The Journal of Nutrition
Nutrition and Disease

Maternal Serum Zinc Concentration during Pregnancy Is Inversely Associated with Risk of Preterm Birth in a Chinese Population[1–3]

Hua Wang,[4–6] Yong-Fang Hu,[4,6] Jia-Hu Hao,[4,5] Yuan-Hua Chen,[4,5] Ying Wang,[4] Peng Zhu,[4,5] Cheng Zhang,[4,5] Yuan-Yuan Xu,[4,5] Fang-Biao Tao,[4,5]* and De-Xiang Xu[4,5]*

[4]School of Public Health and [5]Anhui Provincial Key Laboratory of Population Health and Aristogenics, Anhui Medical University, Hefei, China

Abstract

Background: Evidence exists that maternal zinc status during pregnancy is linked to adverse pregnancy outcomes including abortion, fetal growth restriction, and neural tube defects. However, it remains unclear whether maternal serum zinc concentration (SZC) during pregnancy is associated with risk of preterm birth.

Objective: This study was designed to investigate the association between maternal SZC during pregnancy and risk of preterm birth.

Methods: For this substudy of the China-Anhui Birth Cohort Study, 3081 maternal-singleton pairs with detailed birth records and available serum samples were identified. The maternal SZC was determined with flame atomic absorption spectroscopy. A total of 169 preterm births were identified. In this study, the women were divided into tertiles on the basis of their SZC: low (<76.7 μg/dL), medium (76.7–99.6 μg/dL), and high (≥99.7 μg/dL). The ORs for preterm birth were estimated by using multiple logistic regression models.

Results: The median SZC was 87.3 μg/dL (range: 11.1–211 μg/dL). Incidences of preterm birth were 7.3% and 6.0% among subjects with low and medium SZCs, respectively, which were significantly higher than 3.1% among subjects with a high SZC [ORs (95% CIs) for low and medium SZCs: 2.45 (1.60, 3.74), $P < 0.001$, and 2.00 (1.29, 3.09), $P < 0.01$, respectively]. After adjustment for prepregnancy body mass index, maternal age, time of serum collection, gravidity, parity, and monthly income, adjusted ORs were 2.41 (95% CI: 1.57, 3.70; $P < 0.001$) and 1.97 (95% CI: 1.27, 3.05; $P < 0.01$) among subjects with low and medium maternal SZCs.

Conclusions: Maternal serum zinc concentration during pregnancy is inversely associated with risk of preterm birth in the Chinese population, and the results are driven by maternal SZC in the first trimester. *J Nutr* 2016;146:509–15.

Keywords: maternal serum, zinc, preterm birth, pregnancy, birth cohort study

Introduction

Preterm birth, defined as spontaneous or iatrogenic birth before gestational week 37, is a major reason for neonatal death (1, 2). Numerous epidemiologic studies have shown an association between preterm birth and childhood asthma (3, 4). Moreover, preterm birth increases the risk of cardiovascular diseases in young adulthood (5, 6) and is an important independent risk factor for neurodevelopmental disorders (7). Although maternal obesity, maternal inflammation, and accumulation of nonesterified FAs in maternal serum have been identified as potential risk factors (8–10), the exact etiology and underlying mechanisms for preterm birth remain obscure.

Zinc is a structural constituent that is essential for cell growth, cell differentiation, and development (11). Several earlier reports showed that low maternal zinc concentration during pregnancy is associated with adverse pregnancy outcomes, including abortion, stillbirth, and fetal neural tube defects (12–14). Moreover, the association between maternal zinc insufficiency during pregnancy and intrauterine fetal growth restriction has been investigated in several small epidemiologic studies (15, 16). However, it remains unclear whether maternal serum zinc concentration (SZC) during pregnancy is associated with the risk of preterm birth. According to

[1] Supported by the National Natural Science Foundation of China (81473016, 81172711, 81471467) and the National Key Technology R&D Program (2006BAI05A03 to the China-Anhui Birth Cohort Study).
[2] Author disclosures: H Wang, Y-F Hu, J-H Hao, Y-H Chen, Y Wang, P Zhu, C Zhang, Y-Y Xu, F-B Tao, and D-X Xu, no conflicts of interest. The funders had no role in the research design, implementation, analysis, or interpretation of the data.
[3] Supplemental Table 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
[6] These authors contributed equally to this work.
*To whom correspondence should be addressed. E-mail: fbtao@126.com (F-B Tao), xudex@126.com (D-X Xu).

