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RESEARCH ARTICLE

Association Between Maternal Creatinine to Body Weight Ratio and Small/Large for Gestational Age Newborns Among 11,734 Chinese Women

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Abstract

Background Serum creatinine to body weight ratio (CBWR) is closely associated with non-alcoholic fatty liver disease, diabetes, and all-cause mortality. This study aimed to assess the impact of CBWR in late pregnancy on incident small and large for gestational age (SGA/LGA) deliveries.

Methods This observational study included 11,734 pregnant women with hospital-based hepatic/renal data (2016–2017). Demographic characteristics were compared between CBWR quintiles using appropriate parametric or nonparametric tests. Relationship between CBWR and clinical/laboratory parameters was assessed using Spearman's correlation. Linear regression was employed to evaluate the association of CBWR with fetal birth length/weight, while logistic regression was used to calculate adjusted odds ratios (ORs) for SGA/LGA, with both models adjusting for maternal age, parity, blood pressure, gestational week, assisted reproduction, neonatal sex, and laboratory results. Sensitivity analyses and subgroup stratifications confirmed these associations. Non-linear trends were explored using smooth curve fitting techniques.

Results Among these newborns, 1033 (8.80%) were classified as SGA and 1,827 (15.57%) as LGA. CBWR was associated with smaller birth length (β = -0.21 cm; 95% CI: -0.28, -0.15) and lower birth weight (β = -0.29 kg; 95% CI: -0.31, -0.27) in the highest versus lowest quintile. The multivariate-adjusted ORs of SGA in higher quintiles versus the lowest quintile of CBWR were 1.63 (95% CI: 1.21, 2.21), 2.16 (95% CI: 1.61, 2.89), 2.99 (95% CI: 2.25, 3.97), and 5.24 (95% CI: 3.97, 6.92), respectively; those for LGA were 0.60 (95% CI: 0.52, 0.70), 0.53 (95% CI: 0.46, 0.62), 0.39 (95% CI: 0.32, 0.46), and 0.23 (95% CI: 0.19, 0.29), respectively. Per standard deviation (SD) increase in CBWR was accompanied by a 1.63-fold increase in SGA risk (OR = 1.63, 95% CI: 1.52, 1.75) and a 42% decrease in LGA risk (OR = 0.58, 95% CI: 0.55, 0.63). Sensitivity analysis confirmed the consistence of these findings. Subgroup analysis demonstrated that CBWR was strongly associated with SGA risk in women with CBWR > 0.98 umol/L/kg complicated by preeclampsia or preterm birth, while in those complicated by gestational diabetes mellitus, the association was attenuated.

Conclusion Our findings suggest that elevated CBWR in late pregnancy may be associated with decreased LGA risk and increased SGA risk. While CBWR represents an easily measurable and cost-effective potential indicator, these observational results require validation in prospective, population-based studies before considering clinical application.

Keywords Creatinine to body weight ratio · Birth weight · Small for gestational age · Large for gestational age · Fetal growth

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Abbreviations

CBWR	Creatinine to body weight ratio
SGA/AGA/LGA	Small/appropriate/large for gestational age
GDM	Gestational diabetes mellitus
ICP	Intrahepatic cholestasis of pregnancy
PE	Preeclampsia
PIH	Pregnancy-induced hypertension
PTB	Preterm birth
RBC	Red blood cell
WBC	White blood cell
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
hsCRP	High-sensitive C reactive protein
BMI	Body mass index
BP	Blood pressure
SD	Standard deviation
IQR	Interquartile range
CI	Confidence interval
OR	Odds ratio

1 Background

Birthweight often marks an important indicator of fetal growth and development in utero. Excessive and insufficient birthweight, represented by large and small for gestational age (LGA/SGA) newborns, have been consistently linked to perinatal mortality and morbidity, neurodevelopmental disorders, obesity and diabetes in adolescence, and cardiometabolic problems in adulthood [1–4]. Therefore, enhanced studies on accurate detection and prevention of fetal growth-related disorders are urgently required in modern antenatal care.

Serum creatinine, a routine index of renal function, is easy to measure and relatively stable. Renal insufficiency before and during pregnancy is closely associated with pregnancy outcomes including pregnancy induced hypertension (PIH), pre-eclampsia (PE), preterm birth (PTB), and fetal growth restriction (FGR) [5–9]. Physiologically, serum creatinine levels declined quickly during early pregnancy, reach a platform during mid-pregnancy, and increase slowly during late pregnancy toward preconception levels [10–13]. Until now, limited researches have investigated the relationship of elevated creatinine levels before and/or during pregnancy with pregnancy complications and adverse birth outcomes in women without antecedent renal disorders [14, 15].

Gestational weight gain (GWG) refers to the the amount of weight gained during pregnancy, which is typically calculated by subtracting the mother's pre-pregnancy weight from her weight at delivery. Inappropriate GWG is linked to adverse birth outcomes. Insufficient GWG is associated with higher risk of SGA and PTB and lower risk of LGA and macrosomia, while excessive GWG (usually manifested by high maternal weight at delivery) is opposite [16]. In addition, previous studies revealed that maternal weight at delivery is a better marker for predicting LGA and macrosomia delivery than other traditional predictors [17, 18]. Therefore, we hypothesized that serum creatinine to body weight ratio (CBWR) would be associated with adverse fetal growth-related birth outcomes. Recent reports have demonstrated that CBWR, an interesting new index, could serve as a predictor for incident non-alcoholic fatty liver disease (NAFLD), diabetes mellitus (DM), and all-cause mortality [19–25]. However, no research has investigated the relationship between maternal CBWR and fetal growth and incident LGA/SGA to date in pregnant women. To address this issue, the purpose of the present study was to assess the association between CBWR and LGA/SGA risk in Chinese pregnant women.

