# GFR Estimated From Cystatin C Versus Creatinine in Children Born Small for Gestational Age

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**Background:** Low birth weight caused by intrauterine growth restriction may be a risk factor for renal impairment in the adult life.

**Study Design:** A cross-sectional study.

**Setting & Participants:** 71 children aged 8 to 13 years living in the community of São Paulo, Brazil, were included in the study. Gestational age was within the normal range.

**Predictors:** Birth weight (range, 2,052 to 3,560 g) divided into quartiles: 2,500 g or less; 2,501 to 2,740 g; 2,741 to 3,000 g; and greater than 3,000 g. Birth weight ascertained by birth records in 43 and by recall in 28 participants.

**Outcomes & Measurements:** Cystatin C, creatinine, and glomerular filtration rate (GFR) estimated by equations using cystatin C ($eGFR_{cys}$) or creatinine ($eGFR_{cr}$).

**Results:** Overall, mean serum creatinine level was 0.8 ± 0.01 (SE) mg/dL (range, 0.7 to 1.1 mg/dL); mean plasma cystatin C level was 0.9 ± 0.02 mg/L (range, 0.5 to 1.6 mg/L), and $eGFR_{cr}$ and $eGFR_{cys}$ were 102.4 ± 2.16 (range, 66 to 140) and 91.8 ± 2.46 mL/min/1.73 $m^2$ (range, 49 to 139 mL/min/1.73 $m^2$), respectively. No differences were found for serum creatinine or $eGFR_{cr}$ values among the birth-weight quartiles. There was a significant linear trend of increasing cystatin C levels (decreasing $eGFR_{cys}$) in the lower birth-weight quartile groups ($P = 0.002$ and $P = 0.02$, respectively). Systolic blood pressure correlated with plasma cystatin C level ($r = 0.31$; $P = 0.008$) and $eGFR_{cys}$ ($r = -0.26$; $P = 0.028$). Covariance analysis adjusting for age, sex, body mass index for age compared with standards of the National Center for Health Statistics and expressed as a *z* score, and systolic blood pressure showed that cystatin C values remained greater in the lowest than highest birth-weight quartile (1.01 ± 0.05 versus 0.83 ± 0.05 mg/L; $P = 0.02$).

**Limitations:** Ascertainment of birth weight by recall in some participants. Lack of measurement of microalbuminuria, absence of direct GFR measurement, and small sample size.

**Conclusions:** Lower birth weight is associated with higher levels of cystatin C but not creatinine in 8-13 yr. old children born full-term.

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***INDEX WORDS:*** Intrauterine growth restriction; cystatin C; glomerular filtration rate; birth weight.

It has been proposed that events occurring before birth may influence the risk of cardiovascular disease in later life.[1,2] Epidemiological studies in several countries have shown associations between birth weight and the later development of coronary heart disease, hypertension, stroke, and type 2 diabetes.[3,4] There also is evidence that people with low birth weights have a congenital deficit in nephron number and are more susceptible to the development of renal disease.[5-7] Interestingly, other studies showed a direct relation between birth weight and number of nephrons, with approximately 250,000 more glomeruli per kidney per 1-kg increase in birth weight.[8,9] In addition, early catch-up kidney growth was observed in small-for-gestational-age (SGA) infants, suggesting either an accelerated renal maturation process or early compensatory kidney hypertrophy in this group of infants.[10] Nephrogenesis requires a perfect balance of many factors that can be disturbed by intrauterine growth restriction, leading to impairment of nephron number. The compensatory hyperfiltration in the remaining nephrons results in glomerular and systemic hypertension, which hastens injury to functioning glomeruli and perpetuates the vicious cycle of ongoing nephron loss.[7]

Assessment of renal function is important to detect the extension and progression of nephropathy. Precise renal function can be measured by using inulin clearance or radioactive markers, but these methods are not available in routine daily practice. However, serum creatinine level and creatinine clearance are the most widely

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used indicators for routine glomerular filtration rate (GFR) estimation. Creatinine-based equations improved the accuracy of GFR estimation, but their precision to detect early changes is questionable. Recently, plasma cystatin C level was proposed as a novel surrogate marker of GFR.[11] Cystatin C is a low-molecular-weight protein that functions as an extracellular inhibitor of cysteine protease.[12] Moreover, based on its independence from the effects of age, sex, and body composition,[13] it has been suggested that increased cystatin C level may be a more sensitive indicator of renal dysfunction than conventional creatinine-based measures.[11-13] Based on these observations and that low birth weight can be associated with renal injury in later life, we decided to investigate levels of both cystatin C and creatinine in children 8 to 13 years old and evaluate whether there was an association between GFR estimated by using these markers and low birth weight.

