Association between Maternal Weight Indicators and Iron Deficiency Anemia during Pregnancy: A Cohort Study

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Abstract

Background: The effect of maternal weights on the risk of iron deficiency anemia (IDA) during pregnancy remains unclear. The study aimed to investigate the association between maternal weight indicators and IDA during pregnancy.

Methods: We conducted a cohort study to examine the association between maternal weight indicators, including prepregnancy body mass index and the rate of gestational weight gain (GWG), and the risk of IDA among Chinese pregnant women. Data about new-onset IDA at different trimesters from a national cross-sectional survey were collected; information regarding baseline variables and rate of GWG from women participating in the survey were retrospectively collected. Tested IDA and reported IDA were documented. Multilevel logistic regression to examine the association between maternal weight indicators and the risk of IDA after adjusting for potential confounders was conducted.

Results: This study enrolled 11,782 pregnant women from 24 hospitals from September 19, 2016, to November 20, 2016. Among those, 1515 (12.9%) IDA events were diagnosed through test (test IDA); 3915 (33.3%) were identified through test and patient reporting (composite IDA). After adjusting for confounders and cluster effect of hospitals, underweight pregnant women, compared with normal women, were associated with higher risk of test IDA (adjusted odds ratio [*aOR*]: 1.35, 95% confidence interval [*CI*]: 1.17–1.57 and composite IDA (*aOR*: 1.35, 95% *CI*: 1.21–1.51); on the contrary, overweight and obese women had lower risk of test IDA (*aOR*: 0.68, 95% *CI*: 0.54–0.86 overweight; *aOR*: 0.30, 95% *CI*: 0.13–0.69 obese) and composite IDA (*aOR*: 0.77, 95% *CI*: 0.67–0.90 overweight; *aOR*: 0.34, 95% *CI*: 0.21–0.55 obese). The higher rate of GWG was associated with higher risk of IDA (test *aOR*: 1.86 95% *CI*: 1.26–2.76; composite *aOR*: 1.54, 95% *CI*: 1.16–2.03).

Conclusions: Pregnant women who are underweight before pregnancy and who have faster GWG are more likely to develop IDA. Enforced weight control during pregnancy and use of iron supplements, particularly among underweight women, may be warranted.

Key words: Gestational Weight Gain; Iron Deficiency Anemia; Prepregnancy Body Mass Index

INTRODUCTION

Anemia is a common comorbidity during pregnancy. Worldwide, the prevalence of pregnancy anemia was estimated 38% (95% confidence interval [*CI*]: 33–43%), meaning that 32 millions of pregnant women were affected.[1] Of those, more than 50% was a result of iron deficiency (ID).[1,2] ID anemia (IDA) during pregnancy may cause a catastrophy of serious adverse outcomes, such as premature rupture of membrane, puerperal infection, fetal growth restriction, fetal hypoxia, and premature birth.[1,3] Previous studies have identified several potential risk factors for IDA, such as poor nutritional status, multiple gestations, poor socioeconomic status, age over 30 years, multiparity, and shorter birth spacing.[4,5]

However, the potential impact of body weight on IDA has not been well investigated. Maternal weight indicators, including prepregnancy body mass index (BMI) and gestational weight

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gain (GWG), represent important measures of maternal metabolism and nutritional situation.[6-9] Their potential influences on the development of IDA are multifolds, and the directions of impacts seems inconsistent. On the one end, the demand for iron during pregnancy substantially increases due to expansion of maternal blood volume and rapid growth of placenta and fetus.[4,10,11] Those women with higher BMI before pregnancy may have more iron stores for compensating the iron consumption during pregnancy and appear to less likely develop ID during pregnancy.[12] On the other end, overweight, particularly obesity, is associated with underlying systemic inflammation,[13] and the resulting elevation of hepcidin and serum ferritin[12,14,15] may decrease iron absorption from dietary[16,17] and hemoglobin production.[18,19] Thus, the overweight and obesity status may be associated with increased risk of IDA. In addition, faster weight gain may also suggest a higher likelihood of iron consumption during pregnancy. Consequently, all these potential biological rationales, which are inconsistent in the directions, could jointly affect iron consumption and production during pregnancy.

Up to now, only a few studies examined the association between maternal weight indicators and risk of IDA,[10,20,21] and the findings were inconsistent. There also were important limitations among these published studies, such as the use of surrogate markers[20,21] (rather than the diagnosis of IDA) and restriction to special populations (e.g., obese pregnant women population,[20] pregnant adolescents,[21] or those at the third trimester[20]). The paucity of reliable evidence has made the IDA management during pregnancy a topic of increasing interest. Therefore, we conducted a cohort study to specifically address the association between maternal weight indicators and risk of IDA.

METHODS

Ethical approval
The study was approved by the Research Ethics Committee of West China Second Hospital, Sichuan University (No. 2016-009) and registered at ClinicalTrials.gov (No. NCT02887963). All pregnant women will be informed about details of rights, benefits, and obligations of the study, and they sign informed consent if they agree to participate in the survey.

