Childhood Estimates of Glomerular Filtration Rate Based on Creatinine and Cystatin C: Importance of Body Composition

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Abstract

Background: Creatinine and cystatin C concentrations are commonly used to estimate glomerular filtration rate (eGFR) in clinical practice and epidemiological studies. To estimate the influence of different body composition measures on eGFR from creatinine and cystatin C blood concentrations, we compared the associations of different anthropometric and body composition measures with eGFR derived from creatinine (eGFR$_{creat}$) and cystatin C (eGFR$_{cystC}$) blood concentrations. ***Methods:*** In a population-based cohort study among 4,305 children aged 6.0 years (95% range 5.7–8.0), we measured weight and height and calculated body mass index (BMI) and body surface area (BSA), and lean and fat mass using dual-energy X-ray absorptiometry. At the same age, we measured creatinine and cystatin C blood concentrations and estimated the GFR. ***Results:*** Correlation between eGFR based on creatinine and cystatin C concentrations was $r = 0.40$ (p value <0.01). Higher BMI was associated with lower eGFR$_{cystC}$ but not with eGFR$_{creat}$. Higher BSA was associated with higher eGFR$_{creat}$ and lower eGFR$_{cystC}$ (p value <0.05). Lean and fat mass percentages were associated with eGFR$_{creat}$ but not with eGFR$_{cystC}$. ***Conclusion:*** Our findings suggest that both eGFR$_{creat}$ and eGFR$_{cystC}$ are influenced by BMI and BSA. eGFR$_{creat}$ is more strongly influenced by body composition than eGFR$_{cystC}$.

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Introduction

Glomerular filtration rate (GFR) plays a key role in the management of kidney disease. Ideally, measuring GFR should be based on renal clearances of exogenous markers such as inulin, but this approach is complex, invasive, and expensive [1]. Therefore, GFR is commonly estimated based on creatinine blood concentrations [2]. Using creatinine as marker of renal function has some limitations. Creatinine is actively secreted by the proximal tubule and related to muscle mass, age, sex, ethnicity, and dietary factors [1, 3]. Creatinine concentrations can be higher in individuals with an increased muscle mass, independent of kidney function, leading to an underestimation of eGFR [4]. Studies in adults suggest that eGFR based on creatinine concentrations can be improved if lean mass percentage could be incorporated in the formula [4].

An alternative marker for the estimation of GFR is cystatin C, the concentrations of which are reported to be independent of muscle mass in children [5, 6]. Some authors report a superior sensitivity of cystatin C for detect-

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ing impaired GFR in pediatric patients to that of creatinine, especially in children with low muscle mass [7]. However, studies in kidney disease patients suggest that lean mass affects cystatin C concentrations [8, 9]. Many studies have explored the associations between body mass index (BMI) and eGFR, using BMI as a proxy for body composition [10, 11]. To our knowledge, large population-based studies in healthy children comparing the correlations and associations of detailed body composition measures, next to BMI, with the estimates of GFR are lacking.

To estimate the influence of different body composition measures on eGFR from creatinine and cystatin C blood concentrations, we compared the associations of different anthropometric and body composition measures with eGFR derived from creatinine (eGFR$_{creat}$) and cystatin C (eGFR$_{cystC}$) blood concentrations in a population-based prospective cohort study among 4,305 children who were 6 years of age.

Methods

Design and Study Population

This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onward in Rotterdam, The Netherlands, which has been described in detail previously [12]. The study has been approved by Medical Ethical Committee of Erasmus MC, University Medical Center Rotterdam. All children were born between April 2002 and January 2006 and form a largely prenatally enrolled birth cohort that is currently being followed until young adulthood. Written consent was obtained for all children. The present analyses were performed among 4,305 children whose body composition details and kidney function measures available (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000463395).

Body Composition Measurements

Children's anthropometrics and body composition were measured at a median age of 6.0 years (95% range 5.7–8.0) [12]. Height (m) was determined in standing position to the nearest millimeter without shoes using a Harpenden stadiometer (Holtain Limited, Dyfed, UK). Weight was measured using a mechanical personal scale (SECA, Almere, The Netherlands). We calculated BMI (kg/m^2) and body surface area (BSA; m^2). For BSA, we used the DuBois formula: BSA = weight (kg)$^{0.425}$ × height (cm)$^{0.725}$ × 0.007184. Whole body dual-energy X-ray absorptiometry (DXA) scans (iDXA, GE-Lunar, 2008, Madison, WI, USA) were performed to estimate fat and lean mass. We calculated lean mass percentage as (lean mass [kg]/weight [kg]) and fat mass percentage as (fat mass [kg]/weight [kg]).

Kidney Function Measurements

Non-fasting blood samples were drawn by antecubital venipuncture and centrifuged for 10 min and stored at –80°C at one location in the Stichting Trombosedienst and Artsenlaboratorium

Rijnmond (STAR)-MDC laboratory. As previously described, creatinine concentrations were measured with enzymatic methods and cystatin C concentrations with a particle enhanced immuno-turbidimetric assay (using Cobas 8000 analyzers, Roche, Almere, The Netherlands). Quality control samples demonstrated intra- and inter-assay coefficients of variation of 0.51% for creatinine and 1.65% for cystatin C, and 1.37% for creatinine and 1.13% for cystatin C, respectively [13]. We calculated the eGFR based on creatinine concentrations according to the revised Schwartz 2009 formula: eGFR$_{creat}$ = 36.5 * (height [cm]/serum creatinine [μmol/L]) [14], and eGFR based on cystatin C concentrations using Zappitelli's formula: eGFR$_{cystC}$ = 75.94/(CysC [mg/L]$^{1.17}$) [15].

Statistical Analysis

We performed a non-response analysis by comparing subject characteristics between children with and without kidney function measurements using t tests, chi-square tests, and Mann–Whitney tests. We created SDs scores for all body composition measures to enable comparison between effect estimates. Next, we examined the Pearson rank correlation coefficients between childhood anthropometrics, body composition, and eGFR measures. Third, we used multiple linear regression analyses to examine the associations of anthropometric and body composition measures with creatinine, cystatin C, eGFR$_{creat}$, and eGFR$_{cystC}$. The linear regression models were adjusted for child sex, age at measurements, and ethnicity. Additionally, we explored the associations of childhood BMI clinical cutoffs with creatinine, cystatin C, and eGFRs. Because of the already reported associations of ethnicity with kidney function markers, we performed a sensitivity analysis in children of European ethnicity, the largest ethnic subgroup [16]. Based on previous literature, we assessed whether the explored association differed by sex, which was not the case in this study [17, 18]. All analyses were performed using the Statistical Package for the Social Sciences version 21.0 for Windows (SPSS IBM, Chicago, IL, USA).

Results

Participant Characteristics

Online supplementary Figure 1 describes the selection of the study population. At the median age of 6 years (95% range 5.7–8.0) a total of 8,305 children participated in the study follow-up measurements. Of these children, 6,509 (78%) visited the research center for body composition measurements. In this study, we excluded children with congenital kidney abnormalities (n = 12). A total of 6,497 children were available for kidney function measurements. Of these children, 2,192 children did not have kidney measurements. The present analyses were performed among 4,305 children whose body composition and kidney function measures available.

Table 1 shows the characteristics of the participants. In the full group, the mean (SD) eGFR$_{creat}$ and eGFR$_{cystC}$ were 118.9 mL/min/1.73 m^2 (15.9) and 101.6 mL/min/1.73 m^2 (11.2), respectively. The histograms of creatinine, cystatin

C, eGFR$_{creat}$, and eGFR$_{cystC}$ are provided in online supplementary Figure 2. Results from the non-response analyses are given in the online supplementary Table 1. Children with kidney function measurements had higher lean mass percentage and lower fat mass percentage compared to children who did not have kidney function measurements.

Correlations of Childhood Anthropometrics and Body Composition Measures with eGFR

The Pearson rank correlation coefficient between eGFR$_{creat}$ and eGFR$_{cystC}$ was $r = 0.40$ (p value <0.01; Table 2). Childhood height, weight, BMI, and BSA were positively correlated with creatinine and cystatin C concentrations, with stronger coefficients for creatinine concentrations (p value <0.01). Lean mass percentage was positively correlated with creatinine concentrations and negatively correlated with eGFR$_{creat}$ ($r = 0.13$, p value <0.01). Similar results, but in opposite directions, were observed for fat mass percentage. Lean mass percentage and fat mass percentage were not correlated with cystatin C concentrations or eGFR$_{cystC}$.

Associations of Childhood Body Composition Measures with eGFR

Table 3 shows the results from the linear regression models. Childhood height was associated with creatinine concentrations (p value <0.05), but not with cystatin C concentrations. Higher childhood weight was associated with both higher creatinine and cystatin C concentrations (p value <0.01). Higher childhood height was associated with higher eGFR$_{creat}$ (p value <0.01), but not with eGFR$_{cystC}$ whereas higher childhood weight was associated with higher eGFR$_{creat}$ and lower eGFR$_{cystC}$ (p value <0.01).

