# Pediatric GFR Estimating Equations Applied to Adolescents in the General Population

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## Summary

**Background and objectives** We examined the distribution of estimated GFR (eGFR) in a healthy cohort of adolescents to inform clinical and research use.

**Design, setting, participants, & measurements** Various creatinine-based ($n$ = 3256) and/or cystatin C–based ($n$ = 811) equations, including the recently developed complete and bedside equations from the Chronic Kidney Disease in Children (CKiD) study, were applied to U.S. adolescents 12 to 17 years of age participating in the 1999–2002 National Health and Nutrition Examination Survey (NHANES).

**Results** The median serum creatinine and cystatin C were 0.7 mg/dl and 0.83 mg/L, respectively. The distribution of eGFR varied widely, with the median GFR ranging from a low of 96.6 ml/min per 1.73 $m^2$ (CKiD) to a high of 140.0 ml/min per 1.73 $m^2$ (original Schwartz). The proportions of participants with eGFRs <75 ml/min per 1.73 $m^2$ are as follows: bedside CKiD 8.9%, Counahan 6.3%, Leger 0.4%, original Schwartz 0%, Filler 1.3%, Grubb 3.1%, Bouvet 2.5%, CKiD 1.8%, and Zappitelli 5.6%. By any equation examined, no group of participants with eGFR ≤10th percentile had an increased prevalence of comorbid conditions consistent with a low measured GFR.

**Conclusions** Most pediatric-specific GFR estimating equations resulted in 25% to 50% of the participants having an eGFR <100 ml/min per 1.73 $m^2$. However, participants with eGFR in the lower ranges did not have an increased prevalence of morbidities associated with chronic kidney disease. Clinical validation of creatinine- or cystatin C–based estimated GFRs in healthy children is needed before it is possible to screen the general population for chronic kidney disease.


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## Introduction

Accurate estimation of kidney function in children is important from a clinical, research, and public health perspective. From a clinical standpoint, the most commonly used marker of kidney function, serum creatinine, varies by body size, sex, and race, and given the wide range of maturation of skeletal muscle and growth observed in the pediatric population, recognition of abnormal creatinine values is more challenging (1–4). Estimation of GFR may aid in the identification and management of acute and chronic kidney injury, including facilitation of appropriate fluid and medication dosing. The international epidemic of chronic kidney disease (CKD) in adults mandates research and public health interventions to identify CKD and slow its development and progression, and estimation of GFR is integral to these efforts (5,6). Likely because it is relatively rare, the prevalence of CKD in the general population of children and adolescents has not been extensively examined. As prior longitudinal studies of kidney disease progression have suggested that the overall rate of decline in GFR in adults with CKD is approximately 3 to 5 ml/min per year, some adults presenting with advanced CKD or ESRD may have developed early stages of CKD in childhood or adolescence (7,8). Given this, and the striking increased incidence of CKD risk factors such as hypertension and obesity in children and adolescents over the past few decades, examining GFR and CKD in the general pediatric population is worthwhile (9–12).

Serum creatinine and cystatin C are convenient markers of kidney function. As in adults, GFR estimating equations incorporating creatinine and/or cystatin C have been developed for children over the past 4 decades that attempt to account for the influence of age, body size, and/or sex on these markers, thus improving accuracy. But the limitations of these equations must be recognized. First, the laboratory methods to determine creatinine and cystatin C have changed over time, and thus estimating equations using creatinine or cystatin C derived from a different laboratory method may yield different, and less accurate, results (4,13–15). Second, the equations were developed in small groups of children, primarily with decreased GFR. GFR estimating equations in adults,

also primarily developed in populations with decreased GFR, have been shown to underestimate GFR among those without kidney disease (16–18). Limited studies have examined pediatric GFR estimating equations in the general population (19).

To allow for appropriate clinical and research application, we aimed to examine the distribution of GFRs obtained from several creatinine- and/or cystatin C–based pediatric GFR estimating equations in a large sample of adolescents from the general U.S. population included within the National Health and Nutrition Examination Survey (NHANES). Among adolescents with lower estimated GFR (eGFR), we looked for evidence of morbidities that are commonly associated with decreased GFR to support a potential diagnosis of CKD.

## Materials and Methods

### Study Setting and Population

The National Center for Health Statistics, within the Centers for Disease Control and Prevention (CDC), has been conducting the National Health and Nutrition Examination Survey (NHANES) to assess the health and nutritional status of the adults and children in the United States since the 1960s. In 1999, the survey became a continuous program and data has been released in 2-year increments since 2002. NHANES uses a complex multistage sample design to obtain a representative sample of the U.S. civilian, noninstitutionalized population of all ages. The NHANES study protocols were approved by the institutional review board of the National Center for Health Statistics. Written informed consent was obtained from all participants or, if younger than 18 years, their guardians. Assent was obtained from those aged 7 to 17 years. The overall participation rate for NHANES 1999–2002 (interviewed and examined sample) was 78%.

NHANES routinely collects serum for biochemistry analyses, including serum creatinine, in those aged 12 years and older. For this analysis, we examined adolescents aged 12 to 17 years within NHANES 1999–2002 because serum cystatin C measures were also available in these project years. Of the 3732 adolescents aged 12 to 17 years in NHANES 1999–2002, 467 were missing serum creatinine values. Among those with serum creatinine measures, 29 were missing height and/or weight, resulting in a final creatinine subsample of 3256 adolescents. In 2006, stored surplus serum was used to assay cystatin C in a 25% random sample of participants aged 12 years and older and in all participants with a serum creatinine >1.2 mg/dl in boys and >1.0 mg/dl in girls (20). Among the 818 participants 12 to 17 years old with serum cystatin C measures, 7 had missing height and/or weight, resulting in a final cystatin C subsample of 811. Of this subsample, 6 boys and 2 girls had high serum creatinine as defined above.

### Kidney Function Measures

Serum creatinine was measured by the modified kinetic Jaffé reaction using an Hitachi 917 analyzer. The assay range (without dilution) was 0.1 to 25.0 mg/dl. Interassay coefficients of variation for the assay were 4.4% and 1.1% at mean concentrations of 0.68 and 7.08 mg/dl, respectively. Recognizing the lack of standardization in measurement of serum creatinine in many laboratories, the National Kidney Disease Education Program (NKDEP) is attempting to have all laboratories standardize to a "gold standard" reference method (14). NHANES, via the Cleveland Clinic Foundation laboratory, analyzes serum creatinine in stored serum for each 2-year data release using a Roche coupled enzymatic assay performed on a Roche P Module instrument. Creatinine measures from this "gold standard" enzymatic assay are then compared with creatinine measures obtained via the traditional modified Jaffé reaction used in NHANES, and if a significant difference exists, a regression is recommended to correct the NHANES creatinine. For 1999–2000, results of this comparison led NHANES to recommend a correction for serum creatinine according to the following equation: corrected creatinine ($Y$) = 1.013 × NHANES creatinine ($X$) + 0.147 ($r$ = 0.984). No correction was recommended for 2001–2002 (21).

Serum cystatin C was measured at the Cleveland Clinic Research Laboratory using a particle-enhanced immunonephelometric assay (PENIA, Dade Behring N Latex Cystatin C run on a Dade Behring Nephelometer II; Siemens Healthcare Diagnostics, Deerfield, Illinois) (22). The assay range was 0.23 to 7.25 mg/L. Interassay coefficients of variation for the assay were 5.05% and 4.87% at mean concentrations of 0.97 and 1.90 mg/L, respectively.

GFR was estimated using the creatinine and/or cystatin C-based equations listed in Table 2 (23–31). eGFRs from the formulas by Leger and Bouvet *et al.* (ml/min) were standardized to 1.73 $m^2$ using body surface area determined by the formula of Haycock *et al.* (32). The "gold standard" GFR measurement used to develop the GFR estimating equations, as well as the methods of creatinine and cystatin C measurement, is included in this table.

### Other Variables

Questionnaire information provided the participants' age, sex, race, and ethnicity. Body mass index (BMI) was calculated from the height and weight of each participant ($kg/m^2$). BMI percentiles were calculated based on the CDC's BMI-for-age sex-specific growth charts and participants were categorized as obese if their BMI was ≥95th percentile (33). Three to four BP determinations were taken using a mercury sphygmomanometer using a technique based on recommendations from the American Heart Association (34). The average systolic BP variable was used to calculate BP percentiles (35). Non–first morning random urine samples were analyzed for creatinine (Jaffé rate reaction, Beckman Synchron CX3 Clinical System; Beckman Instruments, Brea, California) and albumin (fluorescence immunoassay, Sequoia-Turner model 450 Fluorometer) (36). Microalbuminuria and macroalbuminuria were defined as urine albumin levels exceeding 30 and 300 μg/mg of creatinine, respectively. Anemia was defined as having a hemoglobin value below the 5th percentile for age and sex (37). Serum phosphorus was dichotomized as ≥5.3 mg/dl (90th percentile for study population) *versus* <5.3 mg/dl. Serum bicarbonate was dichotomized as <21 meq/L (10th percentile for study population) *versus* ≥21 meq/L. Heights were converted to Z-scores based on growth charts from the CDC (38).

### Statistical Analyses

All statistical analyses were performed using Stata statistical software, version 9.0 (StataCorp, College Station, Texas). Survey commands were used to account for the NHANES complex sampling design and special cystatin C–specific sampling weights were used in all analyses involving cystatin C (39). The statistical significance level was set at $\alpha = 0.05$. All statistical analyses were two-sided.

Demographic and clinical characteristics were stratified by creatinine and cystatin C subsamples. The distributions of creatinine, cystatin C, and GFRs derived from the various estimating equations were determined. To examine for an increased prevalence of morbidities potentially associated with CKD among those with lower eGFR, participants were dichotomized by eGFR ≤10th percentile *versus* >10th percentile. Tenth percentile cutoffs were specific to each estimating equation. Primary analyses compared the mean levels of BMI percentile, urinary albumin-to-creatinine ratio, and systolic BP percentile by 10th percentile eGFR cutoff, and secondary analyses compared prevalence of height *Z*-scores ≤ −2, anemia, elevated serum phosphorus (≥5.3 mg/dl), and decreased serum bicarbonate (<21 meq/L). Finally, mean eGFR was examined by obesity status, and percentile distribution of eGFR was compared between the entire population, obese and nonobese.

## Results

Demographic and clinical characteristics were similar among the creatinine and cystatin C subsamples from NHANES (Table 1). Among the creatinine subsample, 17.0% were obese, 3.9% had systolic BP ≥95th percentile, 11.8% had microalbuminuria, 1.3% had macroalbuminuria, and 3% were anemic.

Table 2 displays the various GFR estimating equations used in this analysis, the size and description of the GFR range of the population in which the equation was derived, as well as the methods of measurement for creatinine, cystatin C, and GFR. Table 3 shows the results of the application of these GFR estimating equations to the NHANES sample, displaying percentile distribution of creatinine, cystatin C, and eGFR in a population-based sample of adolescents aged 12 to 17 years. The median serum creatinine was 0.7 mg/dl and the median cystatin C was 0.83 mg/L. The distribution of eGFR varied by estimating equation, with the median GFR ranging from a low of 96.6 ml/min per 1.73 $m^2$ (CKiD) to a high of 140.0 ml/min per 1.73 $m^2$ (original Schwartz). Less than 1% of participants had an eGFR of <60 ml/min per 1.73 $m^2$. The proportions of participants with eGFRs <75 ml/min per 1.73 $m^2$, the reporting cutoff used by pediatric eGFR calculators on the National Kidney Disease Education Program (NKDEP) Web site (40), are as follows: bedside CKiD 8.9%, Counahan 6.3%, Leger 0.4%, original Schwartz 0%, Filler 1.3%, Grubb 3.1%, Bouvet 2.5%, CKiD 1.8%, and Zappitelli 5.6%.

Table 4 shows the comparison of morbidities often associated with CKD including mean BMI percentile, urinary albumin-to-creatinine ratio, and systolic BP among the lower tail of the eGFR distributions *versus* those >10th percentile. Few significant differences in the means of each variable were observed. For BMI, the bedside CKiD, Counahan, and Leger equations had significantly higher BMI percentile means among those with lower GFR. There was a nonsignificant trend toward higher urinary albumin-to-creatinine ratios among those with lower eGFR by every equation. No significant differences were observed in systolic BP by eGFR category. Those with eGFR >10th percentile were significantly more likely to be anemic than those ≤10th percentile for all equations except by original

**Table 1. Demographic and clinical characteristics of adolescents aged 12 to 17 years, NHANES 1999–2002**

| | Creatinine Subsample ($n$ = 3256) | Cystatin C Subsample ($n$ = 811) |
|---|---|---|
| Mean age, years | 14.5 (SE 0.05) | 14.5 (SE 0.08) |
| Girls, % | 49.1 | 49.7 |
| Race/ethnicity, % | | |
| non-Hispanic black | 14.7 | 14.3 |
| Mexican | 11.0 | 11.0 |
| other Hispanic | 7.8 | 7.7 |
| non-Hispanic white | 60.0 | 57.6 |
| other (including multiracial) | 6.6 | 9.4 |
| BMI weight category, % | | |
| underweight (<5th percentile) | 3.3 | 4.3 |
| healthy weight (5th to <85th percentile) | 64.8 | 63.8 |
| overweight (85th to <95th percentile) | 14.9 | 14.9 |
| obese (≥95th percentile) | 17.0 | 16.9 |
| Systolic BP, % | | |
| ≥90th percentile | 5.9 | 4.4 |
| ≥95th percentile | 3.9 | 2.4 |
| Microalbuminuria, % | ($n$ = 3220) | ($n$ = 799) |
| >30 mcg/mg creatinine | 11.8 | 10.4 |
| Macroalbuminuria, % | ($n$ = 3220) | ($n$ = 799) |
| >300 mcg/mg creatinine | 1.3 | 1.4 |
| Anemic, % | 3.0 | 3.1 |

NHANES, National Health and Nutrition Examination Survey; BMI, body mass index.