2 Materials and Methods

2.1 Study Participants

A total of 13,275 consecutive pregnant women who delivered in Changzhou Maternal and Child Health Care Hospital during one observational period (April 1, 2016 to March 31, 2017) were initially enrolled in this study. This study received the approval of the ethics committee in Changzhou Maternal and Child Health Care Hospital (ZD201803). Informed consent was waived, as the information on mother–infant pairs was retrospectively obtained from medical records system. The present study included pregnant women with singleton live birth, exclusion criteria were: (1) preconception diseases (chronic renal, hepatic, cardiac, immune rheumatic, and thyroidal diseases, hypertension, diabetes mellitus, and syphilis); (2) missing serum creatinine levels or data on body weight at the time of admission; (3) took illicit drugs, smoked and drank alcohol during pregnancy. After excluding the participants who had lack of data on the CBWR ($n=622$), pre-gestational diseases ($n=488$), multiple pregnancy ($n=335$), and non-live birth ($n=96$), a total of 11,734 participants were eligible for the final analysis. None of the individuals smoked, drank alcohol or took illicit drugs during pregnancy. A routine investigation of each participant's complete blood count (CBC), liver and kidney function index, and hypersensitive C-reactive protein (hsCRP) at admission for labor was performed using matching automated analyzers (CBC: XN550, Sysmex INC., Japan; liver and kidney function: AU5800, Beckman Coulter Inc., Japan; hsCRP: BN II System, Siemens Diagnostics Inc.). Laboratory findings were downloaded from the Laboratory Information System (LIS) of the hospital. This system maintained a comprehensive and up-to-date record of all laboratory tests conducted, ensuring accurate and reliable data collection. Specifically, for each participant, relevant laboratory parameters such as CBC, liver and renal function tests, and other pertinent biomarkers were extracted. Demographic characteristics of mothers and their newborns were collected from the Electronic Medical Records (EMR) system of the hospital. The EMR system contained detailed records of patient encounters, including demographic information, medical history, and clinical observations. Data collection included: age, weight, height, blood pressure, reproduction history, medical history, pregnancy complications, delivery mode, and neonatal sex, gestational age, birth length and weight, were collected from the electric medical records system of the hospital. Data extraction from both the LIS and EMR systems was performed by trained personnel using standardized protocols to ensure consistency and accuracy. Additionally, quality control measures were implemented to verify the completeness and correctness of the extracted data, including cross-referencing entries and resolving discrepancies. CBWR was determined by dividing each participant's serum creatinine concentration (in μmol/L) by their current body weight (in kg). Given the lack of established population-based reference ranges for CBWR, particularly in pregnant women, we used a data-driven quintile approach to define exposure levels. The highest quintile (Q5, CBWR > 0.98 μmol/L/kg) was classified as the high-level group, while the lowest quintile (Q1, CBWR < 0.72 μmol/L/kg) served as the low-level group. The mid-level group consisted of the three middle quintiles (Q2–Q4, 0.72–0.98 μmol/L/kg). This relative categorization allowed for meaningful comparisons within the cohort, although these thresholds reflected internal distributional patterns rather than clinically validated cutoffs.

2.2 Definitions

The diagnoses of gestational diabetes mellitus (GDM), intrahepatic cholestasis of pregnancy (ICP), PE, and PIH were made according to previous reports [26, 27]. PTB was diagnosed when delivery happened before 37 gestational weeks [28]. Based on the gestational week, birthweight and gestational age-specific reference interval, the newborns were categorized into three groups: (1) SGA (< the 10th percentile); (2) appropriate for gestational age (AGA) (the 10th −90th percentile); (3) LGA (> the 90th percentile) [29, 30].

2.3 Statistical Analysis

Demographic characteristics of mother and their newborns in different CBWR were described. Differences among CBWR quintiles were determined by utilizing parametric and nonparametric methods appropriately. Spearman's correlation analysis was performed to investigate the correlation of CBWR with the clinical parameters and laboratory results. General linear regression analysis was used to examine the association between maternal CBWR and fetal growth indices (birth length and weight). Logistic regression analysis was applied to calculate odds ratios (ORs) and 95% confidence intervals (CI) for LGA and SGA newborns. All regression models were adjusted for the following variables: maternal age, height, parity, blood pressure (BP), gestational week, assisted reproduction, neonatal sex, and laboratory findings. To maximize the robustness of our findings while maintaining methodological rigor, we implemented a comprehensive covariate adjustment strategy that systematically incorporated all clinically pertinent variables available in our dataset. This analytical approach was specifically designed to: (1) substantially reduce potential confounding bias by accounting for the full spectrum of known biological and demographic influences, including maternal characteristics, pregnancy complications, and laboratory parameters; (2) enhance the internal validity of our results by minimizing spurious associations; and (3) ensure methodological transparency through exhaustive, non-selective variable inclusion. To confirm the reliability of these associations, sensitivity analysis based on logistic regression model was conducted among pregnant women with non-advanced age, primipara, natural conception, non-anemia, non-pregnancy complications, and non-PTB. Smooth curve fitting analysis was performed using generalized additive models (GAMs) to flexibly assess potential non-linear relationships between CBWR and SGA/LGA risk. Subgroup analysis was applied to determine whether the stratification of variables (age, parity, assisted reproduction technology use, hemoglobin levels, pregnancy complications, and gestational age) affected the relationship between CBWR and SGA/LGA risk.

Empower version 4.1 (X&Y Solutions, USA) and R package were used for the statistical analysis. The statistical significance presented as a P value < 0.05.