Each 1-SD increase in BSA was associated with 1.81 mL/min/1.73 m^2 (95% CI 1.24–2.37) higher eGFR$_{creat}$ and 0.57 mL/min/1.73 m^2 (95% CI –0.98 to –0.17) lower eGFR$_{cystC}$. BMI was negatively associated with eGFR$_{cystC}$ (p value <0.05) but not with eGFR$_{creat}$. We observed tendencies for similar effect estimates when we restricted the analyses to Europeans only ($n = 2,727$; online suppl. Table 2). The associations of BMI clinical cutoffs with creatinine, cystatin C, and the eGFR are given in online supplementary Table 3.

Higher lean mass percentage was associated with higher creatinine concentrations and with lower cystatin C concentrations (Table 3; p value <0.05). A 1-SD increase in lean mass percentage was associated with 2.74 mL/min/1.73 m^2 (95% CI –3.27 to –2.20) lower childhood eGFR$_{creat}$. No association was observed of lean mass percentage with eGFR$_{cystC}$.

Table 1. Subjects characteristics ($n = 4,305$)

Age at measurements, years	6.0 (5.7–8.0)
Gender, female, %	48.3
Ethnicity, %	
Dutch or European	65.1
Non-European	34.9
Height, m	119.7 (6.0)
SD score*, mean (SD)	–0.2 (1.0)
Weight, kg	23.4 (4.2)
SD score*, mean (SD)	0.1 (1.0)
Body mass index, kg/m^2	16.2 (1.8)
SD score*, mean (SD)	0.3 (0.9)
Body surface area, m^2	0.88 (0.09)
Fat mass percentage, %	24.7 (5.6)
Lean mass percentage, %	71.7 (5.4)
eGFR$_{creat}$, mL/min/1.73 m^2	118.9 (15.9)
eGFR$_{cystC}$, mL/min/1.73 m^2	101.6 (11.2)

Values are percentages for categorical variables, means (SD) for continuous variables with a normal distribution, or medians (95% range) for continuous variables with a skewed distribution. * The SD scores were obtained using Dutch reference growth curves (Growth Analyzer 3.0, Dutch Growth Research Foundation, Rotterdam, The Netherlands). eGFR$_{creat}$, estimated glomerular filtration rate calculated based on creatinine blood concentrations; eGFR$_{creat}$ = 36.5 * (height [cm]/serum creatinine [μmol/L]); eGFR$_{cystC}$, estimated glomerular filtration rate calculated based on cystatin C blood concentrations; eGFR$_{cystC}$ = 75.94/(cysC [mg/L]$^{1.17}$).

Similar results, but in an opposite direction, were observed for fat mass percentage (Table 3). We observed similar effect estimates when we restricted our analyses to European subjects only, although not all associations were significant (online suppl. Table 2).

Discussion

Results of this cross-sectional study in healthy 6-year-old children suggest that BMI and BSA are associated with creatinine-based and cystatin C-based eGFRs. Lean mass percentage and fat mass percentage are associated with creatinine-based eGFR, but not with cystatin C-based eGFR.

Interpretation of Main Findings

To our knowledge, this is the first large population-based study in healthy school-age children comparing the association of detailed measures of body composition using DXA scans with estimates of GFR based on creatinine and cystatin C concentrations. Both creatinine and cystatin C concentrations can be influenced by different factors. Creatinine is produced in active muscle and is re-

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Table 2. Correlation coefficients of the investigated variables

	Height	Weight	BMI	BSA	FMP	LMP	Creat	Cyst C	eGFR$_{creat}$	eGFR$_{cystC}$
Height	1.00									
Weight	0.77*	1.00								
BMI	0.31*	0.83*	1.00							
BSA	0.90*	0.97*	0.69*	1.00						
FMP	0.18*	0.57*	0.69*	0.46*	1.00					
LMP	−0.19*	−0.56*	−0.68*	−0.45*	−0.999*	1.00				
Creat	0.30*	0.28*	0.16*	0.30*	−0.05*	0.05*	1.00			
Cyst C	0.05*	0.06*	0.05*	0.06*	−0.001	0.003	0.40*	1.00		
eGFR$_{creat}$	0.06*	0.01	−0.04*	0.03	0.12*	−0.13*	−0.92*	−0.40*	1.00	
eGFR$_{cystC}$	−0.05*	−0.06*	−0.05*	−0.06*	0.01	−0.01	−0.39*	−0.99*	0.40*	1.00

* Correlation is significant at the 0.01 level (2-tailed).