**Table 2. GFR estimating equations in children[a]**

| | GFR Estimating Equation | *n* | Age[b] | GFR[c] | Creatinine/Cystatin C Assay Analyzer | GFR Measurement Method |
|---|---|---|---|---|---|---|
| Serum creatinine based | | | | | | |
| bedside CKiD (23) | 41.3 [height/creatinine] | 349 | 1 to 16 | 41.3 (16 to 93) | Enzymatic [Advia 2400] | Iohexol |
| Counahan *et al.* (24) | 43 [height/creatinine] | 108 | 2 to 14[d] | 4 to 200 | Modified Jaffé[e] [Technicon] | $^{51}$Cr-EDTA |
| Leger *et al.* (25) | 0.641 [weight/creatinine] + 16.063 [(height)$^2$/creatinine] | 97 | 0.8 to 21 | 100 (31 to 200) | Kinetic Jaffé [Hitachi 911] | $^{51}$Cr-EDTA |
| Schwartz *et al.* (26, 27) | [55 × height]/creatinine; and [70 × height]/creatinine if boy ≥13 years | 186 | 0.5 to 20 | 125 (0 to 220) | Modified Jaffé [Technicon] | Inulin/creatinine clearance |
| Serum cystatin C based | | | | | | |
| Filler *et al.* (28) | 91.62 [1/cystatin C]$^{1.123}$ | 536 | 1 to 18 | 103 (7 to 209) | Particle-enhanced nephelometric immunoassay (PENIA) [Behring BN ProSpec] | $^{99m}$Tc-DTPA |
| Grubb *et al.* (29) | 84.69 [1/cystatin C]$^{1.680}$; and 84.69 [1/cystatin C]$^{1.680}$ × 1.384 if age <14 years | 536[f] | 0.3 to 93 | 63 (11 to 124)[g]; and 113 (37 to 240)[h] | Particle-enhanced turbidimetric immunoassay (PETIA) [Hitachi Modular P] | Iohexol |
| Serum creatinine and cystatin C based | | | | | | |
| Bouvet *et al.* (30) | 63.2 [1.2/cystatin C]$^{0.56}$ × [1.09/creatinine]$^{0.35}$ × [weight/45]$^{0.3}$ × [age/14]$^{0.4}$ | 100 | 1.4 to 22.8 | 95 (18 to 200) | Kinetic Jaffé (Olympus analyzer)/PENIA [BN-ProSpec] | $^{51}$Cr-EDTA |
| CKiD (23) | 39.1 [height/creatinine]$^{0.516}$ × [1.8/cystatin C]$^{0.294}$ × [30/BUN]$^{0.169}$ × 1.099$^{male}$ × [height/1.4]$^{0.188}$ | 349 | 1 to 16 | 41.3 (16 to 93) | Enzymatic [Advia 2400]/PETIA [DAKO] | Iohexol |
| Zappitelli *et al.* (31) | 43.82 [1/cystatin C]$^{0.635}$ × [1/creatinine]$^{0.547}$ × 1.35$^{height}$ | 103 | 2 to 18 | 74 ± 36 | Enzymatic [Vitros; Ortho-Clinical Diagnostics]/PENIA [Behring Nephelometer System] | Iothalamate |

BUN, blood urea nitrogen; $^{51}$Cr-EDTA, 51-cromium edetic acid; $^{99m}$Tc-DTPA, $^{99m}$Tc-diethylene-triamine-pentaacetic acid; CKiD, Chronic Kidney Disease in Children.
[a]Height, m; weight, kg; creatinine, mg/dl; cystatin C, mg/L; BUN, mg/dl.
[b]Age range, years.
[c]GFR, ml/min per 1.73 m$^2$ except Leger's and Bouvet's in ml/min: mean (range) presented for bedside CKiD, Leger, Filler, Bouvet, and CKiD; range presented for Counahan; median (range) presented for Schwartz; median (2.5th and 97.5th percentiles) presented for Grubb; mean ± SD presented for Zappitelli.
[d]103 children and 5 adults.
[e]Plasma creatinine value corrected to account for noncreatinine chromogens.
[f]*n* = 85 for 0.3 to 17 year old category.
[g]≥18 years old.
[h]0.3 to 13 years old.

**Table 3. Percentile distribution of creatinine, cystatin C, and eGFR in adolescents aged 12 to 17 years, NHANES 1999 through 2002**

| | 1st | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 99th |
|---|---|---|---|---|---|---|---|---|---|
| Serum creatinine, mg/dl | 0.5 | 0.5 | 0.6 | 0.6 | 0.7 | 0.8 | 0.9 | 1.0 | 1.1 |
| Serum cystatin C, mg/L | 0.57 | 0.65 | 0.68 | 0.75 | 0.83 | 0.91 | 1.01 | 1.06 | 1.21 |
| Bedside CKiD | 62.9 | 71.1 | 75.6 | 84.4 | 96.6 | 108.8 | 122.1 | 131.6 | 149.1 |
| Counahan *et al.* | 65.5 | 74.0 | 78.7 | 87.8 | 100.5 | 113.3 | 127.2 | 137.0 | 155.2 |
| Leger *et al.* | 77.6 | 87.7 | 94.4 | 105.8 | 122.2 | 139.2 | 156.9 | 170.7 | 195.7 |
| Schwartz *et al.* | 96.0 | 106.8 | 113.4 | 125.4 | 140.0 | 159.1 | 180.6 | 193.2 | 229.0 |
| Filler *et al.* | 74.0 | 85.8 | 90.6 | 101.9 | 112.9 | 126.6 | 141.3 | 148.6 | 172.2 |
| Grubb *et al.* | 62.3 | 80.6 | 90.7 | 106.3 | 130.1 | 157.1 | 189.1 | 208.4 | 261.7 |
| Bouvet *et al.* | 72.3 | 79.6 | 83.6 | 92.4 | 104.6 | 116.6 | 128.5 | 134.3 | 150.6 |
| CKiD | 72.9 | 79.5 | 84.1 | 89.5 | 96.6 | 105.6 | 115.1 | 121.3 | 131.6 |
| Zappitelli *et al.* | 69.0 | 74.8 | 78.5 | 87.2 | 97.6 | 110.0 | 119.1 | 126.8 | 140.2 |

All estimated GFRs in ml/min per 1.73 $m^2$.

Schwartz. Similar trends were observed for bicarbonate and phosphorus. Those with GFRs >10th percentile estimated by the bedside CKiD, Counahan, Leger, Bouvet, and CKiD equations were more likely to have low bicarbonate than their counterparts with GFRs ≤10th percentile. Those >10th percentile estimated by the original Schwartz, bedside CKiD, Counahan, Leger, and CKiD formulas were significantly more likely to have higher phosphorus levels than their counterparts with GFRs ≤10th percentile. Finally, no significant differences in the likelihood of having a height *Z*-score ≤−2 were observed by the eGFR cutoff of the 10th percentile for any equation except for that by Bouvet (0% with eGFR ≤83.6 ml/min per 1.73 $m^2$ had height Z-score ≤ −2, compared with 1.7% for those with GFR >83.6 ml/min per 1.73 $m^2$, $P = 0.008$). Therefore, by any equation examined, participants in the lower GFR group did not have an increased prevalence of comorbid conditions consistent with CKD.

Although no consistent differences in mean BMI percentile were observed among those with lower compared with those with higher eGFR by any equation (Table 4), the potential effect of the high prevalence of obesity in this population on GFR adjusted for body surface area deserves further analysis. Mean GFR among the obese (BMI ≥95th percentile) and nonobese population was examined (Table 5). The creatinine-based equation by Leger, the cystatin C–based equations by Filler and Grubb, and the cystatin C– and creatinine-based equation by Zappitelli show significantly lower mean eGFRs among the obese compared with those among the nonobese. To examine if obesity was affecting the distribution of eGFR, we compared the distribution of eGFR in the entire population to that dichotomized as obese and nonobese using these select equations (Table 6). Although eGFRs tend to be lower at every percentile cutoff among the obese compared with those among the nonobese, the difference tends to be quite small, particularly at the lower end of the distribution that is of greatest interest. It is also noted that there is minimal difference between the nonobese and the total population distributions. Thus, obesity has an effect on the eGFR distribution among some equations, but it does not appear to be playing a significant role in lowering the eGFR distribution in the entire study population.

## Discussion

The renal clearance of inulin has traditionally been considered the gold standard for the evaluation of GFR in children and adults, and mean (SD) GFRs determined by this method range from 115 (24) to 117.2 (16.1) ml/min per 1.73 $m^2$ in young adults without kidney disease (4,41,42). Formal GFR measurements were not performed for those examined in this study, but given the rarity of CKD in the general population of children and as morbidities that commonly associate with CKD were not more prevalent among those with lower eGFRs, it can be safely assumed that most had normal kidney function. Despite this, in this examination of teenagers selected from the general U.S. population, most pediatric-specific GFR estimating equations resulted in 25 to 50% of the participants having an eGFR <100 ml/min per 1.73 $m^2$. On the basis of the normal variation of GFR measured by inulin in studies of healthy children, a portion of this population should be expected to have GFR in the 70 to 99 ml/min per 1.73 $m^2$ range. However, the distribution observed in this study is skewed toward lower eGFR beyond what is expected with normal biologic variation. Bias of pediatric GFR estimating equations is also possible, and two potential explanations should be considered: (1) serum creatinine/cystatin C laboratory methods used by NHANES differed from the method originally used to derive the estimating equation, and (2) pediatric GFR estimating equations systematically underestimate GFR because they were derived in children with CKD.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF/DOQI) Clinical Practice Guidelines, published in 2003, recommend that the formulas by Schwartz *et al.* or Counahan-Barratt *et al.* be used to estimate GFR (24,26,27). Both formulas account for the relationship between creatinine production and muscle mass by using height as a surrogate. The differing constants used in these formulas highlight the significant effect of the laboratory method for creatinine determination on GFR estimating equations. The original Schwartz equation was derived using Jaffé (alkaline picrate) creatinine methodology, and the Counahan-Barratt using the Jaffé reaction after serum adsorption onto an ion-exchange resin to remove noncreatinine chromogens (4,24,26). If the same

