Published in final edited form as:

Am J Kidney Dis. 2017 September ; 70(3): 397–405. doi:10.1053/j.ajkd.2017.03.019.

Relationships of Measured Iohexol GFR and Estimated GFR With CKD-Related Biomarkers in Children and Adolescents

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Abstract

Background—Two valid and reliable estimated glomerular filtration rate (GFR) equations for the pediatric population have been developed from directly measured GFR data in the Chronic Kidney Disease in Children (CKiD) cohort: the full CKiD and bedside CKiD equations. While adult GFR estimating equations replicate relationships of measured GFR with biomarkers, it is unclear whether similar patterns exist among children and adolescents with chronic kidney disease (CKD).

Study Design—Prospective cohort study in children and adolescents.

Settings & Participants—730 participants contributed 1539 study visits.

Predictors—Measured GFR by plasma iohexol disappearance (mGFR), estimated GFR by the full CKiD equation (eGFR_{CKiDfull}; based on serum creatinine, cystatin C, serum urea nitrogen, height, and sex), and estimated GFR by the bedside CKiD equation (eGFR_{CKiDbd}; calculated as $41.3 \times \text{height[m]}/\text{serum creatinine [mg/dL]}$) were predictors of CKD-related biomarkers.

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N Section: Because an author of this article is an editor for AJKD, the peer-review and decision-making processes were handled by an Editorial Board Member (*Kathleen Liu, MD, PhD*) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Information for Authors & Journal Policies.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: DKN, AM; data acquisition: GJS, BAW, SLF; data analysis/interpretation: DKN, AM, GJS, BAW, SLF; statistical analysis: DKN; supervision or mentorship: AM. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Peer Review: Evaluated by 3 external peer reviewers, a statistician, and an Acting Editor-in-Chief.

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Deviations of mGFR from $eGFR_{CKiDfull}$ and deviations of $eGFR_{CKiDfull}$ from $eGFR_{CKiDbed}$ from linear regressions (i.e., residuals) were included in bivariate analyses.

Outcomes & Measurements—CKD-related biomarkers included urine protein-creatinine ratio, blood hemoglobin, serum phosphate, bicarbonate, potassium, systolic and diastolic blood pressure z scores, and height z scores.

Results—The median age of 730 participants with CKD was 12.5 years, with median mGFR, $eGFR_{CKiDfull}$, and $eGFR_{CKiDbed}$ of 51.8, 54.0, and 53.2 ml/min/1.73 m², respectively. $eGFR_{CKiDfull}$ demonstrated as strong or stronger associations with CKD-related biomarkers than mGFR; $eGFR_{CKiDbed}$ associations were significantly attenuated (i.e., closer to the null). Residual information in mGFR did not substantially increase explained variability. $eGFR_{CKiDbed}$ estimated faster GFR decline relative to mGFR and $eGFR_{CKiDfull}$.

Limitations—Simple linear summaries of biomarkers may not capture non-linear associations.

Conclusions— $eGFR_{CKiDfull}$ closely approximated mGFR to describe relationships with CKD-severity indicators and progression in this pediatric CKD population. $eGFR_{CKiDbed}$ offered similar inferences, but the associations were attenuated and rate of progression was overestimated. The $eGFR_{CKiDfull}$ equation from 2012 is preferred for pediatric research purposes.

Keywords

pediatric; glomerular filtration rate (GFR); estimated GFR; measured GFR; iohexol; kidney function; kidney measure; chronic kidney disease (CKD); children; adolescents; Chronic Kidney Disease in Children (CKiD); GFR estimating equation; CKD biomarker

Glomerular filtration rate (GFR) is considered to be the best assessment of kidney health and may be measured directly by the plasma disappearance of an exogenously administered agent. Because direct measurement of GFR is burdensome and invasive, equations developed to determine estimated GFR (eGFR) are part of routine clinical care and are substituted for measured GFR (mGFR) in research studies. The Chronic Kidney Disease in Children (CKiD) cohort has obtained over 2500 iohexol-based mGFRs, which have been used to develop GFR estimating equations. These include the full CKiD equation ($eGFR_{CKiDfull}$) based on serum creatinine, cystatin C, serum urea nitrogen and height, introduced in a 2012 publication¹; and the simple bedside equation² ($eGFR_{CKiDbed}$), which is 41.3 times the ratio of height to serum creatinine. These equations have performed extremely well internally^{1,2} and in diverse external special populations using non-iohexol-based methods^{3–17}. In addition, several publications have used these equations for epidemiologic purposes, including etiologic^{18–21} and prospective studies^{22,23}.