## METHODS

Between 1999 and 2000, a total of 289 children were screened in an anthropometric census performed in 5 shantytowns by the Nutritional Rehabilitation Center of the Federal University of São Paulo, Brazil. Initially, 18 shantytowns were identified within 15 km of the Federal University of São Paulo, located in the southern region of São Paulo. The region was then subdivided into 3 geographic areas, and a secondary sample of 5 shantytowns was randomly selected by taking into account this stratification by region. For the purpose of this study, 113 children aged 8 to 13 years were recruited and evaluated between November 2004 and July 2005. The other 176 children were not included in the study because they were not within this age group, had moved from the region where they were initially screened and were not found at the initiation of this study, or refused to participate. We previously reported the demographic, anthropometric, clinical, and biochemical characteristics of this cohort.[4,14] Personal and family medical histories, including information about birth weight and chronic and familial diseases, were obtained by means of a questionnaire completed during an interview with parents or guardians. Exclusion criteria included the presence of renal disease (assessed by means of medical history and urinalysis), acute or chronic infections, presence of active corticotherapy, and positive family history or clinical signs of cardiovascular disease or endocrinopathy. Of 113 children recruited, 42 were excluded for the following reasons: 31 did not have an adequate amount of blood for evaluation of cystatin C, 7 had a family history of hypertension, 3 had laboratory test results indicative of diabetes mellitus, and 1 had renal disease. Seventy-one children remained eligible and were included in this study.

The validity of birth-weight data from mother's recall was confirmed by using hospital records that were available for 52 children from the 113 initially recruited, who were born in the 5 hospitals closest to the study coordination center. Agreement between birth-weight data from recall and birth record sources was good (n = 52; mean difference [birth record − mother recall] ± 2 SDs of the difference = 67 ± 256 g [limits of agreement = −189 to 323 g]; 95% confidence interval for mean difference, 32 to 102). Of the children included in the study, 43 (61%) had data for birth weight obtained in hospital records, and these values were used in the analysis. In these cases, we observed that the mean difference between recalled and recorded birth weight values was 2.3%. Therefore, for the remaining 28 cases, we imputed a value 2.3% less than the mother's recalled weight.

During enrollment, weight, height, and blood pressure were measured using previously described methods.[4] The anthropometric indicators used to assess child nutritional status were height-for-age (HAZ), weight-for-age (WAZ), and body mass index-for-age (BMIZ), which were compared with standards of the National Center for Health Statistics and expressed as $z$ score. The study was approved by the Ethics Committee of the Federal University of São Paulo, and informed consent was obtained from 1 of the parents of each child enrolled in the study.

### Renal Function Assays

All children provided a blood sample, which was collected in the morning after an overnight fast. For cystatin C assays, aliquots of heparin plasma were centrifuged (1,500$g$ for 5 minutes at 4°C) and stored at −80°C. For serum creatinine, aliquots were centrifuged (1,500$g$ for 20 minutes at 4°C) and immediately processed in the Clinical Laboratory of the São Paulo Hospital. Serum creatinine measurements were performed from 2004 to 2005, whereas cystatin C was measured in 2007 by using frozen heparin plasma. Urinalysis (microscopic examination of urine sediment, pH, glucose, protein, ketones, bilirubin, and urobilinogen) was performed in all participants and did not show significant findings. Cystatin C was measured by using the immunoparticle kit (Dako Corp, Copenhagen, Denmark) by means of the immunoturbidimetric assay. The range of detection of the assay is 0.3 to 7.5 mg/L, with the reference range for young healthy persons reported as 0.55 to 1.15 mg/L. We estimated GFR based on cystatin C level ($eGFR_{cys}$) using the equation described by Zappitelli et al[15]: 75.94/cystatin C [mg/L]$^{-1.17}$. Creatinine was measured by using an automated picric acid assay on the Hitachi 717 analyzer (Roche, Basel, Switzerland) in the Clinical Laboratory of the São Paulo Hospital according to the manufacturer's recommended procedure. GFR based on creatinine level ($eGFR_{cr}$) was estimated by using the Schwartz formula: $k \cdot$ height (cm)/serum creatinine [mg/dL], where $k = 0.55$ in children up to 13 years old.[16] In addition, eGFR was adjusted for body surface area of 1.73 $m^2$.

### Statistical Analysis

To evaluate associations between renal function markers and birth weight, the study population was divided into quartiles of birth weight as follows: first quartile, 2,500 g or