Kidney Medicine

Kidney Function and Incident Stroke and Dementia Using an Updated Estimated Glomerular Filtration Rate Equation Without Race: The Multi-Ethnic Study of Atherosclerosis

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Rationale & Objective: Equations for estimated glomerular filtration rate (eGFR) have previously included a coefficient for African American race. We evaluated and compared risk of incident stroke and dementia between old and new equations of eGFR for African American and non-African American participants.

Study Design: Prospective observational study.

Setting & Participants: Baseline values were collected from 6,814 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort between 2000 and 2002. Participants were followed up until 2018. The analytic sample consisted of 6,646 participants (mean [SD] age 62 [10] years; 53% female; 39% White, 27% African American, 12% Chinese American, and 22% Hispanic/Latino).

Exposure: eGFR equation from 2021 based on serum creatinine and cystatin C levels without race.

Outcome: Incident stroke and dementia.

Analytical Approach: Cox proportional regression adjusting for demographic, lifestyle, and clinical variables was performed to estimate associations between different eGFR measures and risk of incident stroke and dementia.

Results: During a median follow-up period of 17 years, 349 (5.3%) participants experienced an incident stroke event, and 574 (8.6%) participants experienced incident dementia. In the fully adjusted model, overall participants with eGFR <60 compared with those >90 mL/min/1.73 m^2 were at significantly increased risk of dementia (HR, 95% CI: 1.73, 1.21-2.45). A lower eGFR was not significantly associated with incident stroke (1.30, 0.75-2.24). African American participants tended to be reclassified to a lower group of eGFR in the new equations, whereas non-African American participants were reclassified to a higher group of eGFR. When comparing older versus newer equations of eGFR in African American and non-African American participants in association with incident stroke and dementia, differences were minimal.

Limitations: Incident dementia was ascertained through International Classification of Diseases (Ninth and Tenth Revisions) codes.

Conclusