Obesity Related Glomerulopathy in Adolescent Women: The Effect of Body Surface Area

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Key Points
- Body surface area (BSA)-standardized eGFR creates similar rates of hyperfiltration across body mass index (BMI) groups.
- Creatinine clearance and absolute eGFR, adjusted to individual BSA, reflect BMI increase, unlike BSA-standardized eGFR.
- Absolute eGFR, adjusted to individual BSA, unmasks higher prevalence of hyperfiltration in patients who are obese, enabling timely intervention.

Abstract
Background Adolescent obesity, a risk factor for cardiorenal morbidity in adulthood, has reached epidemic proportions. Obesity-related glomerulopathy (ORG) has an early reversible stage of hyperfiltration. Age-appropriate formulae for eGFR, which are standardized to ideal body surface area (BSA) and provide assessment of kidney function in ml/min/1.73 m², may underestimate prevalence of early ORG. We investigated whether adjusting eGFR to actual BSA more readily identifies early ORG.

Methods We studied a cohort of 22,417 young individuals, aged 12–21 years, from a New York metropolitan multi-institutional electronic health records clinical database. eGFR was calculated in two ways: BSA-standardized eGFR, and absolute eGFR. Hyperfiltration was defined above a threshold of 135 ml/min per 1.73 m² or 135 ml/min, respectively. The prevalence of hyperfiltration according to each formula was assessed in parallel to creatinine clearance.

Results Serum creatinine values and hyperfiltration prevalence according to BSA-standardized eGFR were similar, 13%–15%, across body mass index (BMI) groups. The prevalence of hyperfiltration determined by absolute eGFR differed across BMI groups: underweight, 2%; normal weight, 6%; overweight, 17%; and obese, 31%. This trend paralleled the rise in creatinine clearance across BMI groups.

Conclusions Absolute eGFR more readily identifies early ORG than the currently used formulae, which are adjusted to a standardized BSA and are not representative of current population BMI measures. Using absolute eGFR in clinical practice and research may improve the ability to identify, intervene, and reverse early ORG, which has great importance with increasing obesity rates.

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Introduction
Obesity has reached epidemic proportions in the United States over the past three decades, with significant increases in rates of obesity and severe obesity among adolescent females aged 16–19 years (1,2). Obesity is a modifiable risk factor for both CKD and ESKD (1). In children, significant increases in the prevalence of CKD and ESKD have been reported over the last three decades, paralleling the increase in the prevalence of childhood obesity (1,3). Obesity-related glomerulopathy (ORG) is a secondary form of FSGS occurring in patients who are obese, with a body mass index (BMI) >30 kg/m², and results from hemodynamic changes, manifesting as glomerular hyperperfusion and hyperfiltration, due to afferent arteriolar dilation (4). It is well established that, in the first stages of ORG, hyperfiltration occurs as a physiologic adaptation of the kidney to the increased body mass (4). Several studies have reported that obesity-associated hyperfiltration decreases after marked

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weight loss, indicating that hyperfiltration represents a reversible physiologic adaptation (5). Although a universal definition of hyperfiltration does not exist, the commonly used threshold is a GFR value >135 ml/min per 1.73 m² (6,7).

Kidney Disease: Improving Global Outcome (KDIGO) guidelines recommend using age-appropriate, serum creatinine-based equations to calculate eGFR: the Chronic Kidney Disease Epidemiology Collaboration equation in the adult patient population, and the Schwartz equation in the pediatric patient population (8,9,10). However, these equations were empirically developed in populations with kidney function impairment (i.e., reduced GFR), and their performance is modest to poor in healthy populations (10–12).

The eGFR reported by the currently used formulae is standardized to a body surface area (BSA) of 1.73 m², rather than the individual’s actual BSA. The value of 1.73 m² reflects the mean BSA of 25-year-old men and women in the United States in 1927 (9), compared with a mean BSA of 1.98 m² in men and women in 2018 (13). However, the reference value of 1.73 m² is maintained for normalization purposes (9).

We hypothesized that, in a diverse population of young women in a major metropolitan area, deindexing GFR would reveal a large proportion to have hyperfiltration compared with indexed GFR. This will enable timely intervention and reversal of the natural course of ORG before attendant kidney damage has long-term, irreversible consequences.