3 Results

3.1 Participant Characteristics

As shown in Table 1, the study analyzed 11,734 pregnant women (aged 15–47 years) stratified by CBWR quintiles (Q1–Q5: <0.72 to >0.98 μmol/L/kg). Complication rates included GDM (8.45%), ICP (6.17%), PE (3.55%), and PIH (2.11%). The mean CBWR at hospitalization for labor was 0.86 (SD 0.17) umol/L/kg. Higher CBWR levels showed

Table 1 Participants' characteristics in accordance with the quintiles of CBWR ($n = 11,734$)

Characteristics	CBWR (μmol/L/kg)					*P* trend
	Q1 (Bottom) (<0.72)	Q2 (0.72–0.80)	Q3 (0.81–0.88)	Q4 (0.89–0.98)	Q5 (Top) (>0.98)	
n	2346	2348	2345	2344	2351	
Maternal age (years)	28.9±4.6	28.7±4.4	28.6±4.4	28.5±4.3	28.4±4.4	<0.001
Height (cm) [a]	163.1±4.5	162.3±4.4	161.6±4.5	160.9±4.5	160.0±4.5	<0.001
Weight (kg)	81.4±9.3	74.6±7.3	70.7±6.7	67.4±6.3	63.0±6.4	<0.001
BMI (kg/m^2)	30.6±3.3	28.4±2.7	27.1±2.5	26.0±2.4	24.6±2.4	<0.001
Systolic BP (mmHg)	122.2±12.7	121.6±12.0	120.5±11.4	120.2±11.6	120.3±12.6	<0.001
Diastolic BP (mmHg)	75.2±8.7	74.8±8.3	74.3±7.9	74.1±8.0	74.4±8.8	0.003
Primipara (%)	1224 (52.2%)	1326 (56.5%)	1425 (60.8%)	1482 (63.2%)	1593 (67.8%)	<0.001
Assisted reproduction	63 (2.7%)	50 (2.1%)	59 (2.5%)	63 (2.7%)	42 (1.8%)	0.177
Cesarean section	1270 (54.1%)	1119 (47.7%)	958 (40.9%)	882 (37.6%)	806 (34.3%)	<0.001
Pregnancy complications [b]						
GDM	248 (10.6%)	187 (8.0%)	173 (7.4%)	197 (8.4%)	186 (7.9%)	<0.001
ICP	96 (4.1%)	104 (4.4%)	121 (5.2%)	171 (7.3%)	232 (9.9%)	<0.001
PE	116 (4.9%)	77 (3.3%)	58 (2.5%)	64 (2.7%)	101 (4.3%)	<0.001
PIH	68 (2.9%)	66 (2.8%)	36 (1.5%)	43 (1.8%)	35 (1.5%)	<0.001
PTB	201 (8.57%)	142 (6.05%)	146 (6.23%)	165 (7.04%)	149 (6.34%)	0.003
Gestational age (week)	38.6±1.7	38.7±1.7	38.7±1.7	38.7±1.6	38.7±1.6	0.004
Neonatal sex (male)	1246 (53.1%)	1224 (52.1%)	1232 (52.5%)	1227 (52.3%)	1264 (53.8%)	0.800
Neonatal height (cm)	49.9±1.3	49.9±1.4	49.8±1.4	49.8±1.4	49.7±1.5	<0.001
Neonatal weight (g)	3499.1±518.7	3411.6±484.3	3355.3±472.2	3286.3±463.1	3169.1±461.7	<0.001
Laboratory findings						
RBC (10^{12}/L)	4.1±0.3	4.0±0.4	4.0±0.3	4.0±0.4	4.0±0.4	<0.001
WBC (10^9/L)	8.8±2.2	8.8±2.2	8.8±2.3	8.7±2.2	8.6±2.2	<0.001
Platelet (10^9/L)	211.8±54.8	206.3±55.9	203.0±56.9	198.0±54.3	193.7±54.4	<0.001
Hemoglobin (g/L)	119.1±11.6	118.8±11.9	119.1±11.8	118.7±11.7	118.4±12.4	0.711
Total protein (g/L)	63.0±4.2	63.4±4.2	63.7±4.3	63.6±4.4	63.7±4.7	<0.001
Albumin (g/L)	36.4±2.5	36.3±2.5	36.5±2.5	36.5±2.4	36.4±2.7	0.155
Total bilirubin (μmol/L)	7.9±3.0	7.8±2.8	7.9±2.9	8.0±3.1	8.0±3.2	0.171
Direct bilirubin (μmol/L)	1.6±0.9	1.6±0.9	1.5±0.9	1.6±1.1	1.6±1.3	0.026
ALT (U/L)	11.0±8.7	10.6±9.5	11.2±10.7	11.7±14.0	13.5±21.9	<0.001
AST (U/L)	19.0±7.5	19.0±8.5	19.4±7.6	20.6±12.6	22.8±30.3	<0.001
Urea nitrogen (mmol/L)	3.2±0.8	3.4±0.8	3.5±0.8	3.6±0.9	4.0±1.1	<0.001
Creatinine (μmol/L)	52.4±6.3	56.9±5.5	59.5±5.7	62.5±5.9	69.3±10.5	0.638
hsCRP (mg/L)	3.4 (1.9–5.9)	3.1 (1.7–5.4)	3.0 (1.6–4.9)	2.7 (1.5–4.7)	2.5 (1.4–4.4)	<0.001

Notes: Variables were presented as mean±SD, median (IQR), and frequency (percentage). [a] 6 missing height of data. [b] 230 co-existing two kinds of pregnancy complications