While published estimating equations are valid, with low bias and good precision, agreement metrics have been primarily comparisons between the proposed eGFR equation and mGFR in terms of bias, accuracy, precision, and correlation. Investigating potential differences between these two assessments for epidemiologic inference is another metric of agreement and recent analyses in adult populations have explored this^{24–29}. To our knowledge, investigating potential differences in how GFR methods characterize relationships between kidney function and CKD biomarkers in children and adolescents has not yet been fully characterized.

The objective of this study was, in turn, to compare the relationships between different GFR assessment methods and indicators of CKD severity and GFR trajectory in a population of children and adolescents with diverse CKD diagnoses. Using GFR as the predictor, we investigated whether eGFR described the same relationship as mGFR with markers of CKD (e.g., proteinuria, metabolic, cardiovascular and growth variables). For this aim, we not only quantified the strength of the association, but also the variability explained by eGFR and how that was improved by including the information in mGFR that is not present in eGFR. In addition, using GFR as the outcome, we investigated whether the characterization of GFR decline over time by proteinuria level at baseline was different when using mGFR or eGFR. Comparing how mGFR, eGFR_{CKiDfull}, and eGFR_{CKiDbed} describe relationships of CKD severity and progression may provide guidance for pediatric CKD study populations external to CKiD and help facilitate simple and standardized assessments of GFR for research to improve reproducibility.

Methods

Study Population

As of 2016, the CKiD cohort study enrolled 891 children and adolescents aged 1-16 years from the United States and Canada, representing diverse CKD diagnoses with eGFR between 30 and 90 ml/min/1.73m². Details of the study design have been previously described³⁰. The iothexol-based mGFR was obtained at the first two annual visits and every other annual visit thereafter. Blood chemistry, including serum creatinine (Scr), cystatin C, serum urea nitrogen (SUN), and urine data were collected at each annual visit. The study design and conduct were approved by the internal review boards for each of the participating centers and by an external advisory committee appointed by the National Institutes of Health. Written informed consent/assent was obtained from all participants/families according to local IRB requirements.

Glomerular Filtration Rate

mGFR was calculated from a two-compartment model for visits occurring from 2005 to 2011, and from a universal equation for a one-compartment model from 2011 to 2015³¹. Iothexol concentrations from November 2006 to March 2016 were increased by 12% as part of a multi-laboratory assay recalibration (Schwartz et al., manuscript in preparation). Equations for eGFR included 1) a full equation published in 2012¹, referred hereafter as eGFR_{CKiDfull}, and defined as $39.8 \times (\text{height [m]}/\text{Scr [mg/dL]})^{0.456} \times (1.8/\text{cystatin C [mg/dL]})^{0.418} \times (30/\text{SUN [mg/dL]})^{0.079} \times 1.076$ (if male) $\times (\text{height [m]}/1.4)^{0.179}$; and 2) the 2009 bedside equation² (referred hereafter as eGFR_{CKiDbed}) which is commonly used clinically and is simply $41.3 \times \text{height [m]} / \text{Scr [mg/dL]}$.

Biomarkers Related to CKD Severity

Biomarkers as outcomes were urine protein-creatinine ratio (UPCR; in mg per mg of creatinine; measured as a portion of first morning void), blood hemoglobin (g/dl), serum bicarbonate (mEq/L), potassium (mEq/L), and phosphate (mg/dl)²⁷. For the assessment of cardiovascular and growth markers, systolic blood pressure (SBP) and diastolic blood

pressure (DBP) z scores (adjusted for age, sex and height³²) and height z scores (adjusted for age and sex³³) were included as outcomes.

Statistical Methods

The first approach of the analyses employed three separate univariate regression models for each biomarker (as the dependent variable) and mGFR, eGFR_{CKiDfull} and eGFR_{CKiDbd} as separate independent variables (in the log scale to provide measures of percent change) for each model. Biomarkers, with the exception of z scores, were log transformed (to achieve normality) and the slope from this model was expressed as the change in biomarker associated with a 50% lower GFR level. To account for the correlation of repeated measurements within individuals, generalized estimating equations were used to appropriately adjust standard errors for all models. To compare whether estimates by eGFR_{CKiDfull} and eGFR_{CKiDbd} were statistically different from mGFR, we used bootstrap methods and sampled at the individual level to preserve the within-person correlation of biomarkers and of repeated measurements. Specifically, 500 datasets were created from children and adolescents in our analytic dataset sampled with replacement.