Manuscript received July 14, 2015. Initial review completed August 21, 2015. Revision accepted December 11, 2015.
First published online January 27, 2016; doi:10.3945/jn.115.220632.

a small birth cohort study, maternal SZC during pregnancy was associated with an increased risk of preterm delivery (17). A 2015 meta-analysis showed that maternal zinc supplementation caused a 14% relative reduction in preterm births (18). However, a randomized controlled trial found that maternal zinc supplementation did not affect pregnancy duration (19). This result was in agreement with a systematic review, in which the evidence that maternal zinc supplementation reduced the risk of preterm birth was low (20). Thus, whether maternal SZC during pregnancy is associated with risk of preterm birth needs to be further determined. The objective of the present study was to investigate the association between maternal SZC during pregnancy and the risk of preterm birth in a Chinese population.

Methods

Participant recruitment. The China-Anhui Birth Cohort Study is a prospective, population-based cohort study that recruited 16,766 pregnant women from 6 major cities of Anhui province in China between November 2008 and October 2010. A total of 13,454 singleton live births were followed up from this cohort (21). The present study analyzed a substudy of the China-Anhui Birth Cohort Study that recruited 4358 pregnant women from Hefei, a city in Anhui province, from 1 January to 31 December 2009. Exclusion criteria for participation were as follows: inability to provide informed consent, alcohol drinking and cigarette smoking during pregnancy, mental disorders, pregnancy-induced hypertension and pre-eclampsia, gestational diabetes, heart disease, thyroid-related disease, a history of ≥3 previous miscarriages, or plans to leave the area before delivery. For this study, eligible participants were mother and singleton offspring pairs in which serum samples from mothers were available for analysis of SZC and offspring had detailed birth records. In this substudy, 36 pregnant women gave birth to twins, there were 15 fetal deaths, 2 stillbirths, 58 abortions, and 589 withdrew from the study (**Figure 1**). In addition, 464 participants with no maternal sera available, 20 with nonphysiologically plausible SZC values, and 93 with samples collected in the third trimester were also excluded (Figure 1). As a result of differences in time at entry into our cohort, maternal serum samples were collected from 1069 pregnant women in the first trimester (4–12 wk of gestation) and 2012 samples were collected from pregnant women in the second trimester (13–27 wk of gestation). The present study obtained ethical approval from the Human Research Ethics Committee of Anhui Medical University (permit 08-1026). Oral and written consent was obtained from all pregnant women.

Definition of preterm birth. Gestational age was calculated by using the mother's last menstrual period. Preterm birth was defined as a live birth at <37 completed gestational weeks (22). Deliveries at <28 wk of gestational age were considered miscarriages and excluded in the current analysis (23). A total of 169 spontaneous and nonmedical preterm deliveries were identified.

Measurement of maternal SZC. Maternal fasting blood during pregnancy was collected in the morning. The blood samples were allowed to clot at room temperature for 30 min. Maternal serum was then obtained after centrifuging for 15 min at 3000 *g*. After discarding hemolytic specimens, available sera were stored at −80°C until analysis. SZC was determined by flame atomic absorption spectroscopy as previously described (24). Briefly, all tubes and pipette tips were immersed overnight in 10% HNO_3 at room temperature. Serum samples were diluted with 1% HNO_3 at 1:35 (vol:vol). The diluted solution was then detected by using flame atomic absorption spectroscopy. Each sample was analyzed in triplicate. The precision of the method was measured by using CVs. The mean CV for measurement of serum zinc was 4.9% for within-day determinations and 4.3% for day-to-day determinations. The detection limit of this method was 0.2 μg/dL. According to a method described by a 2014 study (25), the pregnant women were divided into tertiles on the basis of their SZC and classified as having low (<76.7 μg/dL), medium (76.7–99.6 μg/dL), or high (≥99.7 μg/dL) SZCs.

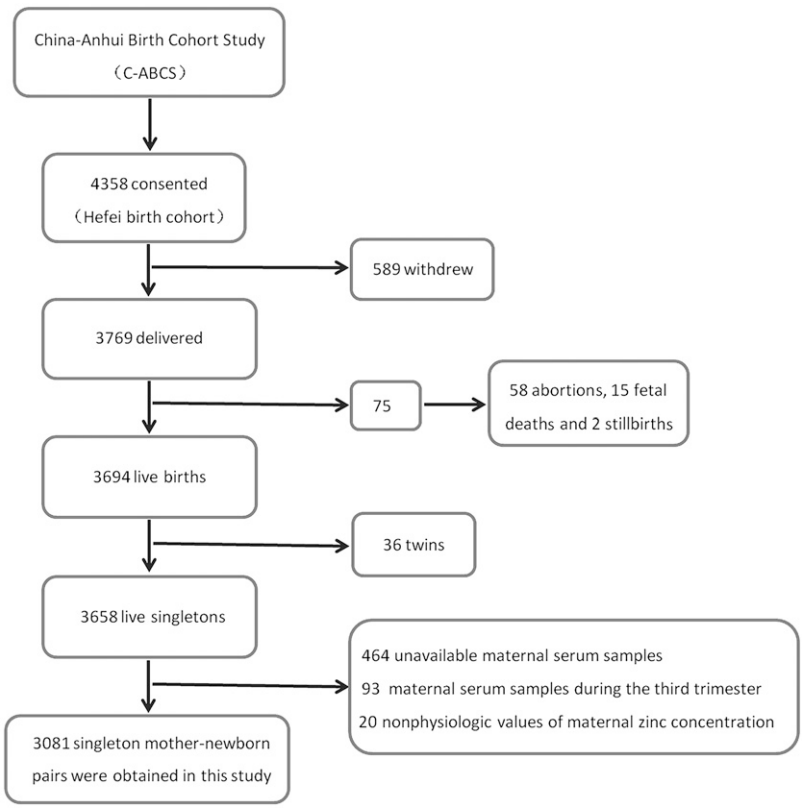

FIGURE 1 Flow diagram of recruitment, follow-up, and identification of serum zinc in a substudy of the China-Anhui Birth Cohort Study.

Confounding factors. According to a previous systemic review (26), potential confounding factors that might influence the association between maternal zinc status during pregnancy and preterm birth were chosen as follows: maternal age (≤24, 25–29, or ≥30 y), prepregnancy BMI (in kg/m^2; <18.5, 18.5–24.9, or ≥25), average monthly income (low income: <2000 yuan renminbi or 312 US$; middle income: 2000–3999 yuan renminbi or 312–624 US$; high income: ≥4000 yuan renminbi or 624 US$), time of serum collection [first trimester: median, 11 wk of gestation (range: 4–12 wk of gestation); second trimester: median, 16 wk of gestation (range: 13–27 wk of gestation)], gravidity (primigravida or multigravida) and parity (nulliparous or multiparous), and multivitamin intake (yes or no).

Statistical analysis. First, the ratios of maternal and neonatal characters, and the rate of preterm birth among tertiles of maternal SZC, were analyzed by using the chi-square test. Continuous measures, including SZC, were compared between 2 groups by using independent-samples *t* tests. For multiple comparisons, we used 1-factor ANOVA followed by Bonferroni's or Tamhane's T2 post hoc test. Next, ORs and 95% CIs for the association between maternal zinc status and preterm birth were estimated by using multiple logistic regression models. We calculated unadjusted and adjusted estimates using exact methods and asymptotic methods, respectively. To identify other variables for inclusion in the multivariable models, we sequentially tested each maternal characteristic listed in **Table 1** in the basic model, which included maternal age, prepregnancy BMI, monthly income, time of serum collection, gravidity, and parity. For any tertile of maternal SZC, 3 covariates (prepregnancy BMI, gravidity, and parity) changed the adjusted OR for the association with preterm birth by >10% (**Table 2**) (27). Because of the low incidence of preterm birth, the OR is a good approximation of the relative risk (28). We performed all statistical analyses with SPSS statistical software (version 16.0). All statistical tests were 2-sided with an α level of 0.05.

Results

Demographic characteristics of pregnant women. Demographic characteristics of the pregnant women are presented in Table 1. No significant differences in maternal age, prepregnancy BMI, gravidity, or monthly income were observed between subjects with low, medium, and high maternal SZCs. With decreasing tertiles of maternal SZC, the proportion of serum samples collected in the first trimester decreased, whereas the percentages of multipara both increased. The characteristics of newborns were then analyzed. As shown in Table 1, the rates

TABLE 1 Characteristics of 3081 mothers and their newborns according to maternal serum zinc concentration in a Chinese population[1]