Abbreviations: CBWR, creatinine to body weight ratio; Q, quintile; BMI, body mass index; BP, blood pressure; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, pre-eclampsia; PIH, pregnancy induced hypertension; PTB, preterm birth; RBC, red blood cell; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferas; hsCRP, high sensitive C-reactive protein; SD, standard deviation; IQR, interquartile range

significant associations with decreased maternal anthropometrics (age, height, weight, BMI), lower cesarean rates and neonatal weights, and reduced platelet counts and hsCRP levels, while correlating with increased primiparity, ICP incidence, and renal markers (urea nitrogen, creatinine). Correlation analyses further revealed that maternal CBWR was negatively correlated with age (r = -0.046), height (r = -0.238), weight (r = -0.677), BMI (r = -0.626), systolic blood pressure (BP; r = -0.058), diastolic BP (r = −0.034), parity (r = -0.120), neonatal length (r = -0.116), and neonatal weight (r = -0.255), as well as the counts of red blood cells (RBC; r = -0.054), white blood cells (WBC; r = -0.045), and platelets (r = -0.123), and hsCRP levels (r = -0.126). CBWR was positively correlated with the levels of total protein (r=0.052), alanine aminotransferase (ALT; r=0.045), aspartate aminotransferase (AST; r=0.189), urea nitrogen (r=0.273), and creatinine (r=0.685) (all $P<0.001$; Table 2).

3.2 Maternal CBWR and Fetal Growth

Higher maternal CBWR levels showed significant dose-dependent associations with reduced neonatal size (Table 3). Compared to Q1, CBWR levels in Q2–Q5 were associated

Table 2 Correlation of CBWR with demographic characteristics and laboratory findings in late pregnancy

	r	*P* value
Age	-0.046	<0.001
Height	-0.238	<0.001
Weight	-0.677	<0.001
BMI	-0.626	<0.001
Systolic BP	-0.058	<0.001
Diastolic BP	-0.034	<0.001
Parity	-0.120	<0.001
Gestational age	0.017	0.066
Neonatal height	-0.116	<0.001
Neonatal weight	-0.255	<0.001
RBC	-0.054	<0.001
WBC	-0.045	<0.001
Platelet	-0.123	<0.001
Hemoglobin	-0.011	0.221
Total protein	0.052	<0.001
Albumin	0.010	0.258
Total bilirubin	0.014	0.123
Direct bilirubin	-0.005	0.570
ALT	0.045	<0.001
AST	0.189	<0.001
Urea nitrogen	0.273	<0.001
Creatinine	0.685	<0.001
hs-CRP	-0.126	<0.001

Abbreviations: CBWR, creatinine to body weight ratio; BMI, body mass index; BP, blood pressure; RBC, red blood cell; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferas; hsCRP, high sensitive C-reactive protein

with progressively decreasing birth length (range: -0.12 to -0.21 cm) and birthweight (range: -91.09 to -291.58 g). Each 0.17 µmol/L/kg (1-SD) increase in CBWR corresponded to a 0.08 cm shorter birth length (95% CI: -0.10, -0.05) and 101.40 g lower birthweight (95% CI: -109.00, -93.79) after adjustment. The mean birth measurements were 3344.22 ± 493.24 g and 49.82 ± 1.40 cm.

3.3 Maternal CBWR and SGA/LGA

The study identified significant associations between maternal CBWR and neonatal growth outcomes among 11,734 births (8.80% SGA, 15.57% LGA). Higher CBWR levels showed progressively increasing associations with SGA risk (Q2–Q5 adjusted ORs: 1.63, 2.16, 2.99, 5.24) and decreasing associations with LGA risk (Q2–Q5 adjusted ORs: 0.60, 0.53, 0.39, 0.23) compared to Q1 (Table 4). Each SD increase in CBWR was associated with 1.63-fold higher SGA risk (95% CI: 1.52, 1.75) and 42% lower LGA risk (95% CI: 0.55, 0.63). Sensitivity analysis demonstrated consistent findings among the participants with non-advanced age, primipara, non-assisted reproduction, non-anemia, non-pregnancy complications, and full-term birth (Table S1 to Table S6). These associations were particularly strong in women with PE (SGA adjusted OR = 8.35; LGA adjusted OR = 0.25) but attenuated in GDM pregnancies (Tables 5 and 6). Figure 1 illustrated the differences in serum creatinine levels, maternal body weight, and CBWR among mothers whose newborns were classified

Table 3 Prospective association between maternal CBWR and fetal development in the study population

Characteristics	CBWR (µmol/L/kg)					*P* trend	Per-SD increase in CBWR
	Q1 (Bottom) (<0.72)	Q2 (0.72–0.80)	Q3 (0.81–0.88)	Q4 (0.89–0.98)	Q5 (Top) (>0.98)		
Neonatal height (cm)							
Model 1, β (95% CI)	0	-0.07 (-0.15, 0.01)	-0.09 (-0.17, -0.01)	-0.16 (-0.24, -0.08)	-0.26 (-0.34, -0.18)	<0.001	-0.11 (-0.13, -0.08)
Model 2, β (95% CI)	0	-0.12 (-0.19, -0.06)	-0.14 (-0.20, -0.07)	-0.20 (-0.26, -0.13)	-0.24 (-0.31, -0.18)	<0.001	-0.09 (-0.11, -0.07)
Model 3, β (95% CI)	0	-0.12 (-0.18, -0.05)	-0.12 (-0.19, -0.06)	-0.17 (-0.23, -0.10)	-0.21 (-0.28, -0.15)	<0.001	-0.08 (-0.10, -0.05)
Neonatal weight (g)							
Model 1, β (95% CI)	0	-87.53 (-115.02, -60.04)	-143.82 (-171.32, -116.32)	-212.76 (-240.26, -185.26)	-329.98 (-357.45, -302.50)	<0.001	-116.58 (-125.25, -107.91)
Model 2, β (95% CI)	0	-93.42 (-114.93, -71.90)	-141.96 (-163.64, -120.29)	-205.30 (-227.18, -183.42)	-299.04 (-321.29, -276.80)	<0.001	-102.36 (-109.44, -95.27)
Model 3, β (95% CI)	0	-91.09 (-112.69, -69.48)	-135.89 (-157.81, -113.96)	-197.02 (-219.33, -174.72)	-291.58 (-314.93, -268.24)	<0.001	-101.40 (-109.00, -93.79)