The objective of the second approach was to quantify the putative additional information that is in mGFR but not in eGFR_{CKiDfull} (i.e., obtaining mGFR deviations from eGFR_{CKiDfull} based on the regression of mGFR on eGFR_{CKiDfull}; i.e., residuals). Specifically, we expanded the model including eGFR_{CKiDfull} in the first approach to the following:

$$\text{Biomarker} = \gamma_0 + \gamma_1 \log(\text{eGFR}) + \gamma_2 \text{mGFR deviations from eGFR}_{\text{CKiDfull}} + \text{error}$$

where the error term is normally distributed with mean 0 and standard deviation σ . This model allows for a comparison of R^2 values in which the null model assumes γ_2 equal zero (i.e., first approach) and the test model allows γ_2 to be estimated from the data. This provides an estimate of the explanatory power of information in mGFR not present in eGFR_{CKiDfull}.

As part of the second approach, we also carried out similar analyses in which the primary predictor was eGFR_{CKiDbd}. That is, we quantified how much more explained variability is added by including the deviations of mGFR from eGFR_{CKiDbd}, and those of eGFR_{CKiDfull} from eGFR_{CKiDbd} to the third univariate model in the first approach (i.e., using only eGFR_{CKiDbd}). The summary measures were the comparisons of the R^2 values for the univariate and bivariate models. Statistical significance was determined by the same bootstrapping method described for first approach.

The third approach in the analysis used longitudinal data to determine changes in GFR over time. In addition to the overall changes in GFR over time, we assessed how each method characterized the clinically and epidemiologically meaningful interaction between initial UPCR and the effect of time. This linear mixed effects model with random intercepts and slopes used GFR as the outcome in the log scale, and the independent variables were baseline UPCR (in the log scale), time in years, and the interaction between the two. This

model for the data provided by the i th individual at the j th visit (where $j=0$ being the baseline CKiD visit) is formally expressed as:

$$\log(\text{GFR}_{ij}) = [\alpha_0 + \alpha_1 \times \log(\text{UPCR}_{i0}) + a_i] + [\beta_0 + \beta_1 \times \log(\text{UPCR}_{i0}) + b_i] \times \text{years from baseline}_{ij} + e_{ij}$$

where a_i and b_i are the random effects and e_{ij} is assumed to be normally distributed with mean 0 and standard deviation, θ , representing the deviations of the observed data from the line of the i th individual.

The population mean GFR level at entry and average percent change per year were presented for UPCR levels that represent doubling across the spectrum commonly observed in CKiD: at 0.25, 0.50, 1, 2 and 4 mg/mg.

Results

Of 891 children and adolescents enrolled, only person-visits with valid mGFR, eGFR_{CKiDfull} and eGFR_{CKiDbed} and complete data on 8 biomarkers were eligible to be included in our analysis (n=832 contributing 2088 person-visits). To ensure that our analytic sample was independent from (i.e., external to) the data used to develop the eGFR_{CKiDfull} equation¹, we further excluded those person-visits from our analysis (n= 102 contributing 533 person-visits). Hence, our analytic sample comprised 730 children and adolescents providing 1539 person-visits. In a comparison of the 730 children and adolescents included in our analysis and the 161 who were excluded, there were no significant differences demographically or by body size. However, GFRs were higher among those included in our analysis corresponding to recruitment in 2012-2014 at which time higher GFR was a criterion for study entry.

Table 1 describes the baseline (i.e., first observation) demographic and clinical characteristics, as well as longitudinal data available. The median mGFR, eGFR_{CKiDfull} and eGFR_{CKiDbed} values were 51.8, 54.0 and 53.2 ml/min/1.73m², respectively. Median baseline UPCR was 0.35 mg/mg. Compared to the age-, sex- and height-adjusted apparently healthy population, our study sample had higher blood pressure z scores, specifically 0.24 standard deviation (SD) for SBP and 0.39 SD for DBP. The participants exhibited substantial deficits in height, specifically about 0.44 SD below the age- and gender-adjusted average.

Using separate models for each GFR measure, Table 2 presents the univariate relationships between markers of CKD severity and three measures of GFR: mGFR, eGFR_{CKiDfull}, and eGFR_{CKiDbed}. A 50% lower mGFR was associated with a 169.7% (95% confidence interval [CI], 139.4%-203.8%) higher UPCR. In contrast, a 50% lower eGFR_{CKiDfull} was associated with a 204.0% (95% CI, 167.2%-245.9%) higher UPCR, a stronger association than mGFR. By contrast, a 50% lower eGFR_{CKiDbed} was associated with a 155.0% (95% CI, 129.8%-182.9%) higher UPCR, a weaker association than mGFR. While both eGFR_{CKiDfull} and eGFR_{CKiDbed} offered the same inference of effect size (i.e., that GFR is significantly associated with proteinuria), eGFR_{CKiDbed} was weaker than the estimate by mGFR, with borderline significance (p= 0.05), and eGFR_{CKiDfull} was significantly stronger than the mGFR estimate (p<0.001).

Similar patterns were observed for the other 7 biomarkers. The relationships between $eGFR_{CKiDfull}$ and phosphate, bicarbonate, and SBP z scores were significantly stronger (i.e., away from the null) than the relationship estimated by $mGFR$ (all $p < 0.001$). The relationship between $eGFR_{CKiDfull}$ and hemoglobin was slightly stronger than that for $mGFR$ but not significantly different (-7.9% versus -7.6% ; $p = 0.1$). This phenomenon was also observed for height z scores (-0.39 versus -0.36 ; $p = 0.09$). The estimates between $eGFR_{CKiDfull}$ and $mGFR$ were the same for potassium ($+3.3\%$ versus $+3.3\%$; $p = 0.7$) and similar for DBP z scores ($+0.05$ versus $+0.06$; $p = 0.6$). In contrast, for $eGFR_{CKiDbd}$, the relationships were attenuated (i.e., toward the null) compared to $mGFR$ for all outcomes, and these were significantly different for hemoglobin, phosphate, bicarbonate, potassium, DBP z scores and height z scores (all $p = 0.002$). For SBP z score, the estimates did not differ statistically between $mGFR$ and $eGFR_{CKiDbd}$ ($+0.15$ versus $+0.13$; $p = 0.5$). Overall, the relationships were inferentially the same across all three GFR assessments in that all estimates were significantly different from 0 (with the exception of DBP z scores), but $eGFR_{CKiDbd}$ consistently demonstrated weaker associations and was most often significantly different from $mGFR$. In contrast, $eGFR_{CKiDfull}$ showed stronger associations with known markers related to CKD severity than $mGFR$.

Figure 1 depicts a diamond graph³⁴ comparing the R^2 values of univariate (GFR only) and bivariate (GFR and deviations) models. The shaded polygon within each cell is proportional to the outcome variability explained by the predictors, scaled to 25% (i.e., an R^2 of 25% represents the full area within each cell). Shown in the upper left row of the graph, $eGFR_{CKiDfull}$ explained 22.2% of UPCR variability, and when $mGFR$ deviations from $eGFR_{CKiDfull}$ were included in a bivariate model, this R^2 value increased slightly (22.4%; $+0.2\%$). Similarly, $eGFR_{CKiDbd}$ in a univariate model explained 21.8% of UPCR variability; the addition of $mGFR$ deviations in the bivariate model increased the R^2 to 22.6% ($+0.8\%$) and when $eGFR_{CKiDfull}$ deviations were added, the R^2 was 22.5% ($+0.7\%$). For the other 7 biomarkers as outcomes, relative to the $eGFR_{CKiDfull}$, the additional explained variability offered by the $mGFR$ deviations was minor, ranging from no difference in phosphate to 1.7% higher R^2 for hemoglobin (15.1% versus 16.8%), which was the only significant difference ($p = 0.01$). However, for $eGFR_{CKiDbd}$ (depicted in the 3 rows in the upper right part of the graph), substantially higher R^2 values were observed from the bivariate model including $mGFR$ deviations as compared to the univariate model of $eGFR_{CKiDbd}$, likely due to the simplicity and constraints of the $eGFR_{CKiDbd}$ equation. In particular, models with hemoglobin, phosphate, bicarbonate, and potassium as outcomes had significantly ($p = 0.003$) higher R^2 increases of $+7.2\%$ (10.6% versus 17.8%), $+3.5\%$ (8.1% versus 11.6%), $+4.2\%$ (9.4% versus 13.6%) and $+3.8\%$ (1.6% versus 5.4%), respectively.

