Black Race Coefficient in GFR Estimation and Diabetes Medications in CKD: National Estimates

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GFR from serum creatinine–based equations informs medication management in CKD. These equations include age, sex, and race (Black versus non-Black), and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation increases eGFR by approximately 16% for Black persons.1 This has led to concern about systematically different care; however, removal of the race factor has led to concern about medication eligibility and dosing.1 Glucose-lowering medication recommendations in CKD depend on eGFR. The Kidney Disease Improving Global Outcomes (KDIGO) Guideline for Diabetes Management in CKD recommends medication classes for CKD.2 Metformin is the first-line medication for type 2 diabetes in general, yet has a lower eGFR threshold (30 ml/min per 1.73 m²). Sodium-glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide 1 receptor agonists (GLP-1ras) have shown kidney and cardiovascular benefits and are preferred in CKD.2 However, the KDIGO guideline outlines lower eGFR limits for initiation (30 ml/min per 1.73 m² for SGLT2i and 15 ml/min per 1.73 m² for GLP-1ra).2 Removal of the race coefficient from eGFR for Black persons means some would newly qualify for CKD-preferred medications (eGFR reduced into CKD range) and some would no longer qualify (eGFR reduced below thresholds). We estimated the proportion of Black adults in the United States with type 2 diabetes for whom medication recommendations could be affected by dropping the eGFR race coefficient.

We used the National Health and Nutrition Examination Survey (NHANES), a study that enables estimates of the United States population. NHANES was approved by the National Center for Health Statistics institutional review board. We combined four 2-year data cycles, 2011–2018, adjusted the weights and applied survey methods to estimate cross-sectional totals and proportions of the population.3 We included persons aged ≥20 years with self-reported Black race and type 2 diabetes.

GFR estimates used CKD-EPI, and CKD was classified using eGFR and albuminuria.4 We further classified by metformin, SGLT2i, and GLP-1ra recommendations from the KDIGO diabetes guideline.2 For those reclassified as having CKD when the race coefficient was omitted, we estimated the proportion with prior indication for SGLT2i or a GLP-1ra based on the American Diabetes Association guideline (for cardiovascular disease or weight loss). Multiple imputation was performed for missing laboratory data (Supplemental References).

We identified 923 observations, representing a cross-sectional estimate of 4,007,966 (95% confidence interval [95% CI], 3,358,243 to 4,657,689) Black adults with type 2 diabetes (Supplemental Table 1). Using race-based eGFR and albuminuria classification, 39.3% (95% CI, 36.2% to 42.4%) were classified as having CKD. This increased to 45.2% (95% CI, 41.9% to 48.5%) using eGFR without the race coefficient. This was an additional 5.9% (95% CI, 4.4% to 7.3%) of the study population classified with CKD—an estimated 235,341 (95% CI, 158,920 to 311,762) individuals. SGLT2i initiation (by the CKD guideline) would be recommended for 35.3% (95% CI, 32.4% to 38.2%) of Black persons with diabetes under race-based GFR estimation, versus 40.3% (95% CI, 37.4% to 43.2%) using eGFR without the race coefficient. GFR without race coefficient would reclassify 0.8% (95% CI, 0.1% to 1.4%) of Black persons with diabetes <30 ml/min per 1.73 m², too low for SGLT2i initiation or metformin continuation, and 0.3% (95% CI, 0.0% to 0.7%) would drop <15 ml/min per 1.73 m², too low for GLP-1ra. Of those newly classified with...
CKD, 27.8% (95% CI, 15.0% to 40.6%) would qualify for SGLT2i or GLP-1ra for cardiovascular indications, and 93.4% (95% CI, 86.0% to 100%) would qualify for weight loss (body mass index >25 kg/m²). Figure 1 presents results in a visual format.

We found that omitting the eGFR race coefficient could affect guideline-directed medications for a substantial number of Black adults with type 2 diabetes. An additional one in 20 would be newly classified as having CKD and would potentially qualify for CKD-preferred glucose-lowering therapy. However, most reclassified into CKD had other indications for these agents: one in four for cardiovascular indications and nine in ten for weight loss. Nearly one in 100 would have eGFR reduction substantial enough to no longer qualify for SGLT2i initiation (on the basis of the KDIGO guideline) or metformin continuation. The effect of eGFR without the race coefficient has been noted previously with metformin therapy: 12%–16% of Black persons in a health database with eGFR 30–44 ml/min per 1.73 m² prescribed metformin would no longer be eligible. Of note, equitable care in diabetes reduced incident CKD in Black persons to rates lower than White persons in the Action to Control Cardiovascular Risk in Diabetes trial. Disease classifications have important effects beyond medication eligibility, influencing anxiety and insurability.

Our study has important limitations. The weights were not derived for the
subpopulation of interest, and our subpopulation was small, resulting in wide 95% CIs. We were limited to single laboratory measurements. Black persons who also identified as Hispanic or multiracial persons were not identified. Our study does not address how race coefficient removal affects eGFR accuracy. Removal of the race coefficient has been associated with systematic underestimation of measured GFR among Black persons.7

The most important consideration is not guideline drug eligibility, nor accuracy of equations, but how to achieve optimal, equitable outcomes for Black persons. Enrollment of more Black participants in clinical trials is essential for this goal. Further investigations into medication effectiveness and safety in these individuals are needed.

DISCLOSURES

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W.C. Winkelmayer reports personal fees from Akebia, AstraZeneca, Bayer, Janssen, Merck, and Vifor FMC Renal Pharma (including Relypsa) outside the submitted work. W.C. Winkelmayer also reports consultancy agreements with Akebia, AstraZeneca, Bayer, Otsuka, and Reata; honoraria from Akebia, AstraZeneca, Bayer, Otsuka, and Reata; scientific advisor or membership with American Journal of Kidney Diseases (editorial board member), American Journal of Nephrology (editorial board member), Journal of the American Medical Association (associate editor), KDIGO (cochair), and Seminars in Dialysis (editorial board member). The remaining author has nothing to disclose.

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SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl?doi:10.1681/ASN.2020121724/-/DCSupplemental.

Supplemental Table 1. Cross-sectional NHANES estimates for United States non-Hispanic Black adults with type 2 diabetes.

Supplemental References. References, supplemental methods.

REFERENCES


Supplement to:

Black race in GFR estimation and diabetes medication recommendations in CKD: National estimates

Study Population

We identified people from NHANES whose self-reported race was non-Hispanic Black. Self-reported multi-racial status, or categorization as Hispanic and Black, are not identifiable from the public NHANES datasets and were thus not included in the analysis.\(^1\) We identified people with diabetes from either 1) Hgb A1c ≥ 6.5 % or 2) both reported diagnosis of diabetes and current use of diabetes medication. We sought to include only people with Type 2 diabetes. NHANES does not explicitly differentiate between type 1 and type 2 diabetes, and people with FR type 1 diabetes have different medication eligibility. However, the CDC estimates that 90-95% of diabetes cases in the US are due to type 2 diabetes,\(^2\) so these make up the majority of the diabetes cases in NHANES. We also used an algorithm (based on two previously published studies) to identify people likely to have Type 1 diabetes, who were then excluded from the analysis.\(^3,4\) People who were started on insulin within one year of diabetes diagnosis, who were younger than age 30 at diabetes diagnosis, and who were using insulin but no oral hypoglycemics at time of questionnaire administration were identified as Type 1 diabetics and excluded. Atherosclerotic cardiovascular disease was ascertained from self-report of prior heart attack, coronary heart disease, angina/angina pectoris, or stroke. Congestive heart failure was ascertained from self-report. Weight and height were measured at time of NHANES examination.