Design overview
We used a cohort study design to examine the association between maternal weight indicators (i.e., prepregnancy BMI and GWG) and the risk of IDA among the Chinese pregnancy population. The data used for the analyses came from two sources: (1) a national cross-sectional study examining new-onset IDA at different gestation stages (i.e., first, second, and third trimesters) during pregnancy and (2) a survey accompanying with the cross-sectional study that used a predefined questionnaire to retrospectively collect information regarding baseline variables (e.g., prepregnancy BMI and other potential baseline confounders) and weight

changes from baseline to the IDA measurement (i.e., at the time of cross-sectional test of IDA). Figure 1 shows the conceptual framework of the cohort study.

Cross-sectional study and ascertainment of iron deficiency anemia
The cross-sectional study was conducted at 24 academic and nonacademic hospitals across China [Supplementary Table 1]. We chose these hospitals using a multistage sampling method according to geographic regions and provinces (or municipal cities). Our study involved 24 hospitals located in 16 provinces or municipal cities across six regions in China (north, northeast, east, south, southwest, and northwest) according to the China National Bureau criteria. These 16 provinces or municipal cities cover about 750 million resident population (China Health Statistical Yearbook, 2012). We selected four hospitals from each region, including one tertiary teaching hospital and three other hospitals. The tertiary teaching hospital served as the coordinating site of that region.

The hospitals participating in the study can routinely test serum ferritin and hemoglobin at local laboratory using the qualified instrument and uniform method by experienced technicians and had a large number of patient visits. Clinician investigators at obstetric outpatient departments consecutively enrolled pregnant women receiving antenatal visits from September 19, 2016, to November 20, 2016.

Eligible pregnant women should meet all of the following inclusion criteria: (1) were receiving antenatal visit during the survey period, (2) agreed to conduct antenatal examination during antenatal visits, and (3) signed informed consent form. Those pregnant women were excluded, if they were participating in any clinical trial.

The IDA was identified through diagnosis at the defined antenatal visit or the latest visit occurred within 1 month (i.e., test IDA) or by patient reporting on pervious diagnosis (occurred more than 1 month). The outcome of our interest
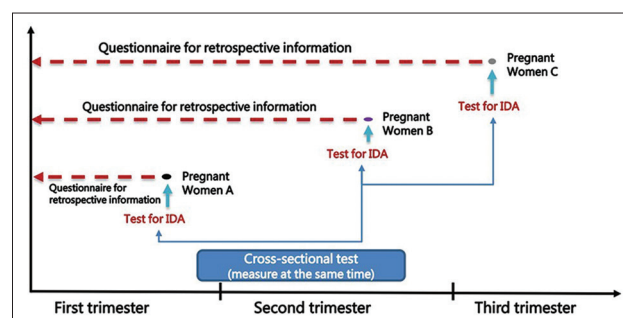
Figure 1: Conceptual framework of the cohort study. The information regarding IDA was collected during the cross-sectional study. The information regarding prepregnancy BMI (baseline), gestational weight gains, and other baseline characteristics (e.g., potential confounders) was retrospectively collected through the predefined questionnaire. The length of follow-up for patients at different gestational ages may differ; this difference was taken accounted of during the analysis. IDA: Iron deficiency anemia; BMI: Body mass index.

was the new-onset IDA, which included the test IDA and the composite of test IDA or patient reporting on previous diagnosis (i.e., composite IDA).

The test IDA was diagnosed with serum ferritin concentration <20 μg/L and hemoglobin <110 g/L at this antenatal visit or the latest antenatal visit (occurred within 1 month), according to the Chinese Guideline for Diagnosis and Treatment of IDA during Pregnancy.[3] The ascertainment of previously diagnosed IDA was identified based on the self-reporting by pregnant women and ascertained by investigators using data recorded in the electronic medical records. We recorded the dates of all tests. All the methods and facilities of laboratory tests were checked for consistency by senior laboratory technicians.

We used a centralized, pilot-tested online electronic data capturing (EDC) system to collect, review, and manage data. The data were entered and stored at the EDC system. The EDC system had the capacity to edit (with tracked changes), store, and manage data. Once the investigators upload and confirm the data, they were not allowed to modify the data.

The statisticians at the Methods Center (Chinese Evidence-based Medicine Center) reviewed the uploaded data and conducted data verification. If missing or erroneous data were identified, the data queries were sent to the investigators for data checking and correction.

Accompanying survey to collect baseline data and weight changes

During the cross-sectional study, we used two predesigned and structured questionnaires to retrospectively collect baseline data and weight changes. The investigators collected information regarding anthropometry indicators, obstetric information from the electronic medical records (EMRs) of the 24 hospitals. All the data in 24 hospitals were further uploaded to EDC system.

The baseline data included demographic characteristics (age, nationality, local resident, education, occupation, marriage, urban or rural residence, and family population and income), diet pattern and nutrients supplements during gestation, history of diagnosis with IDA during this pregnancy, history of gestation, and lifestyle (e.g., active or passive smoking and drinking).

The data we extracted from EMR included anthropometry indicators (height, prepregnancy weight, and present weight at this antenatal visit), obstetric information (gestational week, history of pregnancy and parity, history of abortion and cesarean section, and use of assisted reproductive technology, etc.), medical comorbidities (hepatitis B, cardiovascular diseases, respiratory diseases, thyroid disease, diabetes mellitus [not including gestational diabetes], gynecological diseases, diseases of blood system, immune system, etc.), history of diagnosis with IDA during this pregnancy (timing of diagnosed IDA and treatment regimens), and pregnancy complications (hypertensive

disorders, placenta previa, intrahepatic cholestasis, fetal growth restriction, fetal malformation, and stillbirth).

Among multiple gestational comorbidities, cardiovascular diseases included chronic hypertension, rheumatic heart disease, congenital heart disease, and myocardiosis. Gynecological diseases included uterine fibroids, ovarian cyst, cervicitis, polycystic ovarian syndrome, and ovarian adenomyosis. Diabetes included type 1 diabetes and type 2 diabetes. Thyroid diseases included hyperthyroidism, hypothyroidism, and subclinical hypothyroidism. Autoimmune diseases included systemic lupus erythematosus, antiphospholipid antibody syndrome, and Sjogren's disease. Digestive system disease included chronic gastritis, digestive ulcer, appendicitis, cholecystitis, chronic diarrhea, and hemorrhoids.

We examined two types of maternal weight indicators, including prepregnancy BMI and rate of GWG. The prepregnancy BMI was calculated through dividing prepregnancy weight (kilogram) by the square of height (meter) and was categorized according to the World Health Organization criteria (underweight: BMI <18.5 kg/m²; normal weight: BMI ≥18.5 kg/m² and <25.0 kg/m²; overweight: BMI ≥25.0 kg/m² and <30.0 kg/m²; obese: BMI ≥30.0 kg/m²). The GWG was calculated by maternal weight at antenatal visit and subtracting self-reported prepregnancy weight. The rate of GWG was calculated though GWG dividing by gestational week.

Sample size estimation

The current analysis was primarily based on the cross-sectional study, for which a single population proportion sample estimation formula was used to calculate the required minimum sample size (n), as follows:

$$ n = \left(\frac{Z_{\alpha/2}}{d} \right)^2 \times p \times (1 - p) $$

According to our earlier retrospective database study involving 8 hospitals in Sichuan province, the prevalence of pregnant IDA was 3.96% (i.e., $p \approx 4\%$).[22] Given d (precision of detecting change) = 0.004 (A tenth of the p), $Z_{\alpha/2} = 1.96$ with 2-tailed $\alpha = 0.05$, the estimated sample size is 9,220. Assuming the loss to follow-up is 5%, the expected sample size is 9706.

In discussing with the leading clinician investigators from the six regions, all agreed that the study could increase the sample size to 12,000, given the volume of participants and availability of research resources. At each region, the teaching hospital enrolled 800 participants, and each of the three other care facilities enrolled 400 participants.

Data analysis

We described the distribution of demographic characteristics, gestational characteristics, diet pattern, nutrients supplements, lifestyle, and gestational comorbidities according to prepregnancy BMI categories.

We examined the difference of these characteristics among prepregnancy BMI categories using Pearson's Chi-square or Fisher's exact test for categorical variables, and ANONA analysis or rank-sum (Mann-Whitney) test for continuous variables.

We conducted univariable analyses of the associations between maternal weight indicators and the risk of new-onset IDA (test IDA and composite IDA). In order to adjust for the confounding effects, we conducted multivariable logistic regression analysis. Based on the biological rationale, previous research evidence, and statistical significance of univariable analyses ($P < 0.1$), we chose the following variables as covariates: maternal age (<35 years vs. ≥35 years), maternal race (Han vs. others), education (≥17 years vs. 13–16 years vs. 10–12 years vs. ≤9 years), local citizens (yes vs. no), area of residence (urban vs. rural), annual family income (<30,000 CNY vs. 30,000–79,999 CNY vs. 80,000–119,999 CNY vs. 120,000–199,999 CNY vs. ≥200,000 CNY), multiple gestations (yes and no), parity (<1 vs. ≥1), gestational week at the survey (first vs. second vs. third trimester, defined as <13^{+6}, 14–27^{+6} and ≥28 gestational week), egg intake per week (unit of 0.5 kg), meat intake per week (unit of 0.5 kg), smoking before pregnancy (yes vs. no), nausea and/or vomiting during pregnancy (no vs. slight vs. severe), multivitamins supplement (yes vs. no), calcium supplement (yes vs. no), and multiple gestational comorbidities (yes vs. no).

To explore whether the effects of prepregnancy BMI categories on risk of IDA varied among different trimesters, we included an interaction between prepregnancy BMI groups and gestational week at the survey (first, second, and third trimesters) in multivariable logistic regression analysis.

Given the potential cluster effect of care organization across regions, we additionally developed multilevel logistic regression models to assess the association between maternal weight indicators and risk of IDA, on the basis of the above multiple regression models. In these multilevel logistic regression models, the effects of different hospitals were deemed random. We reported the adjusted odds ratio (aOR), 95% confidence interval (CI), and the responding P value for all models. In light of limited exposure for pregnant women in the first trimester, we conducted a sensitivity analysis by excluding pregnant women at the first trimester.

We checked for missing data across all variables and included the patients with complete data in our analyses. We used STATA 13.0 (StataCorp College Station, Texas, USA) for the statistical analysis.

RESULTS

We enrolled 12,403 pregnant women receiving antenatal visits from September 19, 2016, to November 20, 2016, among 24 hospitals. By excluding 621 pregnant women with preexisted hematological diseases, 11,782 pregnant women were eligible. We checked for missing data among all reported variables. Finally, we included 11,757 and

11,759 pregnant women for the analyses on test IDA and composite IDA [Figure 2].