Lastly, we compared how different GFR assessments may alter inferences related to the longitudinal changes in GFR both overall and at given values of initial UPCR level. Table 3 presents the population average mean GFR at baseline (i.e., study entry) and changes over time, for each GFR assessment ($mGFR$, $eGFR_{CKiDfull}$, and $eGFR_{CKiDbd}$) overall and for varying levels of baseline UPCR. The baseline GFR was similar by GFR assessment overall, and all methods consistently showed lower GFR among those with higher baseline UPCR. The estimated average change per year was slightly attenuated for $eGFR_{CKiDfull}$ compared to $mGFR$ (-3.8% versus -4.3% per year for the overall model) and was very similar when

baseline UPCR was allowed to modify change. When $eGFR_{CKiDbed}$ was used, a higher decline was estimated compared with $mGFR$ or $eGFR_{CKiDfull}$ in the overall model (-6.4% versus -4.3%), and this was consistent across levels of UPCR when baseline UPCR was included as an independent variable. In summary, population averages of GFR at entry were similar across the three methods (within approximately 2 ml/min/1.73m²); estimates of change were similar between $mGFR$ and $eGFR_{CKiDfull}$, but $eGFR_{CKiDbed}$ estimated faster declines, particularly at higher levels of baseline UPCR. Although the measure of change used here is in the multiplicative scale (i.e., percent change per year), using the results in Table 3, one can easily estimate the rate of change in the arithmetic scale (e.g., for $mGFR$, $49.9 \text{ ml/min/1.73 m}^2 \times (-4.3)\% = -2.1 \text{ ml/min/1.73 m}^2$ in the first year).

Discussion

This study assessed how GFR assessment methods differ in describing a diverse panel of biomarkers related to disease severity and disease trajectory in a pediatric population. We showed that the use of $eGFR$ based on the 2012 CKiD equation ($eGFR_{CKiDfull}$ in this study) did not alter inferences in terms of characterizing biomarker relationships and disease progression compared to $mGFR$. Furthermore, the use of this equation offered associations that were consistently as strong as or stronger than that of $mGFR$. In quantifying relationships with biomarkers, $eGFR_{CKiDbed}$ tended to be biased toward the null (i.e., attenuated) and was significantly different from $mGFR$ in 7 of the 8 biomarkers explored. In addition, $eGFR_{CKiDbed}$ overestimated the decline per year compared to $mGFR$ and $eGFR_{CKiDfull}$, which were similar to one another.

While inferentially similar, some relationships with biomarkers were actually stronger for $eGFR_{CKiDfull}$ compared to $mGFR$. These findings were consistent with previous reports demonstrating that $eGFR$ offers stronger predictive power than $mGFR$ ^{24,27,29}. This is likely due to a combination of removing non-informative variability in iohexol-based $mGFR$ ^{31,35,36} and to the predictive power of Scr, cystatin C and SUN for extra-renal indicators of health. The latter explanation may be more plausible, as $eGFR$ is a summary value based on one or more variables (Scr, cystatin C and SUN) that are known to be independently associated with non-CKD comorbidities^{24,37}. For example, in the regression in which $eGFR_{CKiDbed}$ and the residuals from $eGFR_{CKiDfull}$ were included as predictors of phosphate (Figure 1), substantial increases in R^2 values were observed compared to $eGFR_{CKiDbed}$ alone and $eGFR_{CKiDbed}$ plus $mGFR$ residuals. We hypothesize this change is predominantly due to the effect of cystatin C as part of the $eGFR$ formula. For unique patient profiles that can influence cystatin C (e.g., thyroid disease) or serum creatinine levels (e.g., muscle wasting), univariate $eGFR$ equations may be more appropriate³⁸.

For $eGFR_{CKiDbed}$, the associations with biomarkers were attenuated and GFR decline was overestimated. In epidemiologic studies in which strength of association (i.e., the signal) is crucial for inference, attenuation of effects is generally not desirable. Indeed, it is well documented that measurement error is often a cause of attenuation of associations^{39,40}. Given the simplicity of the equation, it was not expected to perform as well as $mGFR$ or the more complex $eGFR_{CKiDfull}$ equation. Nonetheless, despite the attenuated associations, the inferences were similar and $eGFR_{CKiDbed}$ has been shown to be robust in diverse external

populations^{4,7,9,12,15}. While $eGFR_{CKiDbed}$ is simple to use and an excellent clinical tool for efficiency, for research purposes we recommend $eGFR_{CKiDfull}$ rather than $eGFR_{CKiDbed}$.