Antihyperglycemic Agents and eGFR thresholds

We used eGFR of 30 ml/min/1.73m\(^2\) as the cutoff for metformin use, consistent with FDA guidance and KDIGO guidelines.\(^5\) For SGLT2 inhibitors, we used an eGFR lower threshold of 30 ml/min/1.73m\(^2\), consistent with the KDIGO guidelines.\(^5\) This was based on inclusion criteria for the EMPA-REG, CANVAS, and CREDENCE trials.\(^6-8\) DAPA-CKD included participants with baseline eGFR as low as 25 ml/min/1.73m\(^2\), and use of this threshold would have changed our results slightly.\(^9\) For GLP-1 receptor agonists, we used an eGFR lower threshold of 15 ml/min/1.73m\(^2\), as one agent has been studied at eGFRs this low (dulaglutide in the REWIND trial).\(^10\)

Analysis

We estimated weighted totals and proportions for those who met inclusion criteria and for subgroups in our analysis. To enable more stable estimates, we combined four 2 year data cycles (8 years), 2011-2018, and adjusted the weights accordingly, enabling estimates of totals and proportions of the US population with appropriate variances.\(^11\) Inclusion in the study required participation in the NHANES exam phase, and thus we used the examination weights.\(^12\) We used survey methods for all analyses, to account
for clustering, stratification, and weighting. Taylor series linearization was used for estimation of variances.\textsuperscript{12,13}

Urine albumin-to-creatinine ratios were missing for 41 of the 923 included observations (4.4\%) and serum creatinine for 80 of the 923 observations (8.7\%). To try to reduce possible bias, multiple imputation was used, under the Missing At Random (MAR) assumption. Twenty imputations were performed using chained equations and predictive mean matching, using analytic variables (creatinine, albumin, age, sex) and design variables (represented by a composite stratum x cluster indicator variable).\textsuperscript{13} Convergence was assessed using trace plots. Estimated glomerular filtration rates were passively imputed using the imputed serum creatinine levels. All estimations used the multiple imputations according to the combination rules of Rubin.\textsuperscript{14}

NHANES data sets reports ages ≥ 80 years as 80 years to ensure anonymity. The average age of those reported as 80 years is 85 years for 2015-16,\textsuperscript{1} which we used as the approximation for people with age recorded as 80 or older for purposes of eGFR estimation. All analyses were performed using Stata 14.2 (www.stata.com). The figure was created using the R version 4.0.2 (www.r-project.com).
**Supplemental Table 1.** Cross-sectional NHANES estimates for US non-Hispanic Black adults with type 2 diabetes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unweighted observations (N)</td>
<td>923</td>
</tr>
<tr>
<td>Weighted estimate, N, (95% CI)</td>
<td>4,007,966 (3,358,243-4,657,689)</td>
</tr>
<tr>
<td>Age, years, median (IQR)</td>
<td>58 (49-68)</td>
</tr>
<tr>
<td>Female, %</td>
<td>56.8%</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl, median (IQR)</td>
<td>0.95 (0.78-1.18)</td>
</tr>
<tr>
<td>eGFR-Race coefficient, ml/min/1.73m², median (IQR)</td>
<td>87.4 (67.0-109.0)</td>
</tr>
<tr>
<td>eGFR-No race coefficient, ml/min/1.73m², median (IQR)</td>
<td>75.4 (57.8-94.0)</td>
</tr>
<tr>
<td>Urine albumin to creatinine ratio, mg/g, median (IQR)</td>
<td>12.9 (6.6-49.4)</td>
</tr>
<tr>
<td>BMI, kg/m², median (IQR)</td>
<td>33.0 (28.8-38.9)</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
<td>12.2%</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>8.1%</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>10.2%</td>
</tr>
</tbody>
</table>

Notes: 2011-2018 NHANES data were used. All measures except number of observations are weighted estimates. Comorbidities obtained from questionnaire responses. Abbreviations: NHANES, National Health and Nutrition Examination Survey; CI, confidence interval; IQR, interquartile range; BMI, body mass index.
References, Supplementary Methods