Notes: Model 1 was unadjusted. Model 2 was adjusted for age, height, parity, BP, gestational age, assisted reproduction and neonatal sex. The model 3 was adjusted for these variables controlled in the model 2 and the laboratory findings (RBC, WBC, platelet, hemoglobin, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, and hsCRP)

Abbreviations: CBWR, creatinine to body weight ratio; Q, quintile; CI, confidence interval; BP, blood pressure; RBC, red blood cell; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferas; hsCRP, high sensitive C-reactive protein

Table 4 Prospective association between maternal CBWR and risk of SGA/LGA in the study population

Characteristics	CBWR (µmol/L/kg)					*P* trend	Per-SD increase in CBWR
	Q1 (Bottom) (<0.72)	Q2 (0.72–0.80)	Q3 (0.81–0.88)	Q4 (0.89–0.98)	Q5 (Top) (>0.98)		
SGA							
No. of cases (percentage)	76 (3.24%)	129 (5.49%)	170 (7.25%)	239 (10.20%)	419 (17.82%)	<0.001	
Model 1, OR (95% CI)	1.00	1.74 (1.30, 2.32)	2.33 (1.77, 3.08)	3.39 (2.60, 4.42)	6.48 (5.04, 8.33)	<0.001	1.76 (1.66, 1.87)
Model 2, OR (95% CI)	1.00	1.69 (1.26, 2.27)	2.23 (1.68, 2.96)	3.19 (2.43, 4.18)	5.72 (4.40, 7.42)	<0.001	1.67 (1.57, 1.78)
Model 3, OR (95% CI)	1.00	1.63 (1.21, 2.21)	2.16 (1.61, 2.89)	2.99 (2.25, 3.97)	5.24 (3.97, 6.92)	<0.001	1.63 (1.52, 1.75)
LGA							
No. of cases (percentage)	638 (27.20%)	417 (17.76%)	347 (14.80%)	260 (11.09%)	165 (7.02%)	<0.001	
Model 1, OR (95% CI)	1.00	0.58 (0.50, 0.66)	0.46 (0.40, 0.54)	0.33 (0.29, 0.39)	0.20 (0.17, 0.24)	<0.001	0.55 (0.52, 0.59)
Model 2, OR (95% CI)	1.00	0.62 (0.54, 0.72)	0.52 (0.45, 0.61)	0.38 (0.32, 0.45)	0.24 (0.20, 0.29)	<0.001	0.59 (0.56, 0.63)
Model 3, OR (95% CI)	1.00	0.60 (0.52, 0.70)	0.53 (0.46, 0.62)	0.39 (0.32, 0.46)	0.23 (0.19, 0.29)	<0.001	0.58 (0.55, 0.63)

Notes: Model 1 was unadjusted. Model 2 was adjusted for age, height, parity, BP, gestational age, assisted reproduction and neonatal sex. The model 3 was adjusted for these variables controlled in the model 2 and the laboratory findings (RBC, WBC, platelet, hemoglobin, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, and hsCRP)

Abbreviations: CBWR, creatinine to body weight ratio; Q, quintile; SGA/LGA, small/large for gestational age; OR, odds ratio; CI, confidence interval; BP, blood pressure; RBC, red blood cell; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferas; hsCRP, high sensitive C-reactive protein

Table 5 Subgroup analysis of effect modification of maternal characteristics on associations between CBWR and SGA neonates

	Low CBWR (Q1–Q4)		High CBWR (Q5)		Crude		Adjusted	
	Total	SGA (%)	Total	SGA (%)	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age (years)								
< 35	8285	6.75	2084	18.14	3.06 (2.66, 3.52)	<0.001	2.52 (2.16,2.95)	<0.001
≥ 35	1098	5.01	267	15.36	2.51 (1.78, 3.54)	<0.001	2.02 (1.37, 2.98)	<0.001
Parity								
No child	5457	7.64	1593	18.58	2.76 (2.35, 3.24)	<0.001	2.35 (1.97, 2.81)	<0.001
≥ 1 child	3926	5.02	758	16.23	2.34 (1.88, 2.91)	<0.001	2.33 (1.81, 3.01)	<0.001
Assisted reproduction								
No	9148	6.61	2309	17.93	3.08 (2.70, 3.53)	<0.001	2.53 (2.17, 2.94)	<0.001
Yes	235	3.83	42	11.90	1.91 (0.75, 4.87)	0.177	1.32 (0.45, 3.84)	0.613
Anemia (hemoglobin < 110 g/L)								
No	7459	6.96	1819	18.47	3.03 (2.61, 3.51)	<0.001	2.47 (2.10, 2.91)	<0.001
Yes	1925	4.94	531	15.63	2.48 (1.93, 3.18)	<0.001	2.66 (1.92, 3.68)	<0.001
Pregnancy complications [a]								
No	7724	6.43	1861	16.93	2.96 (2.55, 3.45)	<0.001	2.53 (2.15, 2.99)	<0.001
GDM	805	3.73	186	13.44	2.26 (1.47, 3.47)	<0.001	1.69 (1.05, 2.70)	0.029
ICP	492	6.71	232	18.97	3.40 (2.42, 4.78)	<0.001	2.49 (1.69, 3.66)	<0.001
PE	315	16.51	101	48.51	13.70 (9.18, 20.46)	<0.001	8.35 (4.98, 14.01)	<0.001
PIH	213	7.04	35	22.86	4.31 (1.95, 9.53)	<0.001	2.60 (1.07, 6.34)	0.035
PTB								
No	8729	6.14	2202	16.89	3.11 (2.70, 3.58)	<0.001	2.58 (2.21, 3.02)	<0.001
Yes	654	11.93	149	31.54	7.04 (4.93, 10.06)	<0.001	3.98 (2.62, 6.04)	<0.001