Materials and Methods

Statement of Ethics

Data extraction and transmission were reviewed and approved, and a waiver of informed consent for analyzing deidentified data was granted by the institutional review boards at Clinical Directors Network, Biomedical Research Alliance of New York, and the Rockefeller University.

Cohort Construction

This study design grew out of an earlier National Institute of Mental Health–funded clinical trial to compare the effectiveness of two different prenatal care strategies among pregnant adolescent women (14,15). Deidentified electronic health record data were extracted for female adolescents, aged 12–21 years, who received health care services from January 1, 2011 to December 31, 2015 in New York City (NYC) in 12 academic health centers and community health centers, which are part of the Patient Centered Outcomes Research (PCOR)–funded NYC Clinical Data Research Network (16).

Study findings are described in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data-Cleaning Steps for Biologically Plausible Limits

The first encounter for each individual in which height, weight, BP, and serum creatinine were simultaneously available was included in the cohort. Extreme outlier values that may result from data-entry errors rather than true outliers were excluded by setting physiologic limits for systolic BP (60–220 mm Hg), diastolic BP (30–150 mm Hg), BMI (12–80 kg/m²), height (127–200 cm), and weight (24–240 kg). Serum creatinine was limited to 3 mg/dl to avoid confounding by CKD.

BSA was calculated using the metric system according to the Du Bois formula ($\text{BSA} = 0.007184 \times \text{height}^{0.725} \times \text{weight}^{0.425}$) (17).

BMI was calculated by dividing a person’s weight in kilograms by the square of height in meters. For all children and teens of the same age and sex, BMI values were classified according to the Centers for Disease Control and Prevention (CDC) (18) data for BMI-for-age z-score into the following categories: underweight, BMI fifth percentile or lower; overweight, BMI of ≥85th to ≤95th percentile; obese, BMI ≥95th percentile (18).

eGFR Calculation

The BSA-standardized eGFR was determined by the CKD-EPI and modified Schwartz formulae, for adult patients (aged 18–21 years) and for pediatric patients (12< up to 18 years), respectively (10). Hyperfiltration was defined as BSA-standardized eGFR >135 ml/min per 1.73 m².

To eliminate the standardized correction and calculate the actual BSA–based eGFR (absolute eGFR), the BSA-standardized eGFR values were divided by 1.73 and multiplied by individual BSA. This modification was carried out for all patients, regardless of the formula used to calculate eGFR. Hyperfiltration was defined as absolute eGFR >135 ml/min (6).

Statistical Analysis

Statistical analyses were performed using SAS (version 9.4). Nominal variables were expressed as numbers (%). Comparison of proportions between groups was performed using the chi-squared test. Continuous variables were expressed as mean±SD or median (minimum–maximum). The Pearson coefficient was used to assess correlation between continuous variables. Continuous variables were compared using ANOVA including Dunnett approach for multiple comparisons, where $P<0.05$ (two tailed) was considered statistically significant. The Bland–Altman analysis was used to assess the relative agreement between BSA-standardized and absolute eGFR.

Results

The original cohort comprised 123,448 unique patients. After data-cleaning steps to remove biologically implausible values, 22,417 unique female patients (mean±SD age 17±3 years) with recorded serum creatinine values remained in the final analysis (Supplemental Figure 1). Age distribution with a threshold of 18 years, according to the recommended formulae to estimate GFR, was as follows: 9823 (44%) of patients were >18 years of age, and 12,594 (56%) were younger than 18 years.

Distribution of BMI was sorted into BMI-for-age categories according to CDC (18) definitions as follows: underweight, 1085 (5%); normal weight, 11,971 (53%); overweight, 4353 (19%); and obese, 5008 (22%). There were 7315 (33%)
Table 1. Demographic and vital characteristics of the population