	Maternal serum zinc concentration			
	Low (<76.7 μg/dL)	Medium (76.7–99.6 μg/dL)	High (≥99.7 μg/dL)	*P*
n	1027	1027	1027	
Maternal characteristics				
Age, y	27.4 ± 3.3	27.5 ± 3.2	27.5 ± 3.0	0.97
≤24 y, *n* (%)	163 (15.9)	147 (14.3)	161 (15.7)	0.82
25–29 y, *n* (%)	646 (62.9)	665 (64.8)	643 (62.6)	
≥30 y, *n* (%)	218 (21.2)	215 (20.9)	223 (21.7)	
Prepregnancy BMI, kg/m^2	20.1 ± 2.3	20.2 ± 2.2	20.3 ± 2.1	0.36
<18.5 kg/m^2, *n* (%)	247 (24.1)	220 (21.4)	192 (18.7)	<0.01
18.5−24.9 kg/m^2, *n* (%)	740 (72.1)	776 (75.6)	810 (78.9)	
≥25 kg/m^2, *n* (%)	40 (3.9)	31 (3.0)	25 (2.4)	
Gravidity, *n* (%)				0.77
Primigravida	530 (51.6)	545 (53.1)	532 (51.8)	
Multigravida	497 (48.4)	482 (46.9)	495 (48.2)	
Parity, *n* (%)				0.04
Nulliparous	988 (96.2)	999 (97.3)	1007 (98.1)	
Multiparous	39 (3.8)	28 (2.7)	20 (1.9)	
Monthly income,[2] *n* (%)				0.38
Low	482 (46.9)	449 (43.7)	475 (46.3)	
Middle	412 (40.1)	441 (42.9)	403 (39.2)	
High	133 (13.0)	137 (13.3)	149 (14.5)	
Time of serum collection, wk	15.8 ± 4.5	14.6 ± 4.2	14.0 ± 4.3	<0.001
First trimester, *n* (%)	247 (24.1)	364 (35.4)	458 (44.6)	<0.001
Second trimester, *n* (%)	780 (75.9)	663 (64.6)	569 (55.4)	
Newborn characteristics				
Gestational age, wk	38.9 ± 1.8	39.0 ± 1.8	39.1 ± 1.6	0.012
<37 wk, *n* (%)	75 (7.3)	62 (6.0)	32 (3.1)	<0.001
≥37 wk, *n* (%)	952 (92.7)	965 (94.0)	995 (96.9)	
Birth weight, g	3378 ± 483	3403 ± 446	3413 ± 452	0.21
<2500 g, *n* (%)	38 (3.7)	25 (2.4)	17 (1.7)	0.013
≥2500 g, *n* (%)	989 (96.3)	1002 (97.6)	1010 (98.3)	

[1] Values are means ± SDs unless otherwise indicated.
[2] Low income was <2000 yuan renminbi (312 US$) per month; middle income was 2000–3999 yuan renminbi (312–624 US$) per month; and high income was ≥4000 yuan renminbi (624 US$) per month.

TABLE 2 Associations of maternal characteristics with risk of preterm birth in a Chinese population

		Preterm birth	
Maternal characteristics	*n* (%)	OR (95% CI)	*P*
Age			
≤24 y	471 (15.3)	0.99 (0.63, 1.55)	0.96
25–29 y	1954 (63.4)	1.00	—
≥30 y	656 (21.3)	1.11 (0.76, 1.63)	0.58
Prepregnancy BMI (in kg/m^2)			
<18.5	659 (21.4)	1.38 (0.96, 1.97)	0.08
18.5−24.9	2326 (75.5)	1.00	—
≥25	96 (3.1)	2.24 (1.13, 4.42)	0.02
Gravidity			
Primigravida	1607 (52.2)	1.00	—
Multigravida	1474 (47.8)	0.80 (0.58, 1.09)	0.16
Parity			
Nulliparous	2994 (97.2)	1.00	—
Multiparous	87 (2.8)	1.78 (0.85, 3.75)	0.13
Monthly income[1]			
Low	1406 (45.6)	0.90 (0.56, 1.45)	0.67
Middle	1256 (40.8)	1.00 (0.62, 1.61)	0.99
High	419 (13.6)	1.00	—
Time of serum collection			
First trimester	1069 (34.7)	1.00	—
Second trimester	2012 (65.3)	1.14 (0.82, 1.59)	0.44

[1] Low income was <2000 yuan renminbi (312 US$) per month; middle income was 2000–3999 yuan renminbi (312–624 US$) per month; and high income was ≥4000 yuan renminbi (624 US$) per month.

of preterm birth and low birth weight gradually increased with decreasing tertiles of maternal SZC.

Maternal SZC during pregnancy and risk of preterm birth. The median SZC was 87.3 μg/dL. Several maternal characteristics, including age, monthly income, gravidity, and multivitamin intake, were not associated with SZC during pregnancy (**Supplemental Table 1**). Of interest, the mean SZC was significantly lower among subjects with a prepregnancy BMI <18.5 than that in subjects with a normal BMI (18.5–24.9). In addition, the mean SZC among nulliparae was significantly higher than that in multiparae. Subsequently, the mean SZC among different gestational ages was further analyzed (Supplemental Table 1). Results showed that the mean SZC among subjects with 33.0–34.9 and 35.0–36.9 wk of gestation was markedly lower than that in subjects with ≥37.0 wk of gestation (Supplemental Table 1). The associations of other known risk factors and preterm birth were further analyzed. As shown in Table 2, some risk factors, including maternal age, monthly income, gravidity, and prepregnancy BMI, were not associated with the risk of preterm birth.

As shown in **Table 3**, the incidences of preterm birth among the low-, medium-, and high-zinc groups were 7.3%, 6.0%, and 3.1%, respectively. Subjects with low and medium maternal SZCs had a significantly higher risk of preterm birth than did those with a high maternal SZC. After adjusting for maternal age, prepregnancy BMI, time of serum collection, monthly income, parity, and gravidity, the ORs for preterm birth were 2.41 and 1.97 among subjects with low and medium maternal SZCs, respectively (Table 3).

Maternal SZC in the first trimester and risk of preterm birth. As shown in **Table 4**, the incidences of preterm birth were 8.1% and 7.1% among subjects with low and medium first-trimester SZCs, which was significantly higher than the 1.7% incidence among subjects with a high SZC. After adjusting for prepregnancy BMI, maternal age, monthly income, parity, and gravidity, the ORs for preterm birth were 4.90 and 4.35 among subjects with low and medium SZCs, respectively (Table 4).

Maternal SZC in the second trimester and risk of preterm birth. The incidences of preterm birth among the low-, medium-, and high-zinc groups were 7.1%, 5.4%, and 4.2%, respectively (**Table 5**). No significant difference in risk of preterm birth was observed among subjects by SZC in the second trimester.

Discussion

The incidence of preterm birth was 5.5% in our birth cohort and was significantly lower than 11.1% (uncertainty range: 9.1–13.4%), which is the global average preterm birth rate (13% in India and 12.0% in the United States) (29). Our study, however, excluded medically indicated preterm deliveries and miscarriages (<28 wk).

According to several systemic reviews, maternal zinc supplementation resulted in a 14% relative reduction in preterm births (18, 30, 31). To analyze the association between maternal SZC during pregnancy and the risk of preterm birth, the present study calculated the incidence and OR of preterm birth among 3 groups on the basis of tertiles of maternal SZC. Results showed that the incidences of preterm birth in low-, medium-, and high-zinc groups were 7.3%, 6.0%, and 3.1%, respectively. Subjects with low and medium SZCs had a significantly higher risk of preterm birth than did those in the high-SZC group. These results are in agreement with an earlier

TABLE 3 Incidences and ORs of preterm birth on the basis of maternal serum zinc concentration during pregnancy in a Chinese population[1]

	Maternal serum zinc concentration			
	Low (<76.7 μg/dL)	Medium (76.7– 99.6 μg/dL)	High (≥99.7 μg/dL)	*P*
Newborns, *n*	1027	1027	1027	
Preterm births, *n*	75	62	32	
Incidence, %	7.3	6.0	3.1	<0.001
Univariate OR (95% CI)	2.45[b] (1.60, 3.74)	2.00[a] (1.29, 3.09)	1.00	<0.001
Adjusted OR (95% CI)[2]	2.41[b] (1.57, 3.70)	1.97[a] (1.27, 3.05)	1.00	<0.001

[1a,b] Different from reference (high maternal zinc concentration): [a]$P < 0.01$, [b]$P < 0.001$.

[2] Adjusted for prepregnancy BMI, maternal age, time of serum collection, gravidity, parity, and monthly income.

TABLE 4 Incidences and ORs of preterm birth on the basis of maternal serum zinc concentration during the first trimester in a Chinese population[1]

	Maternal serum zinc concentration			
	Low (<76.7 μg/dL)	Medium (76.7– 99.6 μg/dL)	High (≥99.7 μg/dL)	*P*
Newborns, *n*	247	364	458	
Preterm births, *n*	20	26	8	
Incidence, %	8.1	7.1	1.7	<0.001
Univariate OR (95% CI)	4.96[b] (2.15, 11.43)	4.33[b] (1.94, 9.68)	1.00	<0.001
Adjusted OR (95% CI)[2]	4.90[b] (2.12, 11.32)	4.35[b] (1.94, 9.74)	1.00	<0.001

[1b] Different from reference (high maternal zinc concentration), $P < 0.001$.
[2] Adjusted for prepregnancy BMI, maternal age, gravidity, parity, and monthly income.

report from a small birth cohort study, in which low zinc concentration during pregnancy was associated with an increased risk of preterm birth (17). Together, these results suggest that maternal zinc concentration during pregnancy is negatively associated with the risk of preterm birth.

