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Birth weight influences the kidney size and function of Bangladeshi children

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Abstract

Early-life conditions influence organ growth patterns and their functions, as well as subsequent risk for non-communicable chronic diseases in later life. A limited number of studies have determined that in Bangladesh, kidney size relates to its function among children as a consequence of the maternal and postnatal conditions. The present study objectives were to determine early-life conditions in relation to childhood kidney size and to compare their influences on kidney function. The study was embedded in a population-based prospective cohort of 1067 full-term singleton live births followed from fetal life onward. Kidney volume was measured by ultrasound in children at the age of 4.5 years (range 45 – 64 months), and the estimated glomerular filtration rate (eGFR) was assessed at the age of 9 years (range 96 – 116 months). The mean (standard deviation) kidney volume of children at 4.5 years was 64.2 (11.3) cm³, with a significant mean difference observed between low birth weight and normal birth weight children ($p < 0.001$). The multivariable model showed, changes in status from low birth weight to normal birth weight children, with kidney volume increases of 2.92 cm³/m², after adjusting for the child's age, sex, maternal age, and early pregnancy BMI, and socioeconomic index variables. One-unit change in kidney volume (cm³/m²) improved the eGFR to 0.18 mL/min/1.73m². The eGFR in low birth weight children was 5.44 mL/min/1.73m² less than that in normal birth weight children after adjustments. Low birth weight leads to adverse effects on kidney size and function in children.

Keywords

children; estimated glomerular filtration rate (eGFR); kidney volume; birth weight

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Ethical Standards

The study was conducted according to the guidelines laid down in the Declaration of Helsinki. All procedures involving human research participants were approved by the ethics review committees of the icddr,b and Uppsala University. Written informed consent was obtained from the parents.

Introduction

Kidney size is an important indicator not only to evaluate children with renal diseases but also to determine adequate organ growth.¹ It is known that early-life conditions such as maternal age and nutritional status during pregnancy influence growth patterns, body composition, and risk for noncommunicable chronic diseases in later life.² Kidney size is also a potential surrogate measurement for the number of nephrons, which are the structural and functional unit of the kidneys. Since the number of nephrons is determined largely in prenatal life, suboptimal kidney growth and development in fetal life lead to a smaller number of nephrons.³ Some lines of evidence suggest that retarded growth or small-for-gestational-age, low birth weight (LBW), and preterm babies have relatively smaller kidneys with a decreased number of nephrons.^{2, 4}

Whereas cellular proliferation in almost all organs occurs mainly before the third trimester of normal pregnancies, 60% of nephrons form in the third trimester and have developed by 36 weeks of gestation.^{5, 6} In late pregnancy, poor maternal nutrition (such as low protein intake and vitamin A deficiency), reduced placenta perfusion, or steroid administration leads to fetal growth restriction and a permanent nephron deficit of up to 30%, with a 50% reduction in the glomerular filtration rate (GFR) reported in previous studies.^{3, 7, 8} Additionally, protein deficiency and nematode infection during pregnancy impaired organ growth and the growth factors of the fetus thymus, spleen, heart, brain, and kidney.⁷ However, most epidemiological studies have generally investigated pregnancy health status and birth outcome or organ growth during infancy but not in later childhood in prospective birth cohort studies in developing country settings.

Kidney size in relation to the child's conditions at birth along with consideration of the child's socioeconomic status has not been well studied to date. A limited number of observational and experimental studies have been conducted in high-income settings. Research in this area is particularly challenging and important for countries where restricted fetal growth, LBW infants, and infectious disease related to morbidity and mortality are still high and where noncommunicable diseases including hypertension and chronic kidney disease are upcoming threats.

Objective

The aims of the present study were to determine childhood kidney size and function in relation to early-life conditions at birth, with an especial focus on low birth weight.

Methodology

MINIMat study design

The MINIMat (Maternal and Infant Nutrition Intervention in Matlab, trial registration; isrctn.org identifier: ISRCTN16581394) food and multiple-micronutrient trial in pregnancy is a large cohort study conducted in Matlab, a rural area of Bangladesh. In this trial, prenatal food supplementation and different micronutrient alternatives were randomly allocated in an area where maternal malnutrition is common. Recruitment of the women in the MINIMat

trial was conducted in the Matlab HDSS area of Bangladesh over a 2-year period from November 2001 to October 2003. The women were randomized to an Early (around 9 weeks) or a Usual (around 20 weeks) invitation to food supplementation and to 1 of 3 daily micronutrient supplementations. The prenatal supplementation took the form of 6 different food- and micronutrient supplements daily from week 14 during pregnancy: a) the UNICEF/UNU/WHO preparation of 15 different micronutrients including 30 mg iron and 400 µg folic acid, b) 60 mg iron and 400 µg folic acid only, or c) 30 mg iron and 400 µg folic acid only. Women in the early invitation group also received 600 kcal food supplementation starting in the first trimester of pregnancy and women in the usual invitation group received similar amount of food supplements starting as the usual national program suggests in the second trimester. The initial outcome measurements were the effects of prenatal food and micronutrient supplementation on birth weight, infant mortality, and maternal hemoglobin in pregnancy, as described elsewhere.⁹

From November 2001 to October 2003, 4436 pregnant women between 6 and 8 weeks of pregnancy were enrolled in the MINIMat trial. Ultrasound fetal biometry was performed at 14, 19, and 30 weeks of pregnancy. The gestational age of each woman was calculated on the basis of crown rump length (CRL) or biparietal diameter (BPD) before 14 weeks of gestational age.¹⁰ In total, there were 3267 singleton live births. Infants in the MINIMat birth cohort were then followed up at 15 days and at 1, 2, 3, and 4 months. They were weighed and their lengths measured every month until the age of 6 months and then every 2 months until the age of 1 year, and other follow-ups were conducted at the ages of 2 years, 4.5 years, and 9 years. Of these, 2735 children were tracked and followed up at 4.5 years of age. The present study was a part of the MINIMat prospective birth cohort study in which a cross-sectional assessment of the children's kidney size was conducted at 4.5 years of age and their glomerular filtration rate (eGFR) was estimated at 9 years of age. Kidney volume was assessed on a sub-sample of 1156 children by ultrasound (organ biometric study of children born over a span of 1 calendar year of births [June 2003–June 2004], constituting about 50% of the systematic sample, a full 1-year's recruitment out of 2 years' recruitment). Of these, 77 preterm births (< 37 gestational weeks) were excluded from the analysis because of different biological mechanisms of organ development; 7 children, because of refusal to participate; 3 children, because of having only 1 kidney; and 2 children, because of macrosomia (birth weight > 4000 g). Finally, 1067 full-term singleton children were involved for the kidney volume data analysis. When they were aged 9 years, cystatin C was measured in 457 children of the 1067 children who were born at clinics (the immune cohort) to estimate the eGFR rate. Thus, information on 457 children who participated in both the 4.5-years and 9-years follow-ups were used for the kidney function analysis.

For the kidney size measurement, an ultrasound machine (SSA 510A/P3, Famio-5; Toshiba Medical Systems, Tokyo, Japan) with a 3.75 MHz standard convex scanner with the ellipsoid method, which is known as a reliable method to measure kidney volume, was used.¹¹ The children were observed from the vertical dorsal view because in children the dorsal view usually provides a more satisfactory image than does the midaxillary view. If dilatation of the renal pelvis was observed, a postvoiding examination of the kidney was done.

Laboratory analytical methods

Serum cystatin C was determined using the sandwich enzyme immunoassay technique with commercially available quantitative ELISA test kits (Quantikine® ELISA, Human cystatin C Immunoassay, 4.5 hour solid-phase ELISA, and NS0-expressed recombinant human cystatin C, manufactured by USA&Canada) at the clinical laboratory, and the results displayed the levels of cystatin C in nanograms per milliliters in blood.

Biometric measurements

Information such as maternal age and other socioeconomic variables was collected. Additionally, the weight and height of the women were measured at enrollment (early pregnancy before 14 weeks), and their body mass index (BMI) (kg/m^2) was calculated on the basis of that information. The BMI was categorized as follows: underweight (<18.5), normal weight ($18.5\text{--}24.9$), and overweight or obese (≥ 25). The children's length/height and weight were measured at birth, at 4.5 years, and at 9 years. The body surface area (BSA) of each child was assessed using anthropometric measures: weight and height. Height-for-age (HAZ), weight-for-age (WAZ), weight-for-height (WHZ), BMI-for-age (BAZ) z-scores of each child were calculated by using WHO Anthro software, at 4.5 years, and at 9 years (except WHZ at 9 years). Gestational weeks <37 was considered as preterm birth; birth weight <2500 g, as low birth weight (LBW); and ≥ 2500 g, as normal birth weight (NBW). Infants with a birth weight and/or birth length below the 10th percentile for gestational age was considered as Intrauterine Growth Retardation (IUGR).¹² For the present analysis, the kidney volume was considered as the sum of the right and left kidney volumes. To assess kidney function, the eGFR was calculated using the Zappitelli formula ($\text{eGFR}_{\text{Cyst}} = 75.94 / [\text{cystatin C (mg/L)}]^{1.17}$), which is known to be a useful cystatin C-based equation for use in children.¹³ The BSA was calculated using the Haycock formula [$\text{surface area (m}^2\text{)} = \text{weight (kg)}^{0.5378} \times \text{height (cm)}^{0.3964} \times 0.024265$].¹⁴ The BSA was calculated at 2 points of measurement (age 4.5 years and age 9 years) because we measured the kidney size at 4.5 years and the function at 9 years. The present study adjusted the eGFR by the BSA at 9 years of age and the kidney volume adjusted by the BSA at 4.5 years of age because the absolute eGFR¹⁵ and kidney size are strongly correlated with the BSA.¹⁶ The eGFR was scaled to the BSA of 1.73 m^2 with the unit of measurement of milliliters per minute per 1.73 m^2 . Adjusting the BSA for the eGFR and the kidney size basically removes the variability of the kidney size and eGFR with respect to the body size of the growing child.

Data analysis

The present study estimated the kidney size and function of young Bangladeshi children. Descriptive statistics were used to describe the study participants and distribution of LBW and NBW children as well as differences in the distribution between male and female children. The mean differences were assessed using the *t* test for 2 independent groups: birth weight status and sex of the children. The normality of the distributions was also checked. Differences in the proportions of LBW and NBW children were examined using the chi-square test. Univariable and multivariable linear regressions were performed to examine the association of kidney volume and its function with birth status and with maternal and prenatal conditions (birth weight status, child's age, sex, mother's age, mother's early

pregnancy BMI, food groups, micronutrient supplementation groups, and socio-economic index). Several multivariable linear regression models were performed to find out the association between kidney volume and birth weight status as well as association between kidney function and birth weight status. Variables in the multivariable models were chosen based on the ambient risk factors (biological and socio-environmental) which had been theorized earlier.² Three multivariable models were developed to identify the association between kidney volume and birth weight status. In the first model, we adjusted for the sex and age of the child at the 4.5 years follow-up. In the second model, additional variables of mother's age and BMI status during early pregnancy, food groups, and micronutrient supplementation groups were adjusted. The third model was adjusted for the socio-economic index along with the model 2 variables. A further multivariable model was performed in which kidney volume was adjusted initially by the BSA and then placed into the multivariable model to observe the association with birth weight status in which we controlled all variables adjusted in model 3. To understand the association between kidney function and birth weight status, another linear regression model was developed after controlling for the sex of the child, mother's age, mother's early pregnancy BMI, food groups, micronutrient supplementation groups, and socio-economic index. IBM SPSS (version 23.0; IBM Corporation, Armonk, NY, USA) was used for the analysis.

Results

The mean (SD) maternal age at enrollment (6 – 8 weeks of pregnancy) was 26.2 (6.0) years, and 14.2% of the women were aged 19 years or younger. Twenty-seven percent of the women were underweight (BMI <18.5 kg/m²) and 6.6% were overweight or obese at enrollment. One-third of the women were nulliparous. The mean gestational age at birth was lower in the LBW children than in the NBW children. The mean weight, height, and BMI of the LBW children's mothers were lower than those of the NBW children's mothers ($p < 0.001$). Of the study children, 50.6% were male. LBW was more common in the female than in the male children (57.2% vs 42.8.1%; $p = 0.006$). The mean (SD) age of the children at the 4.5-years follow-up was 55.5 (1.4) months. The mean values for length and weight at birth and for height, weight, and BSA at 4.5 years were significantly lower in the LBW children than in the NBW children. Of the study children, 41.6% LBW children and 2.5% NBW children were IUGR, respectively. The LBW children were mostly from low socioeconomic strata as compared with the NBW children (43.6% vs 34.8%; $p = 0.038$). The impacts of the food groups and micronutrient supplementation groups were identical for the LBW and the NBW children (Table 1). The mean gestational age at birth was higher in the growth retarded LBW children than in the non-growth retarded LBW children (39.4 ± 1.1 vs 38.8 ± 1.3 ; $p < 0.001$).