BMI, body mass index; BSA, body surface area; FMP, fat mass percentage; LMP, lean mass percentage; creat, creatinine; Cyst C, cystatin C; eGFR$_{creat}$, estimated glomerular filtration calculated based on creatinine blood concentrations; eGFR$_{cystC}$, estimated glomerular filtration calculated based on cystatin C blood concentrations.

Table 3. Associations of anthropometric and body composition measures with creatinine, cystatin C, and eGFR (n = 4,305)

Anthropometrics and body composition (SDS)	Difference (95% CI)			
	creatinine, μmol/L	cystatin C, μg/L	eGFRcreat, mL/min/1.73 m^2	eGFRcystC, mL/min/1.73 m^2
Height	0.97 (0.79 to 1.15)***	1.99 (−0.70 to 4.70)	2.78 (2.22 to 3.35)***	−0.29 (−0.70 to 0.12)
Weight	0.91 (0.73 to 1.08)***	4.49 (1.91 to 7.07)***	1.16 (0.61 to 1.71)***	−0.66 (−1.05 to −0.27)**
Body mass index	0.52 (0.36 to 0.68)***	4.15 (1.80 to 6.51)***	−0.37 (−0.87 to 0.13)	−0.61 (−0.96 to −0.26)**
Body surface area	1.02 (0.84 to 1.20)***	3.93 (1.27 to 6.59)**	1.81 (1.24 to 2.37)***	−0.57 (−0.98 to −0.17)**
Lean mass percentage	0.30 (0.07 to 0.54)*	−2.73 (−5.28 to −0.18)*	−2.74 (−3.27 to −2.20)***	0.36 (−0.03 to 0.74)
Fat mass percentage	−0.48 (−0.65 to −0.31)***	2.86 (0.32 to 5.40)*	2.68 (2.14 to 3.21)***	−0.38 (−0.76 to 0.01)

Values are beta coefficients and 95% CIs, from linear regression models adjusted for child age, sex, and ethnicity. eGFR$_{creat}$, estimated glomerular filtration rate calculated based on creatinine blood concentrations; eGFR$_{cystC}$, estimated glomerular filtration rate calculated based on cystatin C blood concentrations.

p value for the associations * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

ported to be determined by muscle mass and dietary intake, which may account for the variations in the concentrations of serum creatinine observed among different age and ethnic groups [1, 3]. However, we have previously reported that childhood protein intake does not influence the eGFR [19]. Cystatin C is another marker to evaluate renal function, although it is not used as commonly as creatinine [6, 20]. Cystatin C is produced by all nucleated cells and reported to be less strongly related to body weight and height in children compared to creatinine [5, 7]. Besides, adult studies suggest that cystatin C concentrations are related to age, sex, height, and weight and influenced by corticosteroid use [17, 21].

In children, the Schwartz formula is widely used to estimate GFR from creatinine concentrations [14]. The Schwartz formula is known to overestimate eGFR compared to inulin clearance GFR [6, 22, 23]. Schwartz formula estimates GFR using creatinine concentrations and child height [14]. Therefore, the observed effect estimates in the current study of height on eGFR$_{creat}$ might clinically not be relevant. Next to Schwartz's formula, we estimated GFR using the Zappitelli's formula [15]. This formula is not dependent of any anthropometric measures. It estimates GFR by using only the cystatin C concentrations [15]. In a study among 42 healthy adults, eGFR using creatinine and cystatin C concentrations were compared with measured GFR. This study suggested that eGFR based on cystatin C concentrations was a better marker then eGFR based on creatinine concentrations for estimating kidney function [24].

It has previously been reported that lean body mass, indicating muscular mass, is an important determinant of the GFR [25]. So far, results from studies comparing the effects of body composition measures on creatinine and cystatin C concentrations and their derived eGFR are contradictory [8, 26]. A number of studies have explored the associations of BMI with eGFR, using BMI as a proxy of body composition [10, 11]. The associations of BMI with creatinine and cystatin C differed between populations studied. We observed that higher BMI was associated with higher creatinine and cystatin C concentrations and with lower eGFR$_{cystC}$, but not with eGFR$_{creat}$. In the subgroup of Europeans, we observed that BMI was associated with creatinine, cystatin C concentrations, and their derived eGFRs. In line with our findings in the European subgroup, in the general Japanese population, BMI was associated with lower eGFR$_{creat}$ [11]. Similar to what we observe, studies among both healthy and kidney disease adults suggested that eGFR based on cystatin C concentrations is not independent of BMI [8, 27]. These findings appear to be different among children with various kidney diseases, where BMI does not have a clinically relevant effect on eGFR$_{cystC}$ [10]. Next to BMI, we observed that higher BSA was associated with higher creatinine, cystatin C concentrations, eGFR$_{creat}$, and lower eGFR$_{cystC}$. The effect estimates for the associations of BMI and BSA with eGFRs are relatively small. Studying detailed measures of body composition will therefore likely add to the understanding of the associations of body composition and kidney function measures.