To our knowledge, until now, no report has analyzed the association between maternal zinc status at different gestational ages and the risk of preterm birth. The present study compared differential effects of maternal zinc concentration at early and middle gestational ages on the incidence of preterm birth. Unexpectedly, the incidence of preterm infants was 8.0% among subjects with a low SZC in the first trimester, which is significantly higher than 1.7% among those with a high SZC in the first trimester. Interestingly, the incidence of preterm births was 7.0% among subjects with a low maternal SZC in the second trimester, which was not significantly higher than the incidence of 4.4% among those with a high maternal SZC in the second trimester. These results suggest that maternal zinc status in the first trimester but not middle gestational age is negatively associated with the risk of preterm birth.

The mechanism by which maternal zinc insufficiency during pregnancy elevates the risk of preterm birth remains obscure. Increasing evidence has shown that zinc has anti-inflammatory activity (32). An earlier study found that zinc supplementation alleviated early inflammatory responses during cutaneous wound healing (33). Another study showed that zinc supplementation reduced the number of eosinophils in bronchoalveolar lavage fluid during allergic inflammation (34). According to a small, double-blind, randomized controlled trial, zinc supplementation markedly improved cell-mediated immunity and anti-inflammatory activity in children (35). In an earlier study, we showed that zinc supplementation alleviated LPS-induced placental inflammation (36), and placental inflammation is associated with preterm birth (37–39). Several studies showed that inflammatory cytokines were elevated in cervicovaginal fluid, vaginal fluid, and amniotic fluid in women delivering preterm infants (40–43). Taken together, these results suggest that there might be an association between maternal zinc insufficiency during pregnancy, maternal inflammation, and the risk of preterm birth.

Zinc may be used as a potential protective and therapeutic agent for clinical therapy, especially in high-risk situations in which pregnant women are infected with bacteria. According to a study from our laboratory, oral zinc supplementation ameliorated LPS-induced intrauterine fetal growth restriction (36). Additional study is required to determine whether maternal zinc supplementation during pregnancy reduces the risk of preterm birth in randomized placebo-controlled trials.

The present study has some limitations. First, we did not explore the reasons for low maternal SZC. Second, preterm birth was classified according to menstrual period–based pregnancy dating, not ultrasound-based pregnancy dating. Third, the present study did not have any data on some environmental factors that may be important for preterm birth. However, many lifestyle factors and nutritional status that influence preterm birth are driven by socioeconomic status (26). This study controlled for socioeconomic status (monthly income) as a confounding factor, which may have reduced the bias. Next, we did not adjust for maternal insufficiency of other micronutrients, such as folate and vitamin D, which also elevate the risk of preterm delivery (44, 45). In summary, the present study shows that maternal SZC during pregnancy is inversely associated with the risk of preterm birth, and the results are driven by maternal SZC in the first trimester.

TABLE 5 Incidences and ORs of preterm birth on the basis of maternal serum zinc concentration during the second trimester in a Chinese population

	Maternal serum zinc concentration			
	Low (<76.7 μg/dL)	Medium (76.7– 99.6 μg/dL)	High (≥99.7 μg/dL)	*P*
Newborns, *n*	780	663	569	
Preterm births, *n*	55	36	24	
Incidence, %	7.1	5.4	4.2	0.08
Univariate OR (95% CI)	1.72 (1.05, 2.82)	1.30 (0.77, 2.21)	1.00	0.08
Adjusted OR (95% CI)[1]	1.68 (1.02, 2.75)	1.28 (0.75, 2.18)	1.00	0.10

[1] Adjusted for prepregnancy BMI, maternal age, gravidity, parity, and monthly income.

Acknowledgments

HW, F-BT, and D-XX designed the research, wrote the manuscript, and had primary responsibility for the final content of the manuscript; HW, Y-FH, Y-HC, and YW conducted the research; J-HH, PZ, CZ, and Y-YX provided the essential materials and subjects; and HW, Y-FH, J-HH, and Y-HC analyzed the data. All authors read and approved the final manuscript.