Those children ($n = 457$) participated in both follow-ups, their mean (SD) ages at the 4.5-years follow-up and at the 9-years follow-ups were 55.7 (1.3) and 106.4 (1.5) months, respectively. The mean values for length and weight at birth and for height, weight, and BSA at 4.5 years and at 9 years were significantly lower in the LBW children than in the NBW children. Of those children ($n=457$) who participated in both follow-ups, 31.6% LBW children and 3.3% NBW children were IUGR, respectively (S Table 1).

The mean (SD) kidney volume of the children at 4.5 years was 64.1 (11.1) cm³, with a significant mean difference observed between the NBW and the LBW children (65.3 [11.0] vs 60.3 [11.1]; $p < 0.001$). The mean kidney volume differed between the male and the female children ($p < 0.001$). Moreover, significant mean differences in the kidney volume/BSA were observed between the NBW and the LBW children (104.5 [15.6] vs 102.0 [15.8]; $p < 0.05$). Male children born with the LBW status had a smaller mean kidney volume/BSA than did the male children born with NBW status (101.1 [14.3] vs 104.5 [15.6]; $p < 0.05$) (Table 2). The mean eGFR was lower in the LBW children than in the NBW children (61.8 [12.8] vs 67.4 [16.0]; $p = 0.002$). No significant difference was observed for the mean eGFR between the male and female children (66.2 [15.2] vs 66.3 [15.9]; $p = 0.925$) (Table 3). In those children ($n = 457$) who participated in both follow-ups, the mean kidney volume also differed significantly between the LBW and the NBW children (57.7 [9.3] vs 63.6 [10.7]; $p < 0.001$). The mean kidney volume/BSA was smaller in the LBW children than in the NBW children (97.5 [14.4] vs 101.7 [14.9]; $p = 0.013$).

The LBW children had a smaller kidney volume than did the NBW children. The male children had a larger kidney volume than did the female children. Maternal early pregnancy BMI showed a positive correlation with kidney volume. Higher birth weight and birth length showed a positive association with a larger kidney volume. The BSA of the children at 4.5 years showed the highest positive correlation with kidney volume (β -coefficient = 117.23). Increased score of HAZ of the children at 4.5 years showed significant positive association with kidney volume ($\beta = 1.61$, $p = 0.002$). The poor and middle socio-economic index children had a smaller kidney volume than did the rich socio-economic index children (Table 4). Of the LBW children ($n=243$), no significant association was observed between kidney volume/BSA and IUGR ($\beta = -0.22$, $p = 0.913$), as well as association between eGFR, and IUGR ($\beta = 2.84$, $p = 0.281$). Moreover, there was no significant association observed between eGFR, and WAZ ($\beta = -0.35$, $p = 0.608$), HAZ ($\beta = -0.92$, $p = 0.219$), and BAZ ($\beta = 0.23$, $p = 0.717$) of the children at 9 years, respectively.

Two different multivariable models including all the biological variables were initially prepared. Additional models including the socio-economic index variable were subsequently also prepared. Model 1 indicates that the LBW children had a smaller kidney volume than did the NBW children ($\beta = -5.01$ [95% confidence interval; -6.05 to -3.51], $p < 0.001$) after adjusting for the sex and age of the children at the 4.5-years follow-up. After controlling for the mother's age and BMI status during early pregnancy, food groups, and micronutrient supplementation groups, model 2 also indicated that the LBW children had a smaller kidney volume than did the NBW children ($\beta = -4.64$ [-6.14 to -3.14], $p < 0.001$). Model 3 showed similar findings to those of model 2 ($\beta = -4.52$ [-6.01 to -3.03], $p < 0.001$) after adjusting for the additional variable of socio-economic index. The model of kidney volume/BSA showed a similar outcome in that the LBW children had a smaller kidney volume than did the NBW children after controlling for the sex and age of the children at the 4.5-years follow-up, mother's age and early pregnancy BMI, food groups, micronutrient supplement groups, and socio-economic index (Table 5).

The eGFR showed a positive association with kidney volume/BSA, ($\beta = 0.18$ [95% CI; 0.08 – 0.27], $p < 0.001$) after controlling for the sex of the child, birth weight status, mother's age,

and mother's early pregnancy BMI, food groups, micronutrient supplement groups, and socio-economic index. Table 6 shows that the LBW children had a poorer eGFR than did the NBW children after controlling for the sex of the child, mother's age, and mother's early pregnancy BMI, food groups, micronutrient supplement groups, and socio-economic index.

Discussion

The present cohort study conducted in rural Bangladesh has provided findings on the kidney size and eGFR from a large, homogeneously aged group of children. It has established an objective relationship between kidney size and its function in NBW and LBW children and demonstrated the association between kidney volume and its function with prenatal conditions. To our knowledge, this is the first study to reveal that kidney size in children is associated with prenatal conditions such as maternal age and nutritional status during pregnancy, birth weight, and socioeconomic index and that it is associated with the eGFR in later life.

One advantage of the study was that it covered the largest series of pediatric kidney volume assessed by sonography and eGFR based on cystatin C in a community of children in Bangladesh so far studied. Most previous studies reported the kidney size among different age groups of children, and none of them showed any associations between kidney size and function among a healthy, homogeneously aged group of children at the community level.^{17, 18} Other than this study, only a limited number of studies have considered the effect of maternal pregnancy characteristics and socioeconomic status on child organ development, whereas these characteristics are vital for understanding organ development and function.^{3, 19}

In the present study, the LBW children had a smaller kidney volume and their eGFR was also poorer than that of the NBW children. Its findings are compatible with the finding and assumption of Spencer et al that LBW children have smaller BSA-adjusted kidney volume than do NBW children. It has been proposed that this lower BSA-adjusted kidney volume in LBW children is a consequence of reduced nephron endowment associated with intrauterine growth retardation.²⁰ This statement might also be correct for the present study findings because present study considered babies born full-term only and nearly half of them (42%) were IUGR. However, present study did not find significant association with BSA-adjusted kidney volume and growth retarded LBW children, and association with eGFR and growth retarded LBW children, that might be because of the low statistical power for this particular group of children (n=243). These variations have clinical importance as many diseases such as hypertension and chronic kidney diseases are associated with changes in kidney size and function.^{21, 22} LBW is a known risk factor for progression of kidney diseases, hypertension, and diabetes mellitus in adult life.^{18, 22, 23} LBW children are also known to have a lower nephron mass, where kidney volume is proportional to kidney mass.^{24, 25} In healthy adults and infants, kidney mass and glomerular number are significantly associated with each other, and the clinical correlation of lower nephron mass with increased risk of hypertension and kidney disease is already known.²⁶ Accurate kidney function is extremely important for protection of the kidneys from toxic damage and for prescription of adequate fluid, medication, and diets in clinical practice. An inadequate number of nephrons leads to a

compensatory greater glomerular pressure and progressive glomerular sclerosis and subsequently predisposes the individual to impaired kidney function.¹¹ To increase the eGFR of children, kidney volume adequate to body size would have to be increased. The findings of the current study are also supported by earlier studies stating that kidneys with a reduced number of nephrons would lead to a diminished glomerular filtration rate.² Thus, the present study findings indicate that kidney size determines the eGFR in later life. Moreover, present study observed that the gestational age at birth was slightly but significantly lower in LBW than in NBW children. The variation of gestational age at birth between LBW and NBW children was predominantly from non-growth retarded LBW children, which might be associated with pregnancy related disorders such as placental insufficiency.²⁷ A former study reported that those children born before 39 weeks of gestational age had an increased risk of congenital heart disease than those born after 39 weeks.²⁷

Geelhoed et al reported that a smaller physiological growth rate in early life is associated with kidney volume³, which is also true for the present findings. The anthropometric measurements (height, weight, and BSA) differed significantly with respect to the birth status of the children, indicating that those with LBW could not catch up with the growth of NBW children up to 9 years of age, and therefore, their disease susceptibility might be different in adulthood, as is theorized for different kidney sizes.² The present study found that male children have a larger kidney volume than do female children; however, no statistically significant difference was observed between the male and female children for kidney volume/BSA. Furthermore, male children having LBW had a smaller average kidney volume/BSA than did male children having NBW. However, no significant difference was observed for kidney volume/BSA between female children having the LBW and those having the NBW. This might be due to the diverse role of the hormonal milieu on gender in the course of kidney disease. It has been suggested that sex hormones might play an important determinant role, with greater susceptibility in male individuals to progressive kidney injury. Estrogen has profound effects on transforming growth factor- β transduction and on the renin-angiotensin system, which would lead to alterations in kidney hemodynamics and affect kidney disease progression. It has been also suggested that male gender poses more risk for nondiabetic kidney disease and is arguably also a risk factor for progression of diabetic nephropathy.²⁸ Thus, the present study suggests the importance of prior observation for male children with LBW to prevent their disease susceptibility in the future.

In the present study, the BSA showed the strongest correlation with kidney volume. It has been reported that organ growth shows a high correlation with advances in the BSA, height, and weight during the developing process from infancy through adolescence.¹⁶ Additionally, present study also observed a positive correlation with kidney volume and HAZ of children at 4.5 years. The kidney filters blood from the whole body, and thus, mean differences and multivariable models of kidney volume and eGFR were also established with respect to the BSA. The present study shows the importance of birth weight improvement for this community in which a cohort of LBW children survived but with a possible high risk for kidney and other chronic diseases in adult life. It is known that risk of LBW is affected by maternal nutrition and by health before and during pregnancy as well as by

socioeconomic conditions,² which was also true for the present study. The relationships between birth status and kidney size as well as with kidney function were not changed even after adjusting for the prenatal and post-natal characteristics of the children. Maternal undernutrition is a common phenomenon in Bangladesh and a former study reported higher rates of zinc, vitamin B-12, and folate deficiencies and *Ascaris* infection among MINIMat study participants in their early pregnancy.²⁹ It has been known that maternal micronutrient deficiency has long-term consequences for fetal development and predisposes the infant to metabolic dysfunction in adult life through epigenetic modifications,³⁰ which would be true for the present study children. Therefore, the current study suggests that prenatal programming has an effect on kidney size and its function in children.

The implications of the present study for Bangladeshi clinicians are obvious given the possible variations in the anthropometric parameters of normally growing children where the increasing prevalence of chronic disease is an upcoming threat for the country. According to a recent study, 26.4% of Bangladeshi adults were hypertensive in 2016³¹ whereas the percentage was only 1.10% in 1976³² indicating that this trend is expected to grow in the near future. Anand et al reported that the prevalence of chronic kidney disease was 26% in 2014 in Bangladeshi adults³³ and another study reported a higher salt intake custom in Bangladesh.³⁴ Excessive dietary salt intake bestows a major challenge to the kidneys to excrete large amounts of salt. The kidneys control blood pressure by ultimately determining sodium excretion; thus, the kidneys' ability to excrete sodium is a key factor. If the kidneys cannot deal with this excessive sodium overload, blood pressure will increase. Moreover, an excessive amount of sodium in the bloodstream crushes the delicate balance and reduces the renal functional ability to remove water and to excrete salt.³⁵ Thus, the present study suggests the need for preventive measures for LBW children that must be given high priority in future health care. Thus, it is important for countries to have their own population-specific data on kidney size and eGFR because the population data of developed countries cannot be used as a universal pattern. The present study results could be generalized to the wider international community where the prevalence of restricted fetal growth and LBW children is high. The present study findings may also be utilized as background information to understand disease development in the same population in adulthood.

A limitation of the present study was that kidney function was not measured by inulin clearance, which is known to be a direct measure of kidney function. Another limitation was the unavailability of data about maternal and child dietary habits as well as measurements of eGFR at 4.5-years follow-up and kidney volume at 9-years follow-up. A further limitation was that the association between kidney size and blood pressure of the children was not observed in the present study. Its major strength is its prospective design from fetal life onward within a large, population-based cohort. Furthermore, the study provides information that can be useful for both clinicians and public health professionals.