Notes: Adjusted for age, height, BP, parity, assisted reproduction, gestational age, pregnancy complications, fetal gender, and the laboratory findings (RBC, WBC, platelet, hemoglobin, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, and hsCRP), except for the variable that was categorized. $P > 0.05$ for all interaction tests. [a] 230 co-existing two kinds of pregnancy complications

Abbreviations: CBWR, creatinine to body weight ratio; SGA, small for gestational age; Q, quintile; OR, odds ratio; CI, confidence interval; BP, blood pressure; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, preeclampsia; PIH, pregnancy induced hypertension; PTB, preterm birth; RBC, red blood cell; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferas; hsCRP, high sensitive C-reactive protein

Table 6 Subgroup analysis of effect modification of maternal characteristics on associations between CBWR and LGA neonates. [a]

	Low CBWR (Q1–Q4)		High CBWR (Q5)		Crude		Adjusted	
	Total	LGA (%)	Total	LGA (%)	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age (years)								
< 35	8285	16.45	2084	6.14	0.33 (0.28, 0.40)	<0.001	0.39 (0.32, 0.48)	<0.001
≥ 35	1098	27.23	267	13.86	0.82 (0.57, 1.16)	0.560	0.66 (0.45, 0.98)	0.040
Parity								
No child	5457	13.96	1593	5.15	0.33 (0.26, 0.42)	<0.001	0.37 (0.29, 0.47)	<0.001
≥ 1 child	3926	22.92	10.95	16.23	0.76 (0.60, 0.96)	0.024	0.61 (0.47, 0.80)	<0.001
Assisted reproduction								
No	9148	17.53	2309	7.02	0.35 (0.30, 0.42)	<0.001	0.41 (0.34, 0.49)	<0.001
Yes	235	24.68	42	7.14	0.36 (0.11, 1.17)	0.090	0.38 (0.11, 1.30)	0.123
Anemia Anemia (hemoglobin<110 g/L)								
No	7459	16.69	1819	6.21	0.33 (0.27, 0.40)	<0.001	0.38 (0.31, 0.47)	<0.001
Yes	1925	21.66	531	9.60	0.53 (0.39, 0.71)	<0.001	0.51 (0.36, 0.72)	<0.001
Pregnancy complications [b]								
No	7724	16.16	1861	6.34	0.35 (0.29, 0.43)	<0.001	0.41 (0.33, 0.50)	<0.001
GDM	805	31.93	186	13.98	0.84 (0.55, 1.28)	0.425	0.95 (0.60, 1.50)	0.830
ICP	492	6.71	232	18.97	0.44 (0.27, 0.71)	<0.001	0.46 (0.27, 0.77)	0.003
PE	315	19.37	101	4.95	0.27 (0.11, 0.67)	0.004	0.25 (0.09, 0.73)	0.011
PIH	213	21.60	35	11.43	0.67 (0.24, 1.90)	0.451	0.81 (0.28, 2.39)	0.706
PTB								
No	8729	17.68	2202	6.95	0.35 (0.29, 0.41)	<0.001	0.40 (0.34, 0.49)	<0.001
Yes	654	18.2	149	8.05	0.41 (0.23, 0.74)	0.003	0.46 (0.24, 0.88)	0.018

Notes: Adjusted for age, height, BP, parity, assisted reproduction, gestational age, pregnancy complications, fetal gender, and the laboratory findings (RBC, WBC, platelet, hemoglobin, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, and hsCRP), except for the variable that was categorized. $P>0.05$ for all interaction tests

Abbreviations: CBWR, creatinine to body weight ratio; LGA, large for gestational age; Q, quintile; OR, odds ratio; CI, confidence interval; BP, blood pressure; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, preeclampsia; PIH, pregnancy induced hypertension; PTB, preterm birth; RBC, red blood cell; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferas; hsCRP, high sensitive C-reactive protein

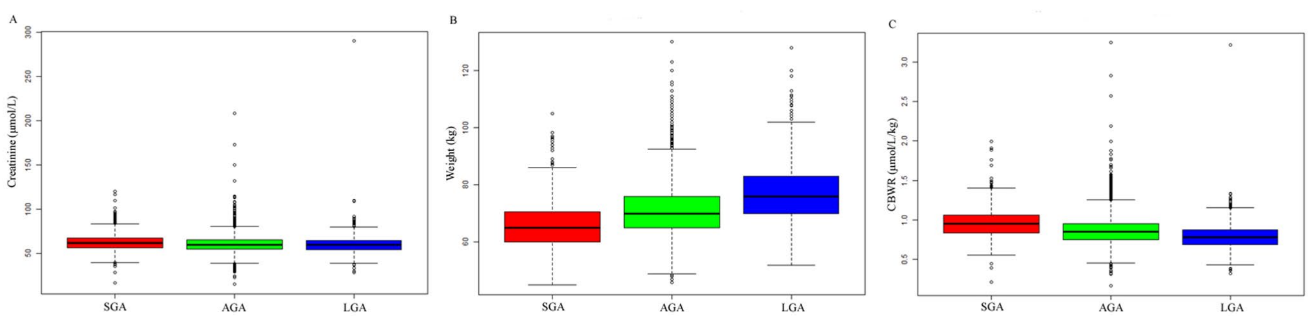

Fig. 1 Comparison of serum creatinine, body weight and CBWR among women who delivered SGA, AGA and LGA newborns (creatinine: 62.34±9.98 vs. 59.97±8.71 vs. 59.63±9.84 μmol/L, body weight: 66.15±8.91 vs. 70.88±9.18 vs. 76.77±9.82 kg, CBWR: 0.96±0.18 vs. 0.86±0.17 vs. 0.79±0.15 μmol/L/kg, all $P<0.001$ except for creatinine in AGA vs. LGA: $P=0.306$; Fig. 1)

SGA, AGA, and LGA. Specifically, serum creatinine levels were 62.34±9.98 μmol/L for SGA, 59.97±8.71 μmol/L for AGA, and 59.63±9.84 μmol/L for LGA groups, with no significant difference observed between the AGA and LGA groups ($P=0.306$). Maternal body weights had been significantly different across all three groups: 66.15±8.91 kg for SGA, 70.88±9.18 kg for AGA, and 76.77±9.82 kg for LGA groups (all $P<0.001$). The CBWR values also showed significant differences: 0.96±0.18 μmol/L/kg for SGA, 0.86±0.17 μmol/L/kg for AGA, and 0.79±0.15 μmol/L/kg for LGA groups (all $P<0.001$). Additionally, the GAMs used for smooth curve fitting analysis visually identified nonlinear relationships between CBWR and the risks of SGA and LGA (Fig. 2).

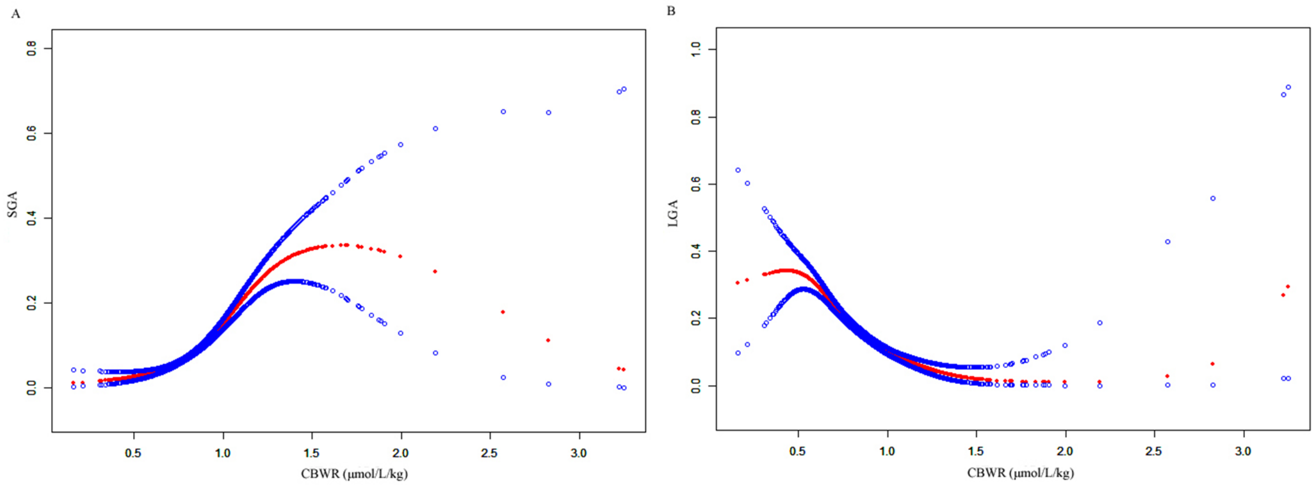

Fig. 2 Smooth curve fitting analysis of CBWR with SGA/LGA risk. Adjusted for maternal age, height, parity, blood pressure, gestational age, assisted reproduction, neonatal sex, and laboratory findings (RBC, WBC, platelet, hemoglobin, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, urea nitrogen, and hsCRP)

4 Discussion

4.1 Main Findings

In this observational study of >11,000 Chinese pregnant women from a real-world database, we explored the impact of CBWR on the fetal growth and incident SGA/LGA delivery for the first time. Our analysis showed a significant negative association between maternal CBWR and birth length and weight, and an increased risk of SGA and a decreased risk of LGA elicited by high CBWR (>0.98 μmol/L/kg). The Sensitivity analysis observed consistent results among the participants with among the participants with non-advanced age, primipara, non-assisted reproduction, non-anemia, non-pregnancy complications, and full-term birth. Additionally, as potential modifiers of the relationship between CBWR and SGA/LGA delivery, PE and GDM were observed to be significant, as stronger associations were detect in participants with PE, while weaker associations were found in those with GDM.

