Background: Adolescent obesity, a risk factor for cardio-renal morbidity in adulthood, has reached epidemic proportions. Obesity-related glomerulopathy (ORG) has an early reversible stage of hyperfiltration. Age-appropriate formulae for estimated glomerular filtration rate (eGFR), which are standardized to ideal body surface area (BSA) and provide assessment of kidney function in mL/min/1.73 m² units, 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 ages 12-21 years from a New York metropolitan multi-institutional electronic health records clinical data base. eGFR was calculated in two ways: BSA-standardized eGFR; and absolute eGFR. Hyperfiltration was defined above a threshold of 135mL/min/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 differed across BMI groups: Underweight - 2.3%; Normal 6.1%; Overweight - 17.4%; Obese - 31.4%. 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, 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.

Key Points:

* BSA-standardized eGFR creates similar rates of hyperfiltration across BMI groups.
* Creatinine clearance and Absolute eGFR, adjusted to individual BSA, reflect BMI increase, unlike BSA-standardized eGFR.
* Absolute eGFR, adjusted to individual BSA, unmask higher prevalence of hyperfiltration in obese patients, enabling timely intervention.

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Obesity Related Glomerulopathy in adolescent women: the effect of Body Surface Area

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Key points:

- BSA-standardized eGFR creates similar rates of hyperfiltration across BMI groups.
- Creatinine clearance and Absolute eGFR, adjusted to individual BSA, reflect BMI increase, unlike BSA-standardized eGFR.
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Abstract:

Background: Adolescent obesity, a risk factor for cardio-renal morbidity in adulthood, has reached epidemic proportions. Obesity-related glomerulopathy (ORG) has an early reversible stage of hyperfiltration. Age-appropriate formulae for estimated glomerular filtration rate (eGFR), which are standardized to ideal body surface area (BSA) and provide assessment of kidney function in mL/min/1.73 m$^2$ units, 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 ages 12-21 years from a New York metropolitan multi-institutional electronic health records clinical data base. eGFR was calculated in two ways: BSA-standardized eGFR; and absolute eGFR. Hyperfiltration was defined above a threshold of 135mL/min/1.73 m$^2$ 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, 13.4-15.3%, across Body Mass Index (BMI) groups. The prevalence of hyperfiltration determined by absolute eGFR differed across BMI groups: Underweight – 2.3%; Normal 6.1%; Overweight – 17.4%; Obese – 31.4%. 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, 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.

Abbreviations used:

CKD: Chronic kidney disease, ESKD: End-stage kidney disease, ORG: Obesity-related Glomerulopathy, eGFR: estimated Glomerular Filtration Rate, BSA: Body Surface Area BMI: Body Mass Index, CDK-EPI: CKD-Epidemiology Collaboration, KDIGO: Kidney Disease: Improving Global Outcome, CrCl: Creatinine Clearance, Absolute eGFR: actual BSA based eGFR
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 ages 16 to 19 years.[1],[2] Obesity is a modifiable risk factor for both chronic kidney disease (CKD) and end-stage kidney disease (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 focal segmental glomerulosclerosis (FSGS) occurring in obese patients with a BMI >30 kg/m², and results from hemodynamic changes, manifesting as glomerular hyperperfusion and hyperfiltration, due to afferent arteriolar dilatation.[4] It is well established that in the first stages of ORG, hyperfiltration occurs as a physiological adaptation of the kidney to the increased body mass.[4] Several studies have reported that obesity-associated hyperfiltration decreases after marked 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 glomerular filtration rate (GFR) value greater than 135 mL/min/1.73 m².[6,7]

Kidney Disease: Improving Global Outcome (KDIGO) guidelines recommend using age-appropriate serum creatinine-based equations to calculate estimated GFR (eGFR): CKD-Epidemiology Collaboration (CDK-EPI) in the adult patient population and Schwartz 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 BSA of 1.73 m$^2$ rather than the individual's actual BSA. The value of 1.73 m$^2$ reflects the mean BSA of 25-year-old men and women in the United States in 1927[9] compared to a mean BSA of 1.98 m$^2$ in men and women in 2018.[13] However, the reference value of 1.73 m$^2$ is maintained for normalization purposes.[9]

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

**Methods**

**Statement of ethics**

Data extraction and transmission were reviewed and approved, and a waiver of informed consent for analyzing de-identified data was granted by the Institutional Review Boards at Clinical Directors Network (CDN), BRANY (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 (NIMH)-funded clinical trial to compare the effectiveness of two different prenatal care strategies among pregnant adolescent women[14] [15]. De-identified electronic health record (EHR) data were extracted for female adolescents aged 12-21 years who
received health care services from 1/1/2011 to 12/31/2015 in New York City (NYC) in 12 academic health centers and community health centers that are part of Patient Centered Outcomes Research (PCOR)-funded NYC Clinical Data Research Network (NYC-CDRN).[16]

Study findings are described in accordance with STROBE guidelines.