The median maternal age was 29 years (interquartile range 27–33). Among the included women, 987 (8.4%) were at the first trimester, 3365 (28.6%) at the second trimester, and 7430 (63.1%) at the third trimester; 2028 (17.2%) were underweight, 8476 (72.0%) normal, 1133 (9.6%) overweight, and 145 (1.2%) obese. In total, we identified 1515 (12.9%) test IDA events and 3915 (33.3%) composite IDA events.

Table 1 reported baseline characteristics of pregnant women according to prepregnancy BMI categories. There were statistically significant differences in region, maternal age, race, education, family income, smoking, parity, meat intake, egg intake, gynecological diseases, diabetes, thyroid diseases, digestive system diseases, and calcium across the prepregnancy items.

By univariable analyses, we found that underweight pregnant women had higher risk of new-onset IDA than those with normal weight. In contrast, both overweight and obese women had lower risk of IDA. The analysis of rate of GWG suggested that more weight gain was associated with higher risk of IDA [Table 2].

The multivariable regression analysis showed that, compared with normal weight, underweight women were associated with higher risk of IDA (test IDA: aOR: 1.33, 95% CI: 1.15–1.53; composite IDA: 1.31, 1.17–1.45), and overweight and obese women had lower risk of IDA (overweight: test IDA: 0.65, 0.52–0.81; composite IDA: 0.80, 0.69–0.92; obese women:
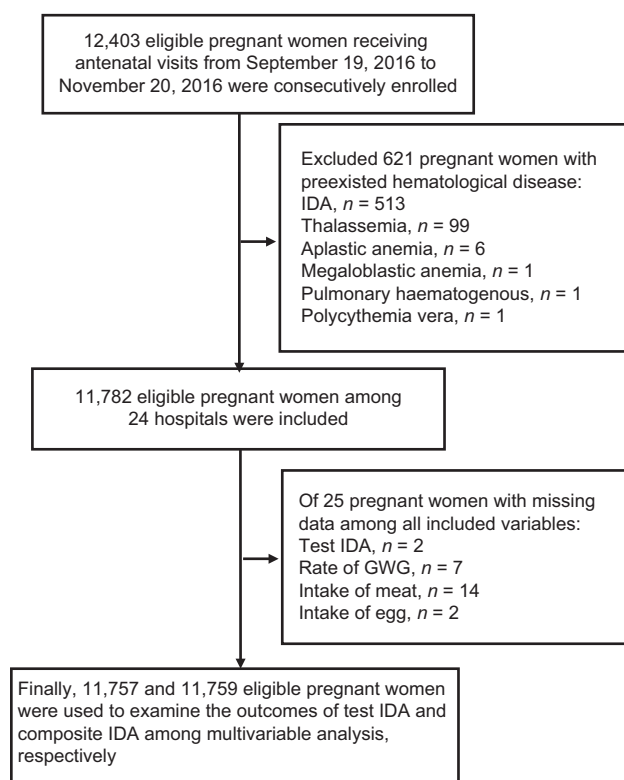
Figure 2: Flowchart of included population. IDA: Iron deficiency anemia; GWG: Gestational weight gain.

Table 1: Characteristics of included women by prepregnancy BMI

Categories	Underweight women	Normal women	Overweight women	Obese women	χ^2	P
n (%)	2028 (17.21)	8476 (71.94)	1133 (9.62)	145 (1.23)		
Region*					156.41	<0.001
North China	276 (13.61)	1345 (15.87)	276 (24.36)	41 (28.28)		
Northeast	314 (15.48)	1483 (17.50)	235 (20.74)	37 (25.52)		
East China	378 (18.64)	1385 (16.34)	154 (13.59)	13 (8.97)		
Central South	315 (15.53)	1449 (17.10)	144 (12.71)	16 (11.03)		
Southwest	424 (20.91)	1429 (16.86)	135 (11.92)	14 (9.66)		
Northwest	321 (15.83)	1385 (16.34)	189 (16.68)	24 (16.55)		
Trimester*					4.89	0.558
First	174 (8.58)	715 (8.44)	90 (7.94)	8 (5.52)		
Second	598 (29.49)	2383 (28.11)	338 (29.83)	46 (31.72)		
Third	1256 (61.93)	5378 (63.45)	705 (62.22)	91 (62.76)		
Maternal age*					155.81	<0.001
<35 years	1886 (93.00)	7186 (84.78)	879 (77.58)	116 (80.00)		
≥35 years	142 (7.00)	1290 (15.22)	254 (22.42)	29 (20.00)		
Maternal race*					7.21	0.066
Han	1902 (93.79)	7905 (93.26)	1050 (92.67)	128 (88.28)		
Others	126 (6.21)	571 (6.74)	83 (7.33)	17 (11.72)		
Education*					85.70	<0.001
≥17 years	193 (9.52)	1036 (12.22)	87 (7.68)	11 (7.59)		
13–16 years	1453 (71.65)	5724 (67.53)	744 (65.67)	88 (60.69)		
10–12 years	259 (12.77)	1133 (13.37)	174 (15.36)	223 (15.17)		
≤9 years	123 (6.07)	583 (6.88)	128 (11.30)	24 (16.55)		
Local citizens*					0.51	0.916
No	234 (11.54)	931 (10.98)	125 (11.03)	16 (11.03)		
Yes	1794 (88.46)	7545 (89.02)	1008 (88.97)	129 (88.97)		
Residential area*					1.17	0.759
Urban	1048 (51.68)	4322 (50.99)	590 (52.07)	70 (48.28)		
Rural	980 (48.32)	5154 (49.01)	543 (47.93)	75 (51.72)		
Annual family income*					59.56	<0.001
<30.0 thousand CNY	190 (9.37)	734 (8.66)	144 (12.71)	25 (17.24)		
30.0–79.9 thousand CNY	572 (28.21)	2236 (26.38)	350 (30.89)	46 (31.72)		
80.0–119.9 thousand CNY	540 (26.63)	2339 (27.60)	286 (25.24)	28 (19.31)		
120.0–199.9 thousand CNY	398 (19.63)	1807 (21.32)	210 (18.53)	32 (22.07)		
≥200.0 thousand CNY	328 (16.17)	1360 (16.05)	143 (12.62)	14 (9.66)		
Active or passive smoking*					8.66	0.034
No	1250 (61.64)	5320 (62.77)	669 (59.05)	81 (55.86)		
Yes	778 (38.36)	3156 (37.23)	464 (40.95)	64 (44.14)		
Multiple gestation*					3.92	0.270
No	1993 (98.27)	8277 (97.65)	1106 (97.62)	140 (96.55)		
Yes	35 (1.73)	199 (2.35)	27 (2.38)	5 (3.45)		
Parity*					122.46	<0.001
<1	1550 (76.43)	5577 (65.80)	670 (59.14)	86 (59.31)		
≥1	478 (23.57)	2899 (34.20)	463 (40.86)	59 (40.69)		
Meat intake†	0.6 (0.3–0.9)	0.6 (0.3–0.9)	0.5 (0.2–0.8)	0.5 (0.2–0.9)	4.73‡	<0.001
Egg intake†	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.5 (0.2–0.7)	3.51‡	0.000
HBsAg positivity*					1.50	0.682
No	1981 (97.68)	8264 (97.50)	1111 (98.06)	142 (97.93)		
Yes	47 (2.32)	212 (2.50)	22 (1.94)	3 (2.07)		
Cardiovascular diseases*					1.96	0.580
No	2017 (99.46)	8411 (99.23)	1122 (99.03)	144 (99.31)		
Yes	11 (0.54)	65 (0.77)	11 (0.97)	1 (0.69)		
Gynecological diseases*					24.02	<0.001
No	1949 (96.10)	7995 (94.33)	1053 (92.94)	129 (88.97)		
Yes	79 (3.90)	481 (5.67)	80 (7.06)	16 (11.03)		

Contd...

Table 1: Contd...

Categories	Underweight women	Normal women	Overweight women	Obese women	χ^2	P
Diabetes*					13.71	0.003
No*	2018 (99.51)	8444 (99.62)	1123 (99.12)	142 (97.93)		
Yes	10 (0.49)	32 (0.38)	10 (0.88)	3 (2.07)		
Thyroid diseases*					10.15	0.017
No	1946 (95.96)	7996 (94.34)	1066 (94.09)	140 (96.55)		
Yes	82 (4.04)	480 (5.66)	67 (5.91)	5 (3.45)		
Autoimmune diseases*					0.73	0.865
No	2021 (99.65)	8442 (99.60)	1129 (99.65)	145 (100.00)		
Yes	7 (0.35)	34 (0.40)	4 (0.35)	0 (0.00)		
Digestive system diseases*					7.80	0.050
No	1977 (97.49)	8326 (98.23)	1119 (98.76)	143 (98.62)		
Yes	51 (2.51)	150 (1.77)	14 (1.24)	2 (1.38)		
NVP*					5.17	0.522
No	480 (23.67)	2020 (23.83)	296 (26.13)	41 (28.28)		
Slight	1241 (61.19)	5115 (60.35)	666 (58.78)	82 (56.55)		
Severe	307 (15.14)	1341 (15.82)	171 (15.09)	22 (15.17)		
Multivitamins supplement*					2.27	0.517
No	675 (33.28)	2922 (34.47)	399 (35.22)	55 (37.93)		
Yes	1353 (66.72)	5554 (65.53)	734 (64.78)	90 (62.07)		
Calcium supplement*					6.60	0.086
No	710 (35.01)	2997 (35.36)	439 (38.75)	58 (40.00)		
Yes	1318 (64.99)	5479 (64.64)	694 (61.25)	87 (60.00)		

Data are presented as *n (%) or †Median (P_{25}, P_{75}); ‡Kruskal-Wallis H test. NVP: Nausea and/or vomiting during pregnancy; HBsAg: Hepatitis B surface antigen; BMI: Body mass index.