4.2 Interpretation

Serum creatinine is generally considered to be an important indicator of renal function. Although it usually appears in clinical practice, the reference interval of creatinine levels for women in different trimesters of pregnancy have not been well established [31]. The upper threshold of creatinine level (97.5th percentile) in healthy pregnant women varies across the published cohort studies. For late pregnancy, the top limits of the reference range include levels of 57, 72, 77, 80, and 90 μmol/L [10, 15, 31–33]. In the present study, the 97.5th values for serum creatinine level in 9585 women without pregnancy complications was 76.7 μmol/L, which was closely aligned with the reported value of 77 μmol/L in the meta-analysis [31]. This discrepancy in variance of serum creatinine level might be attributed to study design, sample size, ethnicity, and different assay methods. For example, the Jaffe method was more susceptible to the influence of interfering substances than the enzymatic assay [34]. In addition, a broader racial mix of pregnant women with different muscle mass and body size might account for the variance of serum creatinine level [33]. A positive correlation (Spearman's rho: $r=0.080$, $P<0.001$) between creatinine levels and gestational weeks (28–41 weeks) was observed in the present study. This result is similar to previous reports that have shown a mild increase with gestational age during the third trimester [10–13]. Kang et al. In Korea found observed a stepwise increase in SGA incidence among pregnant women with antenatal creatinine levels from the quartile (Q) 1 to Q 4 group (from 16.1 to 30.8%) [14]. Similarly, Xu et al. in China reported that elevated serum creatinine levels (ranged from 100 to 120% of its upper reference limit) in late pregnancy significantly increased the risk of FGR, with the ORs from 3.10 (95% CI: 2.43–3.95) to 9.73 (95% CI: 5.78–16.36) [15]. In this study, serum creatinine levels were significantly higher in women who delivered SGA newborns compared with those who delivered AGA newborns (62.34±9.98 vs. 59.97±8.71, $P<0.001$); elevated creatinine levels (>76.7 μmol/L) in late pregnancy also moderately increased SGA risk and slightly decreased LGA risk in unadjusted model (SGA: OR=2.34, 95% CI: 1.80, 3.05, $P<0.001$; LGA: OR=0.72, 95% CI: 0.53, 0.98, $P=0.036$). However, after adjusted for potential confounders (maternal age, BMI, parity, BP, gestational age, assisted reproduction, neonatal sex, and laboratory findings), these associations displayed no statistical significance (SGA: OR = 1.27, 95% CI: 0.93, 1.74, $P = 0.131$; LGA: OR = 0.84, 95% CI: 0.59, 1.18, $P = 0.307$). Considering the established positive correlation between maternal gestational weight gain (GWG) and fetal birth weight, it is advisable to renew traditional single measurement of creatinine level by CBWR in clinical practice of assessing SGALGA risk [35]. CBWR has recently been recognized as an intriguing new biomarker significantly associated with incident NAFLD, DM and all-cause mortality in Japanese and Chinese populations [19–25]. An increased maternal CBWR (>0.98 μmol/L/kg) at the time of admission for labor, rather than higher creatinine level, was strongly associated with incident SGA/LGA delivery in the present study (SGA: OR = 5.24, 95% CI: 3.97, 6.92; LGA: OR = 0.23, 95% CI: 0.19, 0.29; all $P < 0.001$). These findings provide more information regarding the adverse impact of elevated creatinine levels in combination with lower body weight on fetal growth, which potentially lead to an increased SGA risk and a decreased LGA risk.

4.3 Strengths and Limitations

Several crucial strengths in this study are worth mentioning. Firstly, for the first time, the current study detected the negative relationship between maternal CBWR and fetal growth (birth length and weight). Secondly, to best of our knowledge, this is the first demonstration of significant associations between high CBWR and increased SGA risk and decreased LGA risk based on a retrospective analysis of the real-world database. Thirdly, a number of sensitivity analyses were performed in this study to ensure the robustness of these associations. Lastly, to minimize potential confounding, overall confounders including maternal demographics, reproductive history, assisted reproduction technology use, pregnancy complications, PTB, and other laboratory results were taken into strict statistical adjustment.

This research has three inevitable limitations that must be noted. Firstly, because of the nature of the retrospective study, the exact causal association can not be determined. Second, despite adjusting for available confounders, residual bias may persist due to unmeasured factors inherent to retrospective designs. GWG, a critical determinant of fetal growth through its direct impact on nutrient supply and maternal metabolic adaptations, could not be accounted for in our analysis. Other potential confounders, such as physical activity, dietary patterns, family socioeconomic status, and pre-pregnancy BMI, further underscore the limitations of observational data. Therefore, future longitudinal studies should rigorously adjust for all known confounders, such as GWG, maternal lifestyle factors, and socioeconomic status, to strengthen the validity of these associations. Thirdly, this study categorized CBWR using population-wide quintiles without trimester-specific reference stratification. Although participants were in late pregnancy (gestational weeks 28–41), creatinine levels may still vary with gestational week. While quintiles captured exposure trends, non-pregnant reference intervals were not applied.

5 Conclusion

In a real-world database of Chinese pregnant women from a 3 A-class hospital, we observed that those in the top quintile of CBWR (>0.98 μmol/L/kg) during late pregnancy exhibited an increased risk of delivering SGA infants and a decreased risk of delivering LGA infants compared to those in the bottom quintile (<0.72 μmol/L/kg). Notably, this association was influenced by PE and GDM, suggesting condition-specific risk prediction thresholds. These findings position CBWR as a low-cost, rapid-assessment biomarker with potential for risk stratification in antenatal care, particularly in resource-limited settings lacking access to advanced imaging. For example, a CBWR exceeding 0.98 μmol/L/kg may signal pregnancies complicated by PE that require enhanced fetal monitoring or micronutrient supplementation. However, the reliance on laboratory and anthropometric data collected at admission poses inherent limitations, such as the inability to capture dynamic CBWR changes throughout gestation or incorporate other biomarkers, which may reduce predictive precision. Future studies should prioritize developing longitudinal CBWR trajectories and multivariable models integrating CBWR with other biomarkers to enhance clinical utility. Until such evidence is established, CBWR remains a promising yet investigational marker requiring validation through prospective population-based cohorts before implementation in routine care.

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Author Contributions BZ and XY conceived and designed this study. X Y wrote the manuscript. ZZ collected the data. SX and YZ analyzed and interpreted data. All authors reviewed and approved the final manuscript.

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Data Availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval and Consent to Participate The protocol of this study was permitted by Ethics Committee of Changzhou Maternal and Child Health Care Hospital (ZD201803). Anonymous data were analyzed and written informed consents for observational subjects were waived in the present study. This study was performed according to the Declaration of Helsinki.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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