**Data-Cleaning steps for biologically plausible limits**

The first encounter for each individual in which height, weight, blood pressure 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 blood pressure (60-220 mmHg), diastolic blood pressure (30-150 mmHg), BMI (12-80 kg/m^2), height (127-200cm), and weight (24-240 kg). Serum creatinine was limited to 3mg/dl to avoid confounding by CKD.

BSA was calculated using the metric system according to the Du-Bois formula (BSA = 0.007184 * Height^{0.725} * Weight^{0.425}).[17]

BMI was calculated by dividing a person’s weight in kilograms by the square of height in meters. BMI values were classified according to the Center for Disease Control and Prevention [18] data for BMI-for-age z-score into the following categories:

Underweight: BMI ≤5^{th} percentile, Overweight: 95^{th} ≥BMI ≥85^{th} percentile, Obese: BMI ≥95^{th} percentile, all for children and teens of the same age and sex.[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/1.73 m².

To eliminate the standardized correction and calculate 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). Pearson’s coefficient was used to assess correlation between continuous variables. Continuous variables were compared using ANOVA including Dunnett’s approach for multiple comparisons, where a p<0.05 (two-tailed) was considered statistically significant. Bland-Altman’s analysis was used to assess the relative agreement between BSA-standardized and Absolute eGFR.

Results

The original cohort comprised 123,448 unique patients. Following data-cleaning steps to remove biologically implausible values, 22,417 unique female patients (mean age 17±3 years) with recorded serum creatinine values remained in the final analysis (Supplementary Figure 1). Age distribution with a threshold of 18 years, according to the recommended formulae to estimate GFR was: 9,823 (43.8%) of patients were older than 18 years of age, and 12,594 (56.1%) were younger.
Distribution of BMI was sorted into BMI-for-age categories according to CDC[18] definitions: underweight: 1,085 (4.8%), normal weight: 11,971 (53.4%), overweight: 4,353 (19.4%), and obese: 5,008 (22.3%). There were 7,315 (32.6%) Black patients, and 2,877 (12.8%) White patients. 9,068 (40.4%) were Hispanic. Black patients were overrepresented in the obese group compared to White patients, (38.2% vs 7.9%, respectively; \(p<0.001\)) and underrepresented in the underweight group (27.5% vs 20.6%, respectively; \(p<0.001\)) (Table 1).

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 0.74±0.2 mg/dL in the underweight, normal, 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/1.73m\(^2\) vs 106±27ml/min/1.73m\(^2\) in the overweight group, 103±27 ml/min/1.73m\(^2\) in the normal weight group, and 106±30 ml/min/1.73m\(^2\) in the underweight group (Figure1, Table 2). BSA-standardized eGFR values were similar across BMI groups in both the pediatric and adult groups (Table S2, Supplementary Figure 2). 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).

**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.** 2,909 patients (12.9%) met the criteria for hyperfiltration according to BSA-standardized eGFR (>135 mL/min/1.73 m²): 15.5% from the underweight, 12.0% from the normal weight, 14.5% from the overweight, and 13.3% from the obese groups (p<0.001). Using Absolute eGFR, 3,076 (13.7%) individuals met the criteria for hyperfiltration: 2.3% in the underweight group, 6.1% in the normal weight group, 17.4% in the overweight group and 31.4% in the obese group (Table 2, Figure 2, p<0.001).

**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 3a-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 non-obese individuals but might significantly underestimate the true GFR in obese patients,[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 glomerular filtration rate 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 blood pressure, accelerating the progressive deterioration of kidney function over time.[24] Kidney donors are otherwise healthy individuals maintaining metabolic rate but using half of the nephron mass. In a large cohort of donors a strong correlation has been found between hyperfiltration according to age-based unindexed mGFR (using iothalamate clearance) and high BMI[25]. Unindexed mean mGFR was higher than indexed mGFR (113.4±25.3 vs. 101.3±19), 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 ages 12-21 followed in 12 NYC academic and community health centers. While serum creatinine and BSA-standardized eGFR were similar across BMI groups, hyperfiltration rates increased as BMI rose when Absolute eGFR was utilized 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 creatinine clearance 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 vs 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 non-obese adults, but can have a major impact and influence decision making in overweight individuals.[27]

Of note, our cohort has higher prevalence of minority patients, especially in the obese subgroup, compared to patients whose kidney function were not available (Table S2). 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 prior to 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 to 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, based on 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 based on serum creatinine concentrations.

Previous studies investigated the association between baseline hyperfiltration status, and subsequent GFR decline. In a population-based outpatient data set of more than a million individuals[33], higher estimated GFR (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 diabetics [34]. These observations indicate that hyperfiltration, in at least a proportion of participants, may play a role in accelerated GFR decline in both diabetics and non-diabetics [35] [34].

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.\cite{36} In our cohort, CrCl data were available in only 309 patients, serving as internal validation to prove the concept of increased filtration. Since obesity is associated with higher muscle mass\cite{37}\cite{38}, which increases across BMI groups (from underweight to obese), hyperfiltration can be estimated by creatinine clearance.

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 analytes, such as cystatin c or a combination with creatinine, that are not commonly available in clinical care, thus could not be used in this large cohort, which is based on data from electronic health records. Another limitation is that according to the BSA-standardized eGFR, 15% of the underweight patients who are 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 since it is represented only by serum creatinine, and BSA is standardized. Measurement of serum creatinine was non-random in this cohort. As noted above, this likely reflects clinician recognition of at risk patients. Further studies are warranted to assess how our findings extend to individuals at low risk.

Moreover, hyperfiltration in the 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 CKD2 range according to KDIGO guidelines,[9] yet data were not extracted in the current data-set to explore kidney pathology in this BMI group.

Our study has some clear strengths. Our cohort is large and diverse, including urban population with different racial and ethnic composition compared to the American population. Non-Hispanic Whites make up 61% of the country's population[39] compared to less than 15% in our cohort. The high proportion of underrepresented populations in our cohort could account at least partially for the higher-than-expected rates of overweight and obesity, 41% in our cohort compared to 20% the general population, in at ages 12-19.[18] Obesity at ages 2-19 is more common among Hispanics (25.8%) and non-Hispanic Blacks (22.0%) compared to non-Hispanic Whites (14.1%).[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 eGFR 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 to 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.

While the United States Preventive Services Task Force stated in its last report that there are insufficient evidence to recommend routine screening for kidney disease in asymptomatic adults,[40] early identification of individuals with increased cardio-renal 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 following the intervention.[41,42][43]

While the increase in the prevalence of hyperfiltration in the obese group is expected given the mathematical 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 obese adults, including the Black population, among whom kidney morbidity is over represented, and obesity rates are increasing. Successful intervention has the potential to improve quality of life and prevent subsequent comorbidities, along with care costs reduction for a substantial
part of the population at risk, where there is a high representation of underserved minorities.

**Disclosures**

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**Supplementary material**

Supplementary figure 1  
Supplementary figure 2  
Supplementary table 1  
Supplementary table 2
References


2 Childhood Obesity Facts | Overweight & Obesity | CDC


9 KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease


13 Adult Obesity Facts | Overweight & Obesity | CDC


18 Defining Childhood Obesity | Overweight & Obesity | CDC


33 Tonelli M, Klarenbach SW, Lloyd AM, James MT, Bello AK, Manns BJ & Hemmelgarn BR (2011) Higher estimated glomerular filtration rates may be associated with increased risk of adverse outcomes, especially with concomitant proteinuria. Kidney Int. 80, 1306–1314.


35 Thomson HJ, Ekinci EI, Radcliffe NJ, Seah J, MacIsaac RJ, Jerums G & Premaratne E (2016) Elevated baseline glomerular filtration rate (GFR) is independently


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Tables:

Table 1: Demographic and vital characteristics of the population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Underweight (N=1,085)</th>
<th>Normal (N=11,971)</th>
<th>Overweight (N=4,353)</th>
<th>Obese (N=5,008)</th>
<th>Overall (N=22,417)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>16.9±2.8</td>
<td>17.1±2.5</td>
<td>17.3±2.6</td>
<td>17.1±2.6</td>
<td>17.1±2.5</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157±10</td>
<td>159±8</td>
<td>160±8</td>
<td>161±8</td>
<td>160±8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>40±7</td>
<td>53±9</td>
<td>69±9</td>
<td>91±19</td>
<td>±6420</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.9±1.4</td>
<td>21.0±2.3</td>
<td>26.9±1.8</td>
<td>35.2±6.1</td>
<td>25±4.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.3±0.2</td>
<td>1.5±0.2</td>
<td>1.7±0.2</td>
<td>1.9±0.2</td>
<td>1.7±1.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black individuals (column percent)</td>
<td>299 (27.5%)</td>
<td>3,631 (30%)</td>
<td>1,467 (34%)</td>
<td>1,918 (38.2%)</td>
<td>7,315 (32.6%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Black individuals (row percent)</td>
<td>299 (4.1%)</td>
<td>3,631 (49.6%)</td>
<td>1,467 (20.0%)</td>
<td>1,918 (26.2%)</td>
<td>7,315 (100%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>380 (35.0%)</td>
<td>4,695 (39.2%)</td>
<td>4,881 (43.2%)</td>
<td>2,112 (42.1%)</td>
<td>9,068 (40.4%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>58 (6.1%)</td>
<td>791 (7.4%)</td>
<td>375 (8.6%)</td>
<td>454 (9.0%)</td>
<td>1,678 (8.4%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Systolic BP (mmHG)</td>
<td>102±11</td>
<td>105±11</td>
<td>110±11</td>
<td>115±13</td>
<td>109±12</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diastolic BP (mmHG)</td>
<td>64±8</td>
<td>64±8</td>
<td>67±9</td>
<td>69±9</td>
<td>66±9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hemoglobin A1c(%)</td>
<td>5.7±1.4</td>
<td>5.6±1.1</td>
<td>5.6±1.0</td>
<td>5.6±0.8</td>
<td>5.6±1.0</td>
<td>0.052</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± SD. For race and smoking numbers in brackets represent row percent, except for the total which represents column percent. *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. BMI – Body Mass Index, BSA – Body Surface Area, BP – Blood Pressure.
### Table 2 - Kidney characteristics across BMI groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Underweight (N=1,085)</th>
<th>Normal (N=11,971)</th>
<th>Overweight (N=4,353)</th>
<th>Obese (N=5,008)</th>
<th>Overall (N=22,417)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.73±0.2</td>
<td>0.75±0.2</td>
<td>0.74±0.2</td>
<td>0.74±0.2</td>
<td>0.74±0.2</td>
<td>0.001*</td>
</tr>
<tr>
<td>Creatinine Clearance (ml/min)</td>
<td>57±22 (10)</td>
<td>107±54 (124)</td>
<td>130±56 (62)</td>
<td>140±57 (113)</td>
<td>122±58 (309)</td>
<td>0.001</td>
</tr>
<tr>
<td>BSA-standardized eGFR (ml/min/1.73m²)</td>
<td>106±30</td>
<td>103±27</td>
<td>106±27</td>
<td>105±26</td>
<td>104±27</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hyperfiltration BSA-standardized eGFR</td>
<td>167 (15%)</td>
<td>1,445 (12%)</td>
<td>630 (15%)</td>
<td>667 (13%)</td>
<td>2,909 (13%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Absolute eGFR (ml/min)</td>
<td>82±26</td>
<td>92±26</td>
<td>105±29</td>
<td>119±33</td>
<td>100±31</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hyperfiltration Absolute GFR</td>
<td>25 (2.3%)</td>
<td>728 (6.1%)</td>
<td>755 (17.4%)</td>
<td>1,568 (31.4%)</td>
<td>3,076 (14%)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± SD. Absolute numbers are counted individuals with eGFR>135. Numbers in brackets represent column percent. P-value represents ANOVA.

*Dunnet multiple comparison approach reveals that normal weight and overweight group are statistically not different, but mean creatinine of underweight-normal weight and normal weight-obese are significantly different.

eGFR=estimated GFR for ideal body surface area. Absolute GFR=estimated GFR for individuals’ body surface area.
Figure legends

Figure 1. Creatinine clearance and predicted filtration rate by the eGFR formulae.

Bars represent mean values of predicted filtration according to BSA-standardized eGFR, which is normalized to ideal BSA (blue) vs. Absolute eGFR, which is adjusted to individual BSA (orange). Measured creatinine clearance in 309 patients (grey) is shown in parallel. Standard deviations across bars are shown in black lines.

Figure 2. Hyperfiltration prevalence according to BMI group by BSA-standardized eGFR (blue) vs. Absolute eGFR (orange).

Hyperfiltration was defined according to GFR threshold of 135 mL/min/17.3m$^2$ (BSA-standardized eGFR) or 135 mL/min (Absolute eGFR). (p<0.001 for trend of hyperfiltration according to Absolute eGFR across BMI groups, and p=0.1 for trend of hyperfiltration according to BSA-standardized eGFR across BMI groups)

Figure 3. Agreement between BSA-standardized eGFR and Absolute eGFR across BMI groups using the Bland Altman approach.

Creatinine clearance and predicted filtration rate by the eGFR formulae

ml/min

ml/min/1.73m²

BMI group

Underweight

Normal

Overweight

Obese

106 82 57

103 92 107

106 105 130

105 119 140

BSA standardized eGFR ml/min/1.73m²

Absolute eGFR ml/min

Creatinine Clearance (ml/min)
Hyperfiltration Rates according to BMI Group by BSA standardized eGFR vs. Absolute eGFR

- Underweight
- Normal Weight
- Overweight
- Obese

Hyperfiltration Rates

- Hyperfiltration Absolute
- Hyperfiltration BSA Standardized