Our study population included several sources of heterogeneity in CKD-related characteristics beyond GFR (eg, CKD diagnosis). The full analysis was carried out separately by underlying glomerular and non-glomerular forms of CKD, and they were entirely consistent with the present analyses, in which diagnoses were pooled. This was not unexpected because the design of this analysis ensured that the three GFR methods were equally affected by any CKD-related heterogeneities within the data, thus providing a valid and fair comparison. Another source of heterogeneity was therapy use for proteinuria, anemia, blood pressure and/or growth failure in this population. Importantly, the proportions receiving therapy did not vary by GFR method used. While these results do not provide a characterization of treated or untreated relationships of biomarkers with GFR, this study design allows for valid comparisons between measured and estimated GFR methods.

Glomerular filtration rate is commonly used in epidemiologic research in three potential ways: a predictor, an outcome or a covariate. While the present analysis offers a detailed description of select scenarios, researchers should proceed carefully and consider how each GFR method will be used in analyses, and if one method may be better suited than another. For example, previous reports have documented the superiority of $eGFR$ in predicting outcomes^{24,26,37}, and $eGFR$ may therefore be preferable for prognostic purposes. Measured GFR should, on the other hand, be selected for investigations of kidney function outside the range in which $eGFR$ equations were developed, such as in populations at risk for hyperfiltration⁴¹ or in settings in which discrepancies between cystatin C–only $eGFR$ and Scr-only $eGFR$ require resolution³⁸. These examples serve to illustrate that particular research questions should dictate selection of the GFR assessment with careful scientific consideration. Given that the explained variability of biomarkers and characterizations of disease progression were not greatly enhanced by direct measures of GFR in the present analyses, the use of $eGFR_{CKiDfull}$ in a similar pediatric population with CKD for epidemiologic research can now be recommended, especially given the costs and burdens of obtaining mGFRs in children and adolescents.

There were several limitations to this study. First, this study did not characterize nonlinear relationships of GFR with biomarkers; these relationships were summarized using a simple linear assumption. While this approach allows for valid comparison across different GFR assessments (i.e., the relationships from the three methods were equally constrained by the model), it does not account for non-linear relationships and may not best describe the relationship of the biomarker with GFR. Second, our results may not be applicable to adults, or children and adolescents with GFR outside the range presented in these analyses (1412 $eGFR_{CKiDfull}$ observations [92% of our population] were between 20 and 90 ml/min/1.73 m²). However, these results are consistent with numerous studies comparing mGFR with $eGFR$. Third, cystatin C data used in this analysis, and for the CKiD equation development, were obtained prior to the availability of International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)–approved reference materials and are based on standard nephelometric output. Despite these data not being calibrated to IFCC material, the $eGFR_{CKiDfull}$ equation performed very well compared to mGFR. Fourth, GFR may also be

used as a restriction variable in epidemiologic research for selecting subjects who fit a particular profile, and this analysis did not address the impact of potential misclassification by GFR method. Lastly, while $eGFR_{CKiDfull}$ closely replicated the relationships determined by mGFR, consistency with other biomarkers (e.g., fibroblast growth factor 23) or in different populations is not assured. Nonetheless, the diversity of markers presented gives some confidence to expect a high degree of preservation of associations.

In conclusion, our analyses investigated differences in directly measured iohexol-based GFR and two $eGFR$ equations ($eGFR_{CKiDfull}$ and $eGFR_{CKiDbed}$) in a cohort of children and adolescents with CKD by quantifying the relationships of each method with biomarkers, as well as changes over time. While the three methods were inferentially similar for quantifying the relationships with biomarkers, the $eGFR_{CKiDbed}$ Scr-only equation generally had attenuated estimates of effect compared to the $eGFR_{CKiDfull}$ equation using Scr and cystatin C, which was comparable to mGFR. The information contained in mGFR not present in $eGFR_{CKiDfull}$ had minimal effects on explaining relationships with biomarkers. Compared to mGFR, $eGFR_{CKiDfull}$ described similar heterogeneity of longitudinal changes in GFR by UPCR levels, as well as relationships with biomarkers. In summary, our results suggest that the $eGFR_{CKiDfull}$ equation closely replicated mGFR for these selected relationships and should be the preferred GFR method for research studies of pediatric CKD.

Acknowledgments

Data in this manuscript were collected by the CKiD prospective cohort study with clinical coordinating centers (principal investigators) at Children's Mercy Hospital and the University of Missouri-Kansas City (Bradley Warady, MD) and Children's Hospital of Philadelphia (Susan Furth, MD, PhD), Central Biochemistry Laboratory (George Schwartz, MD) at the University of Rochester Medical Center, and data coordinating center (Alvaro Muñoz, PhD) at the Johns Hopkins Bloomberg School of Public Health. The CKiD Website can be found at www.statepi.jhsph.edu/ckid.

Support: The CKiD Study is supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, with additional funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01-DK-66143, U01-DK-66174, U01-DK-082194, U01-DK-66116)..

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Figure 1.

Diamond plot comparison of differences in naïve R^2 values (in %) for univariate directly measured iothexol-based GFR (iGFR), serum creatinine, cystatin C and BUN-based estimated GFR (eGFR) and serum creatinine-based bedside GFR (bedGFR) and for bivariate models including iGFR and eGFR deviations (residuals) among 730 children and adolescents providing 1539 visits. R^2 values are scaled to 25% (total area of each diamond).

Table 1
Baseline demographic and clinical characteristics

Variable	All children (n= 730)
Age, years	12.5 [8.7 to 15.5]
Male sex	62.7% (458)
Black race	21.4% (156)
<i>Growth and development</i>	
Height, cm	147 [127 to 163]
Height percentile	33 [11 to 63]
Weight, kg	42.5 [27.6 to 61.2]
Weight percentile	54 [25 to 86]
Body surface area, m ²	1.31 [0.99 to 1.68]
<i>CKD history and kidney function</i>	
Glomerular diagnosis	29.7% (217)
Time since CKD onset, y	9.2 [4.9 to 13.3]
Scr, mg/dL	1.10 [0.80 to 1.61]
Cystatin C, mg/L	1.37 [1.07 to 1.87]
SUN, mg/dL	23 [17 to 32]
mGFR, ml/min/1.73 m ²	51.8 [36.8 to 68.1]
eGFR _{CKiDfull} , ml/min/1.73 m ²	54.0 [39.0 to 67.4]
eGFR _{CKiDbed} , ml/min/1.73 m ²	53.2 [38.4 to 70.0]
<i>Markers of CKD severity</i>	
Urine protein, mg/mg	0.35 [0.11 to 1.10]
Hemoglobin, g/dL	12.8 [11.7 to 13.8]
Phosphate, mg/dL	4.5 [4.0 to 4.9]
Bicarbonate, mEq/L	24.0 [22.0 to 26.0]
Potassium, mEq/L	4.3 [4.1 to 4.6]
Adjusted SBP z score *	0.24 [-0.52 to 0.98]
Adjusted DBP z score *	0.39 [-0.26 to 1.06]
Adjusted height z score **	-0.44 [-1.24 to 0.34]
<i>No. of observations</i>	
1 visit	31.9% (233)
2 visits	34.5% (252)
3 visits	26.2% (191)
4 visits	7.4% (54)

Note: Baseline demographic and clinical characteristics of children enrolled in CKD in Children (CKiD) Study and contributing at least one study visit with directly measured iohexol-based GFR (mGFR); Scr-, cystatin C-, and SUN-based estimated GFR (eGFR_{CKiDfull}); and Scr-based bedside GFR (eGFR_{CKiDbed}). Values for categorical variables are given as number (percentage); for continuous variables, as median [interquartile range]. Conversion factors for units: creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; SUN in mg/dL to mmol/L, $\times 0.357$.

CKD, chronic kidney disease; Scr, serum creatinine; DBP, diastolic blood pressure; GFR, glomerular filtration rate; SUN, serum urea nitrogen;

* Age-, sex-, and height-adjusted.

^{**}
Age- and sex-adjusted.

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Table 2
Univariate associations of markers of CKD severity and three GFR measures

<i>Variable</i>	<i>mGFR[^]</i>	<i>eGFR_{CKiDfull}</i>	<i>eGFR_{CKiDbed}</i>
UPCR, mg/mg	+169.7% (+139.4% to +203.8%)	+204.0% (+167.2% to +245.9%); <i>P</i> < 0.001	+155.0% (+129.8% to +182.9%); 0.05
Hemoglobin, g/dL	-7.6% (-8.7% to -6.5%)	-7.9% (-9.0% to -6.7%); 0.1	-5.7% (-6.7% to -4.7%); <0.001
Phosphate, mg/dL	+9.4% (+7.6% to +11.2%)	+11.1% (+9.2% to +13.0%); <0.001	+7.3% (+5.7% to +8.9%); <0.001
Bicarbonate, mEq/L	-7.6% (-8.8% to -6.5%)	-8.1% (-9.3% to -6.9%); 0.02	-6.0% (-7.0% to -4.9%); <0.001
Potassium, mEq/L	+3.3% (+2.2% to +4.4%)	+3.3% (+2.1% to +4.6%); 0.7	+1.9%; (+0.9% to +3.0%); <0.001
Adjusted SBP z score [*]	+0.15 (+0.04 to +0.26)	+0.19 (+0.07 to +0.31); 0.009	+0.13 (+0.03 to +0.24); 0.5
Adjusted DBP z score [*]	+0.06 (-0.04 to +0.15)	+0.05 (-0.05 to +0.16); 0.6	0.00 (-0.10 to +0.09); <0.001
Adjusted height z score ^{**}	-0.36 (-0.48 to -0.24)	-0.39 (-0.52 to -0.26); 0.09	-0.28 (-0.39 to -0.17); 0.002

Note: Values are given as univariate associations (95% confidence intervals); P values for 730 children contributing 1539 observations. The measure of association was scaled to a 50% decrease in GFR.

Association and confidence interval values are based on linear regression models accounting for repeated measurements within individuals by generalized estimating equations. P values are based on bootstrap methods.

CKD, chronic kidney disease; GFR, glomerular filtration rate; mGFR, measured GFR (using iohexol); eGFR_{CKiDfull}, GFR estimated with 2012 CKD in Children Study equation based on serum creatinine, cystatin C, and serum urea nitrogen; eGFR_{CKiDbed}, 2009 serum creatinine-based bedside GFR; UPCR, urinary protein-creatinine ratio

[^] Reference.

^{*} Age-, sex-, and height-adjusted.

^{**} Age- and sex-adjusted.

Table 3
Longitudinal analysis describing GFR at entry and percent change per year overall, and for varying baseline UPCR based on 3 GFR measures

	GFR at entry, ml/min/1.73 m ²		Change per year		
	mGFR	eGFR _{CKiDbed}	mGFR	eGFR _{CKiDfull}	eGFR _{CKiDbed}
Overall	49.9 (48.3 to 51.6)	51.1 (49.6 to 52.6)	-4.3% (-5.0% to -3.5%)	-3.8% (-4.5% to -3.1%)	-6.4% (-7.2% to -5.5%)
Baseline UPCR					
0.25 mg/mg (= 43 rd percentile)	52.4 (50.8 to 54.0)	53.4 (52.0 to 54.9)	-4.0% (-4.7% to -3.3%)	-3.4% (-4.0% to -2.7%)	-5.9% (-6.7% to -5.0%)
0.50 mg/mg (= 58 th percentile)	48.0 (46.6 to 49.4)	49.3 (48.0 to 50.6)	-5.1% (-5.8% to -4.3%)	-4.8% (-5.5% to -4.1%)	-7.4% (-8.3% to -6.5%)
1 mg/mg (= 75 th percentile)	43.9 (42.4 to 45.5)	45.5 (44.0 to 46.9)	-6.1% (-7.0% to -5.2%)	-6.2% (-7.1% to -5.3%)	-8.9% (-10.0% to -7.8%)
2 mg/mg (= 88 th percentile)	40.2 (38.5 to 42.1)	41.9 (40.3 to 43.7)	-7.2% (-8.3% to -6.0%)	-7.6% (-8.8% to -6.5%)	-10.4% (-11.7% to -8.9%)
4 mg/mg (= 94 th percentile)	36.9 (34.8 to 39.0)	38.7 (36.8 to 40.7)	-8.2% (-9.7% to -6.7%)	-9.0% (-10.4% to -7.6%)	-11.8% (-13.5% to -10.1%)

Note: Longitudinal analysis among 730 children contributing 1539 person-visits of longitudinal data. Results are from linear mixed effects models with random intercepts and slopes. Values in parentheses are 95% confidence intervals.

GFR, glomerular filtration rate; mGFR, measured GFR (using iohexol); eGFR_{CKiDfull}, GFR estimated with 2012 CKD in Children Study equation based on serum creatinine, cystatin C, and serum urea nitrogen; eGFR_{CKiDbed}, 2009 serum creatinine-based bedside GFR; UPCR, urinary protein-creatinine ratio.