| Characteristic | Underweight (n=1085) | Normal (n=11,971) | Overweight (n=4353) | Obese (n=5008) | Overall (n=22,417) | P Value |
|---------------|-----------------------|-------------------|---------------------|----------------|--------------------|---------|
| Age, yr       | 16.9±2.8              | 17.1±2.5          | 17.3±2.6            | 17.1±2.6       | 17.1±2.5           | <0.001* |
| Height, cm    | 157±10                | 159±8             | 160±8               | 161±8          | 160±8              | <0.001  |
| Weight, kg    | 40±7                  | 53±9              | 69±9                | 91±19          | 64±20              | <0.001  |
| BMI, kg/m²    | 15.9±1.4              | 21.0±2.3          | 26.9±1.8            | 35.2±6.1       | 25±4.2             | <0.001  |
| BSA, m²       | 1.3±0.2               | 1.5±0.2           | 1.7±0.2             | 1.9±0.2        | 1.7±1.7            | <0.001  |
| Race          |                       |                   |                     |                |                    |         |
| Black individuals, column % | 299 (28) | 3631 (30) | 1467 (34) | 1918 (38) | 7315 (33) | <0.001  |
| Black individuals, row % | 299 (4) | 3631 (50) | 1467 (20) | 1918 (26) | 7315 (100) | <0.001  |
| White individuals, column % | 224 (21) | 1807 (15) | 448 (10) | 398 (8) | 2877 (13) | <0.001  |
| White individuals, row % | 224 (8) | 1807 (63) | 448 (16) | 398 (14) | 2877 (100) | <0.001  |
| Hispanic      | 380 (35)              | 4695 (39)         | 1881 (43)           | 2112 (42)      | 9068 (40)          | <0.001  |
| Smoking       | 58 (6)                | 791 (7)           | 375 (9)             | 454 (9)        | 1678 (8)           | <0.001  |
| Systolic BP, mm Hg | 102±11    | 105±11            | 110±11              | 115±13         | 109±12             | <0.001  |
| Diastolic BP, mm Hg | 64±8    | 64±8              | 67±9                | 69±9           | 66±9               | <0.001  |
| Hemoglobin A1c, % | 5.7±1.4 | 5.6±1.1           | 5.6±1.0             | 5.6±0.8        | 5.6±1.0            | 0.05    |

Continuous variables are presented as mean±SD. For race and smoking, values are given in n (%), where percentages in brackets represent the row percentages, except for the total which represents column percentage. BMI, body mass index; BSA, body surface area.

*Dunnet multiple comparison approach reveals that differences exist only between normal weight and overweight group, but mean age of underweight-normal weight and obese are not significantly different.

Kidney Function Characteristics

Mean serum creatinine values were 0.73±0.2 mg/dl, 0.75±0.2 mg/dl, 0.74±0.2 mg/dl, and 0.72±0.2 mg/dl in the underweight, normal weight, overweight, and obese groups, respectively (Table 2). These values were statistically different due to the multiple comparison approach, although clinically similar. BSA-standardized eGFR values were observed to be statistically different across BMI groups, but the differences were of borderline significance, and the increase in eGFR across BMI groups was not monotonic. The mean BSA-standardized eGFR in the obese group was 105±26 ml/min per 1.73 m² versus 106±27 ml/min per 1.73 m² in the overweight group, 103±27 ml/min per 1.73 m² in the normal weight group, and 106±30 ml/min per 1.73 m² in the underweight group (Figure 1, Table 2). BSA-standardized eGFR values were similar across BMI groups in both the pediatric and adult groups (Supplemental Figure 2, Supplemental Table 1). In contrast, there was a statistically significant increase in mean absolute eGFR across BMI groups: 82±26 ml/min in the underweight group, 92±26 ml/min in the normal weight group, 105±29 ml/min in the overweight group, and 119±33 ml/min in the obese group (P<0.05; Figure 1, Table 2).

Table 2. Kidney characteristics across BMI groups

| Characteristic | Underweight (n=1085) | Normal (n=11,971) | Overweight (n=4353) | Obese (n=5008) | Overall (n=22,417) | P Value |
|---------------|-----------------------|-------------------|---------------------|----------------|--------------------|---------|
| Serum creatinine, mg/dl | 0.73±0.2 | 0.75±0.2 | 0.74±0.2 | 0.74±0.2 | 0.74±0.2 | 0.001* |
| Creatinine clearance, ml/min | 57±22 (10) | 107±54 (124) | 130±56 (62) | 140±57 (113) | 122±58 (309) | 0.001  |
| BSA-standardized eGFR, ml/min/1.73 m² | 106±30 | 103±27 | 106±27 | 105±26 | 104±27 | <0.001  |
| Hyperfiltration BSA-standardized eGFR, n (%) | 167 (15) | 1445 (12) | 630 (15) | 667 (13) | 2909 (13) | <0.001  |
| Absolute eGFR, ml/min | 82±26 | 92±26 | 105±29 | 119±33 | 100±31 | <0.001  |
| Hyperfiltration absolute GFR, n (%) | 25 (2) | 728 (6) | 755 (17) | 1568 (31) | 3076 (14) | <0.001  |