Table 2: Univariable analyses of associations between maternal weight indicators and risk of IDA

Maternal weight	Test IDA				Composite IDA			
	Test IDA	Non-IDA	OR (95% CI)	P	Composite IDA	Non-IDA	OR (95% CI)	P
Prepregnancy BMI								
Underweight	311 (20.53)	1716 (16.72)	1.22 (1.07–1.40)	0.004	765 (19.54)	1263 (16.05)	1.22 (1.11–1.35)	<0.001
Normal	1092 (72.08)	7383 (71.92)	Reference	–	2805 (71.65)	5671 (72.09)	Reference	–
Overweight	104 (6.86)	1029 (10.02)	0.68 (0.55–0.84)	<0.001	321 (8.20)	812 (10.32)	0.80 (0.70–0.92)	0.001
Obese	8 (0.53)	137 (1.33)	0.39 (0.19–0.81)	0.011	24 (0.61)	121 (1.54)	0.40 (0.26–0.62)	<0.001
Rate of GWG (kg/week)	0.36 (0.28–0.44)	0.32 (0.22–0.42)	3.89 (2.88–5.26)	<0.001	0.35 (0.27–0.44)	0.31 (0.21–0.42)	4.47 (3.56–5.62)	<0.001

Data are presented as n (%). IDA: Iron deficiency anemia; BMI: Body mass index; OR: Odds ratio; CI: Confidence interval; GWG: Gestational weight gain; –: Not applicable.

0.27, 0.12–0.63; and 0.36, 0.22–0.57). The higher rate of GWG was associated with higher risk of IDA (test IDA: 1.76, 1.21–2.57; composite IDA: 1.55, 1.16–2.03). The additional analysis by including interaction between prepregnancy BMI categories and trimesters in the multivariable regression analysis was not statistically significant (interaction $P = 0.981$ for test IDA, $P = 0.495$ for composite IDA), suggesting that the effect of pregnancy BMI on the risk of IDA was consistent across the trimesters and that the analysis by including all women at the three trimesters was plausible. To explore the cluster effect of 24 hospitals, we test the random-effects parameters. The results suggested that there was substantial cluster effect among 24 hospitals (estimate 0.61, standard error 0.19, $P < 0.001$). Therefore, we further conducted multilevel regression analysis to adjust the cluster effect of hospitals. We found that, compared with normal

weight, underweight women increased the risk of IDA (test IDA: aOR, 1.35, 95% CI: 1.17–1.57; composite IDA: 1.35, 1.21–1.51), and overweight and obese women had lower risk of IDA (overweight: test IDA: 0.68, 0.54–0.86; composite IDA: 0.77, 0.67–0.90; obese women: 0.30, 0.13–0.69; and 0.34, 0.21–0.55). The higher rate of GWG was associated with higher risk of IDA (test IDA: 1.86, 1.26–2.76; composite IDA: 1.54, 1.16–2.03) [Table 3]. The sensitivity analyses by excluding pregnant women at the first trimester showed similar findings, suggesting robustness of the results [Table 4].

Discussion

Main findings and implications

In our study, we found that women with lower BMI

Table 3: Multivariable logistic regression and multilevel regression analyses

Maternal weights	Test IDA				Composite IDA			
	aOR (95% CI)	P	Multilevel aOR (95% CI)	P	aOR (95% CI)	P	Multilevel aOR (95% CI)	P
Prepregnancy BMI								
Underweight	1.33 (1.15–1.53)	<0.001	1.35 (1.17–1.57)	<0.001	1.31 (1.17–1.45)	<0.001	1.35 (1.21–1.51)	<0.001
Overweight	0.65 (0.52–0.81)	<0.001	0.68 (0.54–0.86)	0.001	0.80 (0.69–0.92)	0.002	0.77 (0.67–0.90)	0.001
Obese	0.27 (0.12–0.63)	0.002	0.30 (0.13–0.69)	0.005	0.36 (0.22–0.57)	<0.001	0.34 (0.21–0.55)	<0.001
Rate of GWG (kg/week)	1.76 (1.21–2.57)	0.003	1.86 (1.26–2.76)	0.002	1.55 (1.18–2.03)	0.002	1.54 (1.16–2.03)	0.003

We adjusted the following confounders: Maternal age (<35 vs. ≥35 years), maternal race (Han vs. others), education (≥17 vs. 13–16 vs. 10–12 vs. ≤9 years), local citizens (yes vs. no), area of residence (urban vs. rural), annual family income (<30,000 vs. 30,000–79,999 vs. 80,000–119,999 vs. 120,000–199,999 vs. ≥200,000 CNY), multiple gestations (yes and no), parity (<1 vs. ≥1), gestational week at the survey first versus second versus third trimester, defined as $<13^{+6}$, $14–27^{+6}$ and ≥28 gestational week, egg intake per week (unit of 0.5 kg), meat intake per week (unit of 0.5 kg), active or passive smoking (yes vs. no), nausea and/or vomiting during pregnancy (no vs. slight vs. severe), multivitamins supplement (yes vs. no), calcium supplement (yes vs. no), and multiple gestational comorbidities including hepatitis B, cardiovascular diseases, gynecological diseases, diabetes mellitus (not including gestational diabetes), thyroid disease, diseases of immune system and digestive system (yes vs. no, respectively). IDA: Iron deficiency anemia; aOR: Adjusted odds ratio; CI: Confidence interval; BMI: Body mass index; GWG: Gestational weight gain.