References

1. Englund-Ögge L, Brantsaeter AL, Sengpiel V, Haugen M, Birgisdottir BE, Myhre R, Meltzer HM, Jacobsson B. Maternal dietary patterns and preterm delivery: results from large prospective cohort study. BMJ 2014;348:g1446.
2. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science 2014;345:760–5.
3. Goyal NK, Fiks AG, Lorch SA. Association of late-preterm birth with asthma in young children: practice-based study. Pediatrics 2011;128:e830–8.
4. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, Annesi-Maesano I, Arshad SH, Barros H, Basterrechea M, Bisgaard H, Chatzi L, Corpeleijn E, et al. Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. J Allergy Clin Immunol 2014;133:1317–29.
5. Kessous R, Shoham-Vardi I, Pariente G, Holcberg G, Sheiner E. An association between preterm delivery and long-term maternal cardiovascular morbidity. Am J Obstet Gynecol 2013;209:368, e1–8.
6. Ueda P, Cnattingius S, Stephansson O, Ingelsson E, Ludvigsson JF, Bonamy AK. Cerebrovascular and ischemic heart disease in young adults born preterm: a population-based Swedish cohort study. Eur J Epidemiol 2014;29:253–60.
7. Crump C, Winkleby MA, Sundquist K, Sundquist J. Preterm birth and psychiatric medication prescription in young adulthood: a Swedish national cohort study. Int J Epidemiol 2010;39:1522–30.
8. Scharfe-Nugent A, Corr SC, Carpenter SB, Keogh L, Doyle B, Martin C, Fitzgerald KA, Daly S, O'Leary JJ, O'Neill LA. TLR9 provokes inflammation in response to fetal DNA: mechanism for fetal loss in preterm birth and preeclampsia. J Immunol 2012;188:5706–12.
9. Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikstrom AK, Granath F. Maternal obesity and risk of preterm delivery. JAMA 2013;309:2362–70.
10. Catov JM, Bertolet M, Chen YF, Evans RW, Hubel CA. Nonesterified fatty acids and spontaneous preterm birth: a factor analysis for identification of risk patterns. Am J Epidemiol 2014;179:1208–15.
11. Hirano T, Murakami M, Fukada T, Nishida K, Yamasaki S, Suzuki T. Roles of zinc and zinc signaling in immunity: zinc as an intracellular signaling molecule. Adv Immunol 2008;97:149–76.
12. Buamah PK, Russell M, Bates G, Ward AM, Skillen AW. Maternal zinc status: a determination of central nervous system malformation. Br J Obstet Gynaecol 1984;91:788–90.
13. Lehti KK. Stillbirth rates and folic acid and zinc status in low-socioeconomic pregnant women of Brazilian Amazon. Nutrition 1993;9:156–8.
14. Graham TW, Thurmond MC, Gershwin ME, Picanso JP, Garvey JS, Keen CL. Serum zinc and copper concentrations in relation to spontaneous abortion in cows: implications for human fetal loss. J Reprod Fertil 1994;102:253–62.
15. Simmer K, Thompson RP. Maternal zinc and intrauterine growth retardation. Clin Sci (Lond) 1985;68:395–9.
16. Neggers YH, Cutter GR, Acton RT, Alvarez JO, Bonner JL, Goldenberg RL, Go RC, Roseman JM. A positive association between maternal serum zinc concentration and birth weight. Am J Clin Nutr 1990;51:678–84.
17. Scholl TO, Hediger ML, Schall JI, Fischer RL, Khoo CS. Low zinc intake during pregnancy: its association with preterm and very preterm delivery. Am J Epidemiol 1993;137:1115–24.
18. Ota E, Mori R, Middleton P, Tobe-Gai R, Mahomed K, Miyazaki C, Bhutta ZA. Zinc supplementation for improving pregnancy and infant outcome. Cochrane Database Syst Rev 2015;2:CD000230.
19. Caulfield LE, Zavaleta N, Figueroa A, Leon Z. Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. J Nutr 1999;129:1563–8.
20. Chaffee BW, King JC. Effect of zinc supplementation on pregnancy and infant outcomes: a systematic review. Paediatr Perinat Epidemiol 2012;26(Suppl 1):118–37.
21. Tao FB, Hao JH, Huang K, Su PY, Cheng DJ, Xing XY, Huang ZH, Zhang JL, Tong SL. Cohort profile: the China-Anhui Birth Cohort Study. Int J Epidemiol 2013;42:709–21.
22. Athalye-Jape G, Deshpande G, Rao S, Patole S. Benefits of probiotics on enteral nutrition in preterm neonates: a systematic review. Am J Clin Nutr 2014;100:1508–19.
23. Baqui AH, Rosen HE, Lee AC, Applegate JA, El Arifeen S, Rahman SM, Begum N, Shah R, Darmstadt GL, Black RE. Preterm birth and neonatal mortality in a rural Bangladeshi cohort: implications for health programs. J Perinatol 2013;33:977–81.
24. Stáhlavská A, Slansky V, Benediktova B. The use of spectrum analytical methods in drug analysis. 3. Determination of iron using atomic absorption spectrophotometry. Pharmazie 1973;28:241–2.
25. Shan Z, Bao W, Zhang Y, Rong Y, Wang X, Jin Y, Song Y, Yao P, Sun C, Hu FB, et al. Interactions between zinc transporter-8 gene (SLC30A8) and plasma zinc concentrations for impaired glucose regulation and type 2 diabetes. Diabetes 2014;63:1796–803.
26. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, Kinney M, Lawn J, Born Too Soon Preterm Birth Action G. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health 2013;10(Suppl 1):S2.
27. Yoon BW, Bae HJ, Hong KS, Lee SM, Park BJ, Yu KH, Han MK, Lee YS, Chung DK, Park JM, et al. Phenylpropanolamine contained in cold remedies and risk of hemorrhagic stroke. Neurology 2007;68:146–9.
28. Huybrechts KF, Hernandez-Diaz S, Avorn J. Antidepressant use in pregnancy and the risk of cardiac defects. N Engl J Med 2014;371:1168–9.
29. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162–72.
30. Mahomed K, Bhutta Z, Middleton P. Zinc supplementation for improving pregnancy and infant outcome. Cochrane Database Syst Rev 2007;12:CD000230.
31. Mori R, Ota E, Middleton P, Tobe-Gai R, Mahomed K, Bhutta ZA. Zinc supplementation for improving pregnancy and infant outcome. Cochrane Database Syst Rev 2012;7:CD000230.
32. Haase H, Rink L. Functional significance of zinc-related signaling pathways in immune cells. Annu Rev Nutr 2009;29:133–52.
33. Lim Y, Levy M, Bray TM. Dietary zinc alters early inflammatory responses during cutaneous wound healing in weanling CD-1 mice. J Nutr 2004;134:811–6.
34. Lang C, Murgia C, Leong M, Tan LW, Perozzi G, Knight D, Ruffin R, Zalewski P. Anti-inflammatory effects of zinc and alterations in zinc transporter mRNA in mouse models of allergic inflammation. Am J Physiol Lung Cell Mol Physiol 2007;292:L577–84.
35. Sandstead HH, Prasad AS, Penland JG, Beck FW, Kaplan J, Egger NG, Alcock NW, Carroll RM, Ramanujam VM, Dayal HH, et al. Zinc deficiency in Mexican American children: influence of zinc and other micronutrients on T cells, cytokines, and antiinflammatory plasma proteins. Am J Clin Nutr 2008;88:1067–73.
36. Chen YH, Zhao M, Chen X, Zhang Y, Wang H, Huang YY, Wang Z, Zhang ZH, Zhang C, Xu DX. Zinc supplementation during pregnancy protects against lipopolysaccharide-induced fetal growth restriction and demise through its anti-inflammatory effect. J Immunol 2012;189:454–63.
37. Andrews WW, Goldenberg RL, Faye-Petersen O, Cliver S, Goepfert AR, Hauth JC. The Alabama Preterm Birth Study: polymorphonuclear and mononuclear cell placental infiltrations, other markers of inflammation, and outcomes in 23- to 32-week preterm newborn infants. Am J Obstet Gynecol 2006;195:803–8.
38. Defranco EA, Jacobs TS, Plunkett J, Chaudhari BP, Huettner PC, Muglia LJ. Placental pathologic aberrations in cases of familial idiopathic spontaneous preterm birth. Placenta 2011;32:386–90.
39. Kim MA, Lee YS, Seo K. Assessment of predictive markers for placental inflammatory response in preterm births. PLoS One 2014;9:e107880.