Continuous variables are presented as mean±SD. Absolute numbers are counted individuals with eGFR >135 ml/min/1.73 m². Numbers in brackets represent column percentages. P value represents ANOVA. BMI, body mass index; BSA, body surface area; eGFR, eGFR for ideal body surface area; absolute GFR, eGFR for individuals’ BSA.

*Number of individuals with available data.
Creatinine clearance (CrCl) was assessed in 309 patients. Similar to the trend of increasing absolute eGFR with increasing BMI, CrCl also increased across BMI groups: mean CrCl was 57±22 ml/min in the underweight group, 107±54 ml/min in the normal weight group, 130±56 ml/min in the overweight group, and 140±57 ml/min in the obese group (P<0.05; Figure 1).

Hyperfiltration

A total of 2909 patients (13%) met the criteria for hyperfiltration according to BSA-standardized eGFR (>135 ml/min per 1.73 m²): 16% from the underweight group, 12% from the normal weight group, 15% from the overweight group, and 13% from the obese group (P<0.001). Using absolute eGFR, 3076 (14%) individuals met the criteria for hyperfiltration: 2% in the underweight group, 6% in the normal weight group, 17% in the overweight group, and 31% in the obese group (P<0.001; Figure 2, Table 2).

Bland–Altman Analyses

Bland–Altman analyses were performed to test the agreement between BSA-standardized eGFR and absolute eGFR across the different BMI groups. Bias was clearly differential across BMI groups; there was a positive bias for the underweight BMI group, no observed bias for the normal BMI group, an increasing negative bias for the overweight BMI group, and a relatively large negative bias for the obese BMI group (Figure 3, A–D). For the overall group, there was relatively small negative bias (Figure 3E).

Discussion

Accurate calculation of eGFR has a vital role in the diagnosis of kidney disease and CKD management and prognosis. Currently used BSA-standardized eGFR formulae may be adequate in individuals who are not obese but might significantly underestimate the true GFR in patients who are obese (19), leading to underdiagnosis of the early stages of ORG and, thus, missing an opportunity for intervention. The increasing prevalence of overweight and obesity in children and young adults raises the concern that this metabolic risk gradient probably begins in childhood.

Our rationale for examining absolute eGFR is rooted in the pathophysiology of ORG. As body size increases, the number of nephrons remains the same (20); therefore, obesity must result in an increase in single-nephron GFR if the ratio of total GFR to body size is maintained (21). Absolute eGFR reflects this phenomenon, whereas ideal BSA (1.73 m²)–standardized eGFR obscures it (22,23). As body size increases, the increased single-nephron GFR is also burdened by increased sympathetic and renin-angiotensin system activity, which leads to an increment of BP, accelerating the progressive deterioration of kidney function over time (24). Kidney donors are otherwise healthy individuals maintaining their metabolic rate but using half of the

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**Figure 1.** Absolute eGFR prediction is closer to creatinine clearance than eGFR. Bars represent mean values of predicted filtration according to body surface area (BSA)–standardized eGFR, which is normalized to ideal BSA (blue) versus absolute eGFR, which is adjusted to individual BSA (orange). Measured creatinine clearance in 309 patients (gray) is shown in parallel. SDs across bars are shown in black lines. BMI, body mass index.
nephron mass. In a large cohort of donors, a strong correlation was found between hyperfiltration according to age-based unindexed measured GFR (mGFR; using iothalamate clearance) and high BMI (25). Unindexed mean mGFR was higher than indexed mGFR (113.4±25.3 ml/min versus 101.3±19 ml/min), and associated more strongly with risk factors for hyperfiltration, such as obesity, and the implied mechanism of higher single-nephron GFR (25).