Table 4: Sensitivity analyses by excluding pregnant women at the first trimester

Maternal weights	Test-IDA				Composite-IDA			
	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P
Prepregnancy BMI								
Underweight	1.33 (1.15–1.54)	<0.001	1.35 (1.17–1.57)	<0.001	1.30 (1.16–1.45)	<0.001	1.33 (1.19–1.49)	<0.001
Overweight	0.65 (0.52–0.82)	<0.001	0.69 (0.55–0.86)	0.001	0.80 (0.69–0.93)	0.003	0.78 (0.67–0.91)	0.001
Obese	0.28 (0.12–0.64)	0.003	0.30 (0.13–0.69)	0.005	0.36 (0.23–0.58)	<0.001	0.34 (0.21–0.56)	<0.001
Rate of GWG (kg/week)	1.81 (1.23–2.68)	0.003	1.93 (1.28–2.89)	0.002	1.59 (1.19–2.12)	0.002	1.62 (1.20–2.19)	0.001

We adjusted the following confounders: Maternal age (<35 vs. ≥35 years), maternal race (Han vs. others), education (≥17 vs. 13–16 vs. 10–12 vs. ≤9 years), local citizens (yes vs. no), area of residence (urban vs. rural), annual family income (<30,000 vs. 30,000–79,999 vs. 80,000–119,999 vs. 120,000–199,999 vs. ≥200,000 CNY), multiple gestations (yes and no), parity (<1 vs. ≥1), gestational week at the survey first versus second versus third trimester, defined as $<13^{+6}$, $14–27^{+6}$ and ≥28 gestational week, egg intake per week (unit of 0.5 kg), meat intake per week (unit of 0.5 kg), active or passive smoking (yes vs. no), nausea and/or vomiting during pregnancy (no vs. slight vs. severe), multivitamins supplement (yes vs. no), calcium supplement (yes vs. no), and multiple gestational comorbidities including hepatitis B, cardiovascular diseases, gynecological diseases, diabetes mellitus (not including gestational diabetes), thyroid disease, diseases of immune system and digestive system (yes vs. no, respectively). IDA: Iron deficiency anemia; aOR: Adjusted odds ratio; CI: Confidence interval; BMI: Body mass index; GWG: Gestational weight gain.

before pregnancy were more likely to develop IDA during pregnancy, and that faster GWG was also associated with higher risk of IDA. The results were similar, regardless of the use of different outcomes measures (i.e., test IDA and composite IDA).

One may argue that our study enrolled pregnant women at different trimesters, and the magnitude of association between prepregnancy BMI and the risk of IDA may differ across different trimesters (i.e., presence of interaction). However, our analysis of the interaction effect was not statistically significant, suggesting that the effects of prepregnancy BMI on the risk of IDA were consistent across the whole gestation period. The sensitivity analysis by excluding women at the first trimester supports the results from the main analyses.

Our study findings are important and timely to clarify the roles of maternal weight indicators on the development of IDA. In particular, the conflicting biological rationales, stated earlier, have made the clinical practice challenging and evidence-based recommendations are not readily available.[23-25] In summary, our findings may have three important implications for weight management and the use

of iron supplements. First, our findings clearly emphasize, on top of other studies investigating adverse effects of excessive weight gain, that fast weight gain during pregnancy is undesirable. Weight control has to be reinforced among pregnant women. Second, those women who are underweight pregnancy are probably high-risk population for IDA, and prophylactic use of iron supplements may be warranted. Third, the development of IDA could occur at any gestational age (first to third trimester), regardless of BMI before pregnancy. Early use of oral supplements might be desirable, particularly those who are underweight. Meanwhile, because the study is observational in nature, one should use the finding with cautions. In the test of the hypotheses that early use of iron supplements and weight control reinforcement could reduce the risk of IDA, randomized trials continue to serve the best source of evidence.

Comparison with previous studies

Several studies examined the association between BMI and iron status, in pregnant population and other populations. The findings were inconsistent.[12,20,21,26] In pregnant adolescents' population, BMI was found to be inversely associated with surrogate markers of ID, such as hemoglobin, serum ferritin,

and transferrin receptor.[26] In another study, obese women were less likely to have low serum ferritin or the risk of ID.[12,27] These findings came from cross-sectional analyses and were limited for making causal inference. In the third study, maternal obesity during pregnancy was found to be inversely associated with ID, which was however measured by transferrin receptor and body iron.[20] The latest study, involving only 255 women, found no association between maternal weight indicators and ID.[21]

In comparison, our study, including a large number of participants, clearly suggested that maternal weight indicators were statistically associated with the risk of IDA, a more clinically important outcome measure. We used the cohort study design to explore the association, by which a causal inference is possible. Given the large number of events, we were able to adjust for the confounding effects. We also were able to investigate the impacts of both prepregnancy BMI and rate of GWG on the IDA risk. In addition, we have examined the underweight population in association with the IDA risk. All these analyses were not explored in the previous studies. Therefore, our findings provided more comprehensive and clinically meaningful findings.

Strengths and limitations
Our study has several strengths. To the best of knowledge, this is the largest study that investigates the impact of maternal weights indicators on the risk of IDA. We used rigorous methods for data collection and data management. Second, we prespecified and adjusted for a number of potentially important confounders, given the large number of events we collected. Third, we have conducted through analyses by examining the consistency of findings using two relevant outcomes (i.e., test IDA and composite IDA). Fourth, we examined for the putative interaction between prepregnancy BMI categories and different trimesters and suggested the effects of prepregnancy BMI categories on IDA among different trimesters were not varied. We additionally used multilevel regression model to control for the cluster effect among different hospitals. We also conducted a sensitivity analysis to check for robustness of findings.