Conclusions

Low birth weight can potentially lead to adverse effects on the kidney size and function in children. The size of the kidney necessitates knowing the normal ranges of its volume and function with respect to the body surface area in LBW and NBW children. This study can be

used as reference data for health professionals to understand the relationship between kidney size and function in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Participants' characteristics, n=1067

	LBW, n = 243	NBW, n = 824	p value
Maternal characteristics			
Age at enrollment, y (mean $\pm$ SD)	26.0 $\pm$ 6.0	26.3 $\pm$ 6.0	0.480
< 20 (%), n = 152	14.8	14.1	0.943
20–34 (%), n = 810	75.7	76.0	
35 (%), n = 105	9.5	10.0	
Maternal illiteracy (%), n = 285	30.9	25.5	0.250
Height, cm (mean $\pm$ SD)	148.3 $\pm$ 5.1	150.4 $\pm$ 5.3	< 0.001
Early pregnancy weight, kg (mean $\pm$ SD)	42.9 $\pm$ 5.3	46.5 $\pm$ 7.3	< 0.001
Early pregnancy BMI, kg/m ² , n = 1064 (mean $\pm$ SD)	19.5 $\pm$ 2.2	20.6 $\pm$ 2.9	< 0.001
< 18.5 (%), n = 284	34.7	24.3	< 0.001
18.5–< 25 (%), n = 710	63.2	67.8	
25 (%), n = 70	2.1	7.9	
Parity (median, range), n = 1068	1 (0–6)	1 (0–10)	
Nulliparous (%), n = 317	34.2	28.4	0.094
Characteristics at birth			
Gestational age at birth, wk (mean $\pm$ SD)	38.6 $\pm$ 1.2	39.2 $\pm$ 1.2	< 0.001
Birth weight, g (mean $\pm$ SD)	2286.8 $\pm$ 192.3	2898.7 $\pm$ 275.1	< 0.001
Birth length, cm (mean $\pm$ SD)	46.0 $\pm$ 1.6	48.4 $\pm$ 1.6	< 0.001
IUGR (%), n=122	41.6	2.5	<0.001
Child's sex, %			
Female, n = 526	57.2	47.0	0.006
Male, n = 541	42.8	53.0	
Age (mo) of children at 4.5-y measurement (mean $\pm$ SD)	55.3 $\pm$ 1.5	55.6 $\pm$ 1.4	0.004
Child's weight at 4.5 y, kg (mean $\pm$ SD)	13.0 $\pm$ 1.5	14.1 $\pm$ 1.6	< 0.001
Child's height at 4.5 y, cm (mean $\pm$ SD)	97.7 $\pm$ 4.1	100.4 $\pm$ 3.9	< 0.001
Body surface area at 4.5 y, m ² (mean $\pm$ SD)	0.59 $\pm$ 0.04	0.62 $\pm$ 0.05	< 0.001
Socioeconomic index, %			
Rich, n = 215	16.9	21.1	0.038
Middle, n = 459	39.5	44.1	
Poor, n = 393	43.6	34.8	
Food group, %			
Early intervention group, n = 555	48.6	53.0	0.242
Usual intervention group, n = 512	51.4	47.0	
Micronutrient group, %			
30 mg iron + 400 μ g folic acid, n = 351	34.6	32.4	0.585
60 mg iron + 400 μ g folic acid, n = 363	31.3	34.8	
Multiple micronutrients, n = 353	34.2	32.8	

Abbreviations: BMI, body mass index; BSA, body surface area; CI, confidence interval; IUGR, Intrauterine Growth Retardation; LBW, low birth weight; NBW, normal birth weight; SD, standard deviation; Wk, week; Mo, month; Y, year.

Table 2

Kidney volume of children by birth weight status and sex

	Kidney volume ^a , cm ³					
	Overall		NBW		LBW	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Male	541	65.3 (11.3) ^c	437	66.2 (11.3) ^c	104	61.1 (10.3) ^b
Female	526	63.0 (10.8)	387	64.2 (10.7)	139	59.7 (10.5) ^b
Total	1067	64.1 (11.1)	824	65.3 (11.0)	243	60.3 (11.1) ^b
	Kidney volume ^a /BSA, cm ³ /m ²					
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Male	541	103.8 (15.4)	437	104.5 (15.6)	104	101.1 (14.3) ^b
Female	526	104.0 (15.9)	387	101.1 (14.3)	139	102.7 (16.8)
Total	1067	103.9 (15.6)	824	104.5 (15.6)	243	102.0 (15.8) ^b

Abbreviations: BSA, body surface area; LBW, low birth weight; NBW, normal birth weight; SD, standard deviation.

^a Sum of right and left kidneys.^b $p < 0.05$ between groups.^c $p < 0.05$ between boys and girls.