We describe a large practice-based cohort of young women and girls, aged 12–21 years, followed in 12 NYC academic and community health centers. Whereas serum creatinine and BSA-standardized eGFR were similar across BMI groups; when absolute eGFR was used, hyperfiltration rates increased with increasing BMI in a manner that points to obesity as a possible risk factor for kidney disease. This observation, which may be indicative of a higher prevalence of early stages of ORG, is supported by increased CrCl as BMI increased. As BMI rises, the kidneys are forced to hyperfiltrate (26); however, the CKD-EPI and Schwartz formulae do not reflect this process adequately.

The lack of agreement between absolute eGFR versus BSA-standardized eGFR in the obese group supports the notion of underestimation of eGFR and hyperfiltration according to traditional calculations, as we have observed. Thus, standardizing eGFR for BSA appears to have minimal influence in adults who are not obese, but it can have a major effect and influence decision making in individuals who are overweight (27).

Of note, our cohort had a higher prevalence of minority patients, especially in the obese subgroup, compared with patients whose kidney function were not available (Supplemental Table 2). This indicates increased awareness among primary care physicians to individuals at high risk for health issues. Yet, the currently available formulae do not support early identification of ORG in this population, and hence this opportunity to improve cardio-renal health is missed.

The course and timeline of ORG in the adolescent has not been thoroughly described. On average, GFR decline is minimal before age 35 years, after which the rate of decline accelerates (28), highlighting the concept of “kidney reserve.” Aging is characterized with decline in eGFR attributed to either increased glomerulosclerosis or cortical volume decline in parallel with hypertrophy of remaining nephrons (29).

The trajectory of GFR decline over time in relation to BMI is very grim. As BMI increases, kidney function declines, and the decline is more rapid with higher BMI (30). Over time, the risk of incident ESKD is also increased in the presence of obesity (31). Our study is the first to show differential hyperfiltration across BMI groups and increased hyperfiltration when using absolute eGFR and in adolescence. Early intervention, on the basis of absolute eGFR values, could reverse the initial damage of ORG. Creatinine-based eGFR is strongly influenced by body composition (32), and our findings suggest that body measures, such as BSA, should be incorporated when eGFR is calculated on the basis of serum creatinine concentrations.

Previous studies investigated the association between baseline hyperfiltration status and subsequent GFR decline. In a population-based outpatient dataset of more than a million individuals (33), higher eGFR was associated with increased risk for doubling in serum creatinine level during a median follow-up of 35 months. Other studies found that higher baseline eGFRs predicted a steeper eGFR decline in large community cohorts of individuals with diabetes (34). These observations indicate that hyperfiltration, in at least a proportion of participants, may play a role in accelerated GFR decline in both people with and without diabetes (34,35).
Our study has some limitations. First, we lack parallel data of a gold-standard filtration marker for validation of our findings. GFR was not measured directly using inulin or radioisotope methods, which are considered the best measures of kidney function. Clearly, the use of these exogenous markers to estimate GFR is impractical in clinical practice; however, in patients with normal GFR, CrCl calculated from a 24-hour urine collection provides estimates that are very similar to those obtained with inulin or radioisotopes (36). In our cohort, CrCl data were available in only 309 patients, serving as internal validation to prove the concept of increased filtration. Because obesity is associated with higher muscle mass (37,38), which increases across BMI groups (from underweight to obese), hyperfiltration can be estimated by CrCl.

Second, eGFR was calculated using formulae that are recommended by KDIGO, which were designed for different age groups. There are additional formulae, based on serum

Figure 3. Agreement between BSA-standardized eGFR and absolute eGFR across BMI groups using the Bland–Altman approach. (A) Underweight, (B) normal weight, (C) overweight, (D) obese, and (E) entire cohort. Diff, difference.
analytes, such as cystatin c or a combination with creatinine, that are not commonly available in clinical care and thus could not be used in this large cohort, which relied on data from electronic health records.

Another limitation is that, according to the BSA-standardized eGFR, 15% of the patients who were underweight who were not at risk for ORG met the criteria for hyperfiltration. The underweight group might be populated by individuals with chronic conditions leading, eventually, to reduced muscle mass. Muscle mass confounds GFR estimation because it is represented only by serum creatinine, and BSA is standardized. Measurement of serum creatinine was nonrandom in this cohort. As noted above, this likely reflects clinician recognition of patients who are at risk. Further studies are warranted to assess how our findings extend to individuals at low risk.