40. Menon R, Thorsen P, Vogel I, Jacobsson B, Morgan N, Jiang L, Li C, Williams SM, Fortunato SJ. Racial disparity in amniotic fluid concentrations of tumor necrosis factor (TNF)-alpha and soluble TNF receptors in spontaneous preterm birth. Am J Obstet Gynecol 2008;198:533, e1–10.
41. Menon R, Camargo MC, Thorsen P, Lombardi SJ, Fortunato SJ. Amniotic fluid interleukin-6 increase is an indicator of spontaneous preterm birth in white but not black Americans. Am J Obstet Gynecol 2008;198:77, e1–7.
42. Wei SQ, Fraser W, Luo ZC. Inflammatory cytokines and spontaneous preterm birth in asymptomatic women: a systematic review. Obstet Gynecol 2010;116:393–401.
43. Taylor BD, Holzman CB, Fichorova RN, Tian Y, Jones NM, Fu W, Senagore PK. Inflammation biomarkers in vaginal fluid and preterm delivery. Hum Reprod 2013;28:942–52.
44. Bodnar LM, Platt RW, Simhan HN. Early-pregnancy vitamin D deficiency and risk of preterm birth subtypes. Obstet Gynecol 2015;125:439–47.
45. Chen LW, Lim AL, Colega M, Tint MT, Aris IM, Tan CS, Chong YS, Gluckman PD, Godfrey KM, Kwek K, et al. Maternal folate status, but not that of vitamins B-12 or B-6, is associated with gestational age and preterm birth risk in a multiethnic Asian population. J Nutr 2015;145:113–20.