Our study also has a few limitations. First, we used the local laboratory facilities to examine the concentrations of serum ferritin and hemoglobin. We realized that the variable performance of laboratory facilities may occur. This decision was made primarily because of the study feasibility, limited availability of resources, and efficacy of the study. Nevertheless, we contacted all the 24 hospitals to ensure that their facilities were well calibrated and required that the key parameters were provided. Second, the data for the cohort study primarily came from a cross-sectional study and the accompanying survey that collected prepregnancy baseline data. In nature, the data on the exposure and confounders were collected retrospectively. There was a risk of bias associated with retrospective data collection (e.g., more misclassifications and inaccuracies).

In conclusion, our study suggested that lower prepregnancy BMI was associated with higher risk of IDA, and pregnant women with faster GWG may be more likely to develop IDA. These findings apply to pregnant women at all trimesters. Given the potential harms of IDA on pregnant women and prenatal infants, prophylactic iron supplement should be administered for high risk population of IDA.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Conflicts of interest
There are no conflicts of interest.

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孕妇体重与孕期缺铁性贫血的相关性研究：基于一项队列研究的结果

摘要

背景： 孕妇体重对孕期缺铁性贫血的影响仍然是不清楚的，本文旨在调查孕妇体重与孕期缺铁性贫血的相关性。

方法： 我们在中国实施了一项队列研究来评估孕妇体重与孕期缺铁性贫血的相关性，孕妇体重包括孕前体重指数和孕期体重增长速度两个指标。其中，不同孕期缺铁性贫血的诊断数据来自一项全国性的横断面研究，我们同时考察了经实验室诊断的缺铁性贫血和孕妇自报的缺铁性贫血。此外，我们回顾性收集了相关基线信息（孕前体重指数）和孕期体重增长速度。我们采用多水平logistic模型来评估孕妇体重与孕期缺铁性贫血的相关性并控制潜在混杂因素的影响。

结果： 从2016年9月19日到2016年11月20日，我们从中国24家医院总共纳入11,782例孕妇。其中，1515 （12.9%）例发生经实验室诊断的缺铁性贫血，3915 （33.3%）发生复合缺铁性贫血（经实验室诊断和孕妇自报任意一种情况）。在调整了混杂和医院间的聚集效应后，我们发现：孕前低体重孕妇，相比于孕前体重正常孕妇，有更高的缺铁性贫血风险（实验室诊断缺铁性贫血：*aOR*:1.35, 95%*CI*:1.17-1.57 ；复合缺铁性贫血：*aOR*: 1.35, 95%*CI*:1.21-1.51）；相反，孕前超重和肥胖的孕妇有更低的经实验室诊断的缺铁性贫血风险（超重：*aOR*: 0.68, 95%*CI*: 0.54-0.86; 肥胖：*aOR* 0.30, 95%*CI* 0.13-0.69）和复合缺铁性贫血风险（超重：*aOR*: 0.77, 95%*CI*: 0.67-0.90; 肥胖：*aOR*: 0.34, 95%*CI*:0.21-0.55）。此外，更快的孕期体重增长速度也与缺铁性贫血的风险呈正相关（实验室诊断缺铁性贫血： *aOR*: 1.86, 95%*CI*: 1.26-2.76; 复合缺铁性贫血：*aOR*: 1.54, 95%*CI*:1.16-2.03）。

结论： 孕妇孕前低体重和孕期体重增长速度过快更容易发生孕期缺铁性贫血，对上述人群应加强孕期体重管理和补充铁元素。

Supplementary Table 1: List of 24 selected hospitals in our study

Regions	Cities	Selected hospitals
Southwest	Chengdu	West China Second Hospital, Sichuan University*
	Chengdu	Sichuan Provincial Hospital for Women and Children
	Panzhihua	Panzhihua Central Hospital
	Chongqing	Chongqing Medical Center for Women and Children
East China	Hangzhou	Obstetrics and Gynecology Hospital of Zhejiang University*
	Xiamen	Xiamen Medical Center for Women and Children
	Wenzhou	Wenzhou People's Hospital
	Suzhou	Suzhou Municipal Hospital
Central South	Wuhan	Union Hospital Affiliated to Huazhong University of Science and Technology*
	Wuhan	Maternal and Child Health Hospital of Hubei Province
	Zhengzhou	The First Affiliated Hospital of Zhengzhou University
	Nanning	The First Affiliated Hospital of Guangxi Medical University
Northwest	Xi'an	Shanxi Provincial Hospital for Women and Children*
	Xianyang	The Second Affiliated Hospital of Shanxi University of Traditional Chinese Medicine
	Yan'an	The Affiliated Hospital of Yan'an University
	Wulumuqi	Xinjiang Provincial Hospital for Women and Children
North China	Beijing	Beijing Obstetrics and Gynecology Hospital*
	Tianjin	Tianjin Central Hospital of Gynecology Obstetrics
	Shijiazhuang	The Fourth Hospital of Shijiazhuang City
	Beijing	Beijing Friendship Hospital

*Coordinator of each region.