifeen SE, Wahed M, Baqui AH, Fuchs GJ. 2000. A randomized, placebo-controlled trial of the effect of zinc supplementation during pregnancy on pregnancy outcome in Bangladeshi urban poor. *American Journal of Clinical Nutrition* **71(1)**:114–119 DOI 10.1093/ajcn/71.1.114.

Palma S, Perez-Iglesias R, Prieto D, Pardo R, Llorca J, Delgado-Rodriguez M. 2008. Iron but not folic acid supplementation reduces the risk of low birthweight in pregnant women without Anaemia: a case-control study. *Journal of Epidemiology and Community Health* **62(2)**:120–124 DOI 10.1136/jech.2006.052985.

Parodi E, Ferrero A, Perrone B, Saracco P, Giraudo MT, Regoli D. 2018. Current practice of iron prophylaxis in preterm and low birth weight neonates: a survey among Italian neonatal units. *Pediatrics and Neonatology* **59(6)**:581–585 DOI 10.1016/j.pedneo.2018.01.013.

Peña Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. 2015. Daily oral iron supplementation during pregnancy. *Cochrane Database of Systematic Reviews* **2015(7)**:CD004736 DOI 10.1002/14651858.CD004736.pub5.

Prasad AS. 2003. Zinc deficiency. *BMJ* **326(7386)**:409–410 DOI 10.1136/bmj.326.7386.409.

Rahman SM, Siraj MS, Islam MR, Rahman A, Ekström EC. 2021. Association between maternal plasma ferritin level and infants' size at birth: a prospective cohort study in rural Bangladesh. *Global Health Action* **14(1)**:1870421 DOI 10.1080/16549716.2020.1870421.

Rasmussen KM, Yaktine AL, Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines (eds.) 2009. *Weight gain during pregnancy: reexamining the guidelines.* National Academies Press (US) DOI 10.17226/12584.

Ribot B, Aranda N, Viteri F, Hernández-Martínez C, Canals J, Arija V. 2012. Depleted iron stores without anaemia early in pregnancy carries increased risk of lower birth-weight even when supplemented daily with moderate iron. *Human Reproduction* **27(5)**:1260–1266 Epub Feb 21 2012 DOI 10.1093/humrep/des026.

Roohani N, Hurrell R, Kelishadi R, Schulin R. 2013. Zinc and its importance for human health: an integrative review. *Journal of Research in Medical Sciences* **18(2)**:144–157.

Saaka M, Oosthuizen J, Beatty S. 2009. Effect of joint iron and zinc supplementation on malarial infection and anaemia. *East African Journal of Public Health* **6(1)**:55–62 DOI 10.4314/eajph.v6i1.45748.

Shastri L, Mishra PE, Dwarkanath P, Thomas T, Duggan C, Bosch R, McDonald CM, Thomas A, Kurpad AV. 2015. Association of oral iron supplementation with birth

outcomes in non-anaemic South Indian pregnant women. *European Journal of Clinical Nutrition* **69(5)**:609–613 Epub Nov 19 2014 DOI 10.1038/ejcn.2014.248.

Shen L, Wang J, Duan Y, Yang Z. 2021. Prevalence of low birth weight and macrosomia estimates based on heaping adjustment method in China. *Scientific Reports* **11(1)**:15016 DOI 10.1038/s41598-021-94375-2.

Shinzawa M, Tanaka S, Tokumasu H, Takada D, Tsukamoto T, Yanagita M, Kawakami K. 2019. Association of low birth weight with childhood proteinuria at age 3 years: a population-based retrospective cohort study. *American Journal of Kidney Diseases* **74(1)**:141–143. Epub May 24 2019 DOI 10.1053/j.ajkd.2019.02.018.

Siyoum M, Melese T. 2019. Factors associated with low birth weight among babies born at Hawassa University Comprehensive Specialized Hospital, Hawassa, Ethiopia. *Italian Journal of Pediatrics* **45(1)**:48 DOI 10.1186/s13052-019-0637-7.

Ten Have SM, Van der Lely AJ, Lamberts SW. 1997. Increase in haemoglobin concentrations in growth hormone deficient adults during human recombinant growth hormone replacement therapy. *Clinical Endocrinology* **47(5)**:565–570 DOI 10.1046/j.1365-2265.1997.3241124.x.

Tussing-Humphreys L, Pusatcioglu C, Nemeth E, Braunschweig C. 2012. Rethinking iron regulation and assessment in iron deficiency, anemia of chronic disease, and obesity: introducing hepcidin. *Journal of the Academy of Nutrition and Dietetics* **112(3)**:391–400 DOI 10.1016/j.jada.2011.08.038.

Warthon-Medina M, Moran VH, Stammers AL, Dillon S, Qualter P, Nissensohn M, Serra-Majem L, Lowe NM. 2015. Zinc intake, status and indices of cognitive function in adults and children: a systematic review and meta-analysis. *European Journal of Clinical Nutrition* **69(6)**:649–661 Epub Apr 29 2015 DOI 10.1038/ejcn.2015.60.

World Health Organization. 2004. Fund low birthweight: country, regional and global estimates. World Health Organization. *Available at* https://iris.who.int/handle/10665/43184.

Xie L, Chen X, Pan J. 2001. The effects of zinc supplementation to Chinese rural pregnant women and their pregnancy outcome. *Journal of Shanghai Second Medical University* **13(2)**:119–124.

Yadav DK, Shukla GS, Gupta N, Shrestha N, Singh A, Kaphle HP. 2020. Maternal and obstetric factors associated with low birth weight. *Journal of Nepal Health Research Council* **17(4)**:443–450 DOI 10.33314/jnhrc.v17i4.2263.

Yamaji S, Tennant J, Tandy S, Williams M, Singh Srai SK, Sharp P. 2001. Zinc regulates the function and expression of the iron transporters DMT1 and IREG1 in human intestinal Caco-2 cells. *FEBS Letters* **507(2)**:137–141 DOI 10.1016/s0014-5793(01)02953-2.

Yang WP, Chang HH, Li HY, Lai YC, Huang TY, Tsai KS, Lin KH, Lin DT, Jou ST, Lu MY, Yang YL, Chou SW, Shih SR. 2020. Iron overload associated endocrine dysfunction leading to lower bone mineral density in thalassemia major. *Journal of Clinical Endocrinology and Metabolism* **105(4)**:dgz309 DOI 10.1210/clinem/dgz309.

Yang YX, Wang GY, Pan XC. 2009. *China food composition.* Beijing: Peking University Medical Press.

Zahiri Sorouri Z, Sadeghi H, Pourmarzi D. 2016. The effect of zinc supplementation on pregnancy outcome: a randomized controlled trial. *Journal of Maternal-Fetal and Neonatal Medicine* **29(13)**:2194–2198 DOI 10.3109/14767058.2015.1079615.