Table 3

Estimated GFR by birth weight status and sex

Estimated GFR adjusted by BSA, mL/min/1.73m ²				
	NBW		LBW	
	n	Mean (SD)	n	Mean (SD)
Male, n=230	191	67.2 (15.6)	39	61.0 (12.0) ^a
Female, n=227	171	67.6 (16.4)	56	62.4 (13.3) ^a
Total, n=457	362	67.4 (16.0)	95	61.8 (12.8) ^a

Abbreviations: BSA, body surface area; GFR, glomerular filtration rate; LBW, low birth weight; NBW, normal birth weight; SD, standard deviation.

^a p < 0.05 between groups.

Table 4

Univariable model of kidney volume by maternal and child characteristics

	Kidney volume, cm ³		
	β -coefficient	95% CI	p value
Maternal characteristics			
Maternal age, y	-0.15	-0.26 to -0.04	0.007
Early pregnancy BMI, kg/m ²	0.63	0.39–0.87	<0.001
Gestational week at birth	0.05	-0.50 to 0.60	0.872
Child's characteristics			
Child's sex, female	-2.12	-3.47 to -0.77	0.002
Birth weight, g	0.08	0.006–0.01	< 0.001
Birth length, cm	1.53	1.20–1.84	< 0.001
Weight in kg at 4.5 y	3.30	2.95–3.66	< 0.001
Height in cm at 4.5 y	1.25	1.10–1.40	< 0.001
BSA in m ² at 4.5 y	117.23	105.27–129.79	< 0.001
HAZ at 4.5 y	1.61	1.79–14.03	0.002
WAZ at 4.5 y	1.04	-0.05–2.13	0.062
WHZ at 4.5 y	-0.10	-1.23–1.03	0.858
BAZ at 4.5 y	-0.29	-1.45 – 0.88	0.630
Birth weight status			
NBW		1	
LBW	-4.98	-6.49 to -3.47	< 0.001
Intervention			
Food group			
Early intervention group		1	
Usual intervention group	-0.62	-1.95 to 0.71	0.360
Micronutrient group			
Multiple micronutrients		1	
30 mg iron + 400 µg folic acid	0.89	-2.31 to 1.01	0.444
60 mg iron + 400 µg folic acid	-0.38	-1.98 to 1.22	0.641
Socioeconomic index			
Rich		1	
Middle	-4.74	-6.64 to -2.84	< 0.001
Poor	-5.22	-7.13 to -3.30	< 0.001

Abbreviations: BMI, body mass index; BAZ, BMI for age z-score; BSA, body surface area; CI, confidence interval; HAZ, Height for age z-score; LBW, low birth weight; NBW, normal birth weight; WAZ, weight for age z-score; WHZ, weight for height z-score; WK, week; Y, year.

Table 5

Kidney volume at 4.5 years by birth weight status, n=1067

	Kidney volume/BSA, cm ³ /m ²			Kidney volume/BSA, cm ³ /m ²		
	Unadjusted			Adjusted ^a		
	β -coefficient	95% CI	p value	β -coefficient	95% CI	p value
Birth weight status						
NBW		1			1	
LBW	-2.45	-4.69 to -0.20	0.033	-2.92	-5.14 to -0.70	0.010

Abbreviations: BMI, body mass index; BSA, body surface area; CI, confidence interval; LBW, low birth weight; NBW, normal body weight.

^a Adjusted variables: Child's sex and age at kidney volume measurement, mother's age at conception, mother's early pregnancy BMI, food groups, micronutrient groups, and socioeconomic index variables.

Table 6

Kidney function (eGFR) at 9 years by birth weight status, n = 457

	eGFR, mL/min/1.73m ²					
	Unadjusted			Adjusted ^a		
	β -coefficient	95% CI	p value	β -coefficient	95% CI	p value
Birth weight status						
NBW		1			1	
LBW	-5.58	-8.62 to -2.54	<0.001	-5.44	-8.53 to -2.36	0.001

Abbreviations: BMI, body mass index; BSA, body surface area; CI, confidence interval; eGFR, estimated glomerular filtration rate; LBW, low birth weight; NBW, normal birth weight.

^a Adjusted variables: sex of the child, mother's age at enrollment, mother's early pregnancy BMI, food groups, micronutrient groups, and socioeconomic index variables.