**Table 4. Comparison of mean BMI percentile, urinary albumin-to-creatinine ratio, and systolic BP percentile among those with eGFR ≤10th percentile *versus* >10th percentile by various pediatric GFR estimating equations**

| | BMI Percentile | | | Urinary Albumin-to-Creatinine Ratio (mcg/mg Creatinine) | | | Systolic BP Percentile | | |
|---|---|---|---|---|---|---|---|---|---|
| | eGFR ≤10th Percentile | eGFR >10th Percentile | *P* | eGFR ≤10th Percentile | eGFR >10th Percentile | *P* | eGFR ≤10th Percentile | eGFR >10th Percentile | *P* |
| Bedside CKiD | 67.19 | 62.88 | 0.04 | 50.92 | 26.31 | 0.42 | 42.83 | 40.53 | 0.31 |
| Counahan *et al.* | 67.19 | 62.88 | 0.04 | 50.92 | 26.31 | 0.42 | 42.83 | 40.53 | 0.31 |
| Leger *et al.* | 70.05 | 62.56 | 0.002 | 50.92 | 26.32 | 0.42 | 42.81 | 40.53 | 0.34 |
| Schwartz *et al.* | 64.06 | 63.23 | 0.72 | 53.29 | 26.09 | 0.37 | 40.49 | 40.78 | 0.90 |
| Filler *et al.* | 61.08 | 64.46 | 0.56 | 46.24 | 27.70 | 0.50 | 49.84 | 40.96 | 0.18 |
| Grubb *et al.* | 56.63 | 65.01 | 0.11 | 92.79 | 21.89 | 0.21 | 47.65 | 41.24 | 0.30 |
| Bouvet *et al.* | 66.34 | 64.01 | 0.69 | 110.67 | 27.18 | 0.39 | 39.84 | 42.02 | 0.78 |
| CKiD | 67.37 | 63.71 | 0.38 | 47.35 | 27.74 | 0.52 | 46.21 | 41.46 | 0.25 |
| Zappitelli *et al.* | 69.21 | 63.50 | 0.19 | 43.18 | 28.22 | 0.62 | 47.59 | 41.30 | 0.24 |

**Table 5. Mean eGFR by obesity status**

| | Mean eGFR (ml/min per 1.73 $m^2$) | | |
|---|---|---|---|
| | Obese | Nonobese | *P* |
| Bedside CKiD | 97.2 | 98.0 | 0.49 |
| Counahan *et al.* | 101.2 | 102.0 | 0.49 |
| Leger *et al.* | 121.0 | 124.8 | 0.01 |
| Schwartz *et al.* | 144.1 | 144.1 | 0.96 |
| Filler *et al.* | 109.2 | 115.6 | 0.01 |
| Grubb *et al.* | 128.1 | 135.4 | 0.03 |
| Bouvet *et al.* | 90.8 | 108.0 | <0.001 |
| CKiD | 97.2 | 98.4 | 0.45 |
| Zappitelli *et al.* | 95.0 | 99.7 | <0.01 |

Obesity defined as ≥95th percentile for BMI.

laboratory method is used for creatinine determination, the difference between the constants leads to a 22% and 39% reduction in eGFR by the Counahan-Barratt compared with the Schwartz equation in adolescent females and males, respectively. The recently published GFR estimating equations from the CKiD Study were derived using creatinines determined by an enzymatic assay that is more specific and sensitive than the Jaffé method (14,15,23). Compared with the Jaffé method, the enzymatic method results in lower creatinine values; hence, the lower constant in the bedside CKiD estimating equation, compared with the original Schwartz equation, reflects this (13).

Differences in cystatin C assays and lack of standard calibrators may also affect GFR estimation and the results of this study. NHANES determined cystatin C using the Dade Behring particle-enhanced nephelometric immunoassay (PENIA) method (22). The equations by Bouvet and CKiD used a particle-enhanced turbidimetric immunoassay (PETIA) (43). Previous comparisons of these two assays have shown that the PETIA method provided significantly higher results compared with PENIA, and differences in sensitivity and precision have been reported (44). If a common calibrator was used, assay results were found to be comparable, but currently there is no recognized agreement on calibration for clinically available cystatin C assays (22,44).

Thus, creatinine and cystatin C laboratory methodologies vary and the coefficients of each GFR estimating equation are critically dependent on assay methodology (4). This further complicates the interpretation and accuracy of GFRs obtained from estimating equations, and clinicians and researchers must be aware of such limitations when applying GFR estimating equations. There is currently a global creatinine standardization initiative that seeks to reduce interlaboratory variation in creatinine by referencing all creatinine assays to isotope dilution mass spectroscopy (IDMS) standards (14). This may allow for the development of more universal GFR creatinine-based estimating equations in which the accuracy does not depend on the clinician knowing the creatinine assay of a given laboratory and applying the equation that was developed using that assay. Standardization of cystatin C assay calibrators would also have obvious clinical and research benefits (45).

As creatinine values in NHANES are traceable to enzymatic methods, and the novel bedside CKiD equation was

**Table 6. Percentile distribution of eGFRs by select estimating equations for entire population and population dichotomized as obese and nonobese**

| | 1st | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 99th |
|---|---|---|---|---|---|---|---|---|---|
| Leger *et al.* | | | | | | | | | |
| entire population | 77.6 | 87.7 | 94.4 | 105.8 | 122.2 | 139.2 | 156.9 | 170.7 | 195.7 |
| obese | 80.5 | 86.8 | 90.6 | 103.2 | 119.6 | 134.4 | 153.3 | 165.4 | 182.8 |
| nonobese | 77.4 | 88.3 | 95.0 | 106.4 | 123.0 | 139.9 | 157.8 | 171.6 | 195.8 |
| Filler *et al.* | | | | | | | | | |
| entire population | 74.0 | 85.8 | 90.6 | 101.9 | 112.9 | 126.6 | 141.3 | 148.6 | 172.2 |
| obese | 72.6 | 80.7 | 88.6 | 97.1 | 107.1 | 119.4 | 130.5 | 141.3 | 151.2 |
| nonobese | 74.7 | 86.7 | 91.6 | 101.9 | 112.9 | 128.5 | 141.3 | 151.2 | 172.2 |
| Grubb *et al.* | | | | | | | | | |
| entire population | 62.3 | 80.6 | 90.7 | 106.3 | 130.1 | 157.1 | 189.1 | 208.4 | 261.7 |
| obese | 67.0 | 80.6 | 83.3 | 103.0 | 125.8 | 147.1 | 170.5 | 185.9 | 248.1 |
| nonobese | 62.3 | 80.6 | 90.7 | 107.0 | 131.4 | 158.0 | 194.3 | 208.4 | 261.7 |
| Bouvet *et al.* | | | | | | | | | |
| entire population | 72.3 | 79.6 | 83.6 | 92.4 | 104.6 | 116.6 | 128.5 | 134.3 | 150.6 |
| obese | 66.4 | 73.4 | 74.4 | 80.6 | 88.7 | 99.2 | 108.7 | 114.2 | 122.8 |
| nonobese | 75.2 | 82.2 | 86.5 | 96.2 | 107.5 | 118.0 | 129.8 | 136.9 | 153.5 |
| Zappitelli *et al.* | | | | | | | | | |
| entire population | 69.0 | 74.8 | 78.5 | 87.2 | 97.6 | 110.0 | 119.1 | 126.8 | 140.2 |
| obese | 69.8 | 76.6 | 77.0 | 85.1 | 94.4 | 102.5 | 114.2 | 119.1 | 127.8 |
| nonobese | 69.0 | 74.8 | 79.2 | 87.9 | 98.8 | 110.9 | 119.9 | 127.3 | 141.7 |

Obesity defined as ≥95th percentile for BMI.
All eGFRs in ml/min per 1.73 $m^2$.

also derived using enzymatic creatinine laboratory methods, it would be expected that the range of eGFR using the CKiD equation in the NHANES population would be close to that expected for healthy adolescents. However, >50% of the cohort had an eGFR <100 ml/min per 1.73 $m^2$, and there may be several possible reasons for this. First, creatinine assays, particularly Jaffé, are known to be less precise at lower levels of creatinine typical of the healthy adolescent cohort we studied, and this could potentially lead to measurement error in creatinine, and thus GFR estimation (15). Second, as described in the Materials and Methods section, creatinine values obtained via a modified Jaffé reaction by NHANES are compared with values in the same patient measured by a gold standard IDMS assay. If a difference exists, a correction is recommended by NHANES so that the creatinine values reflect those traceable to the IDMS standard, as recommended by NKDEP. A difference existed for the 1999–2000 NHANES cycle, and a correction was recommended, but not for the 2001–2002 cycle. The correction was made via a regression equation (see Materials and Methods section) and resulted in serum creatinine values being increased for half the cohort, and the percentage increase varied by the creatinine value. For a serum creatinine of 0.6, the correction led to a 20% increase in serum creatinine, and for a creatinine of 1.0, the increase was 14%. The differential in percentage increase of serum creatinine based on the correction would be expected to slightly bias toward a greater increase in creatinine among those with lower creatinines, and as the median creatinine in this cohort was 0.7 mg/dl, this must be considered. However, the range of serum creatinine in this cohort was narrow, and the differential percentage increase based on the correction was also small. To determine if this correction was responsible for the low eGFRs observed among the cohort, a subanalysis stratified the participants in 1999–2000 (corrected creatinine) and 2001–2002 (no correction). The distributions were similar to each other, and to the combined cohort: the 5th, 50th, and 95th percentiles for bedside CKiD eGFR for 1999–2000 were 71.1, 97.8, and 130.6 ml/min per 1.73 $m^2$; for 2001–2002 they were 71.2, 96.0, and 132.3 ml/min per 1.73 $m^2$; and for 1999–2002 they were 71.1, 96.6, and 131.6 ml/min per 1.73 $m^2$, respectively.

Finally, adult GFR estimating equations such as the Modification of Diet in Renal Disease (MDRD) have been shown to underestimate GFR among those with higher, or normal, GFRs (16,17,46), and this possibility should be considered with pediatric GFR estimating equations, although this has not yet been examined in detail (47). Multiple reasons have been offered to explain why GFR estimating equations developed from populations with CKD may underestimate measured GFR in adults without CKD. Creatinine measurement error, especially at lower levels of creatinine, must be considered as described above. Variations in serum creatinine in those without CKD may be more reflective of a difference in muscle mass, growth, or protein intake, and possibly measurement error, rather than the GFR. In contrast, creatinine variations among those with CKD are more likely to be representative of changes in GFR. Thus, the magnitude of the relationship between creatinine and GFR may be greater among those with CKD compared with those without CKD (3,16,46). The novel Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed in adults to be as accurate as the MDRD equation at lower GFRs and more accurate at higher GFRs (48). To accomplish this, the CKD-EPI equation included more participants with higher GFRs; the CKD-EPI development data set mean GFR (SD)

was 68 (40) ml/min per 1.73 $m^2$, compared with 39.8 (21.2) in the MDRD cohort (49). Additionally, a spline term is included in the CKD-EPI equation that accounts for a weaker relationship between creatinine and GFR at lower creatinine levels than at higher levels. It is anticipated that the CKD-EPI equation should lead to more accurate estimates of eGFR and the burden of CKD in the adult U.S. population (48). Studies including formal GFR measurement in children with normal kidney function are needed to confirm age- and sex-specific normative values, and evaluate the accuracy of current pediatric GFR estimating equations at higher or normal levels of GFR (50).

Accurate estimation of GFR in children has obvious clinical and research benefits. This analysis underscores that appropriate application of pediatric estimating equations requires an understanding of the creatinine and cystatin C laboratory methods used in a given clinical or research setting and the methods used to develop the equations. Efforts by NKDEP to standardize laboratory assay calibrators will help minimize the measurement variation that affects the accuracy of all GFR estimating equations. The novel CKiD GFR estimating equations have been shown to have excellent precision and accuracy at GFRs between 15 and 75 ml/min per 1.73 $m^2$ (4). The precision and accuracy in children with higher or normal GFRs cannot be fully addressed in this analysis because of the lack of formally measured GFR. However, the low range of eGFR in this healthy population without evidence of CKD observed in this study is of interest. From a CKD screening standpoint, the Laboratory Working Group of NKDEP recommends reporting eGFR values above 60 ml/min per 1.73 $m^2$ as ">60 ml/min per 1.73 $m^2$" in adults (14). There is no pediatric-specific recommendation, but the NKDEP eGFR calculator currently reports ">75 ml/min per 1.73 $m^2$" for GFRs >75 using the beside CKiD equation (40). On the basis of this study, approximately 9% of the adolescent population may fall below 75 ml/min per 1.73 $m^2$ using the bedside CKiD equation, and the broader clinical context should be considered while evaluating this population for CKD. The population-based eGFR percentiles for each equation provided in Table 3 may help clinicians determine the normal range of eGFR, and thus better identify children at risk for loss of kidney function. However, clinical validation of eGFR in the general pediatric population is needed before using these equations to screen for CKD whenever a serum creatinine or cystatin C is obtained.

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**Disclosures**

None.

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