Studies among healthy adults have shown lean mass percentage to be associated with serum creatinine and eGFR based on creatinine concentrations but not with cystatin C concentrations [4, 26]. A study among 67 healthy individuals of ages between 18 and 52 years has shown that creatinine concentrations were highly affected by muscle mass, whereas cystatin C concentrations were affected by fat mass [28]. The associations between lean mass and cystatin C are reported to be different among kidney disease patients [8]. Among 77 chronic kidney disease patients lean mass affected cystatin C concentrations, and GFR estimation based on cystatin C concentrations improved when lean mass was included in the formula, especially in patients with extreme body composition [8]. In severely obese children, lean mass percentage has been reported to correlate with both creatinine and cystatin C concentrations [29]. In the current study, we observed that lean and fat mass percentage correlate with creatinine concentrations and eGFR$_{creat}$. Higher lean mass percentage and lower fat mass percentage were associated with higher creatinine concentrations and lower eGFR$_{creat}$. We did not observe a significant correlation of lean mass percentage or fat mass percentage with cystatin C concentrations. Our study shows that eGFR based on cystatin C concentrations is independent of lean mass percentage and fat mass percentage.

Our findings suggest that eGFR$_{creat}$ is more strongly influenced by body composition than eGFR$_{cystC}$. However, their impact on clinical care may be limited. As the revised Schwartz formula (eGFR$_{creat}$) is the most widely used formula both in epidemiological studies and clinical practice, our findings suggest that body composition measures should be considered when eGFR is based on creatinine concentrations. Ideally, body composition measures would have been incorporated in the eGFR$_{creat}$ equations and compared with GFR based on renal clearances of exogenous markers, but unfortunately this is not possible in our study. Considering the feasibility and costs of performing DXA scans in school-age children, whether and to what extent detailed body composition measures should be used in the clinical practice when estimating GFR can be argued. Other studies are needed to assess whether using eGFR$_{cystC}$ instead of eGFR$_{creat}$ leads to better care for pediatric kidney patients.

Strengths and Limitations

To the best of our knowledge, this is the first and largest cross-sectional multiethnic study in a healthy pediatric population-based cohort examining the associations of body composition with estimates of GFR. GFR was estimated based on creatinine and cystatin C concentrations. Except height and weight to calculate BMI and BSA, we also measured fat mass and lean mass with DXA. Of all children, 61% provided blood samples for measuring creatinine and cystatin C concentrations. Children without data on kidney function measures were shorter, had a higher fat mass percentage, and lower lean mass percentage. The difference in fat and lean mass percentage may be explained by the higher percentage of girls in the group without available kidney measures. There was no difference in BMI between the children with and without available kidney function measures. We observed tendencies for similar effect estimates among Europeans only, although not all associations were significant in this subgroup. This might be due to the smaller study group, but may also reflect an effect of ethnicity. Ideally, we would have been able to compare the explored associations with the measured GFR and validate our findings.

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Unfortunately, we do not have the urinary or plasma clearance of an ideal filtration marker, such as inulin, iothalamate, or iohexol, as the gold standard for the measurement of GFR [30]. Our findings are based on a healthy pediatric population of a narrow age category and may not be generalizable to older, younger, or diseased populations.

Conclusion

Our results suggest that eGFR based on both creatinine and cystatin C concentrations are influenced by BMI and BSA, whereas only eGFR based on creatinine concentrations is influenced by lean mass percentage and fat mass percentage. Beside anthropometric measurements, body composition measures should be considered when estimating GFR in children. Further studies to compare these results with measured GFR are needed.

Author Contributions

K.M. and V.W.V.J. designed the research and wrote the paper. K.M. analyzed the data. H.B., E.M.D., K.C., O.H.F., and J.F.F. provided comments and consultation regarding the analyses, interpretation of the results, and manuscript. K.M. had primary responsibility for final content. All authors gave final approval of the version to be published.

Disclosure Statement

The authors declare no conflict of interest.

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