Moreover, hyperfiltration in individuals who were underweight was not paralleled by an increase in urinary creatinine in these patients, which questions the reliability of this observation. After adjustment to BSA, absolute eGFR values in the underweight group correspond to the currently defined CKD stage 2 range, according to KDIGO guidelines (9); however, data were not extracted in the current dataset to explore kidney pathology in this BMI group.

Our study has some clear strengths. Our cohort is large and diverse, including an urban population with a different racial and ethnic composition compared to the American population. Non-Hispanic White individuals make up 61% of the country’s population (39), compared with <15% in our cohort. The high proportion of under-represented populations in our cohort could account, at least partially, for the higher-than-expected rates of overweight and obesity, 41% in our cohort compared with 20% the general population, at ages 12–19 (18). Obesity at ages 2–19 years is more common among Hispanic (26%) and non-Hispanic Black individuals (22%) compared with non-Hispanic White individuals (14%) (13). The higher rates of obesity among minorities highlight the urgent unmet clinical need for change in asymptomatic screening and health management among populations affected by health disparities, whose clinical management currently does not adequately address the slippery slope of childhood obesity, when early signs of ORG may already be present.

The age range of our cohort, although included under the same definition of adolescence, mandated the use of two different formulae to calculate eGFR. However, the relation we describe between BSA-standardized eGFR, absolute GFR, and hyperfiltration rates across BMI groups in the entire cohort exists also separately for the two different age groups and related formula.

In sum, the hypothesis behind this investigation is that eGFR equations may perform differently in those who are obese and overweight compared with those with a normal weight. Currently recommended equations for estimating GFR were empirically developed in populations with reduced GFR, and their performance is modest to poor in healthy populations or during early ORG, when hyperfiltration may predominate.

Although the US Preventive Services Task Force stated in its last report that there is insufficient evidence to recommend routine screening for kidney disease in adults who are asymptomatic (40), early identification of individuals with increased cardiorenal risk could provide opportunities for behavioral, lifestyle, and pharmacologic interventions to improve long-term outcomes.

The most severe form of ORG, associated with significant glomerulosclerosis, has a poor prognosis, where up to 30% of affected individuals reach ESKD 2–6 years after development of glomerulosclerosis (5). Lifestyle modification and bariatric surgery can reverse hyperfiltration, reducing GFR for patients with eGFR >90 ml/min after the intervention (41,42,43).

Although the increase in the prevalence of hyperfiltration in the obese group is expected given the mathematic adjustment that was performed, our data show that this seemingly simple adjustment may better represent the true distribution of hyperfiltration in the population and prevalence of ORG in this patient group.

Using absolute eGFR in clinical practice and research may improve the ability to identify, intervene, and reverse early ORG. Application of this tool may address missed opportunities for screening, early diagnosis, and intervention in adults who are obese, including those in the Black population, among whom kidney morbidity is overrepresented, and obesity rates are increasing. Successful intervention has the potential to improve quality of life and prevent subsequent comorbidities, along with reductions in care costs for a substantial part of the population at risk, where there is a high representation of underserved minorities.

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Author Contributions

O.S. Bentur and D. Bielopolski were responsible for investigation; O.S. Bentur, D.M. Charytan, R.G. Kost, and J.N. Tobin, and R.D. Vaughan reviewed and edited the manuscript; D. Bielopolski wrote the original draft; D. Bielopolski, D. M. Charytan, R. MacArthur, and R.D. Vaughan were responsible for methodology; D. Bielopolski, R.G. Kost, R. MacArthur, N. Singh, and J.N. Tobin were responsible for formal analysis; D. Bielopolski, R.G. Kost, and J.N. Tobin conceptualized the study; D. Bielopolski and Y. Renert-Yuval were responsible for visualization; D.M. Charytan, J.N. Tobin, and R.D. Vaughan provided supervision; R.G. Kost, O.S. Bentur, D.M. Charytan, R.G. Kost, and J.N. Tobin were responsible for validation; and all authors approved the final version of the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kiddo.org/supplemental.

Supplemental Table 1. Renal characteristics across BMI groups and age-related formulae.

Supplemental Table 2. Demographic characterization of patients without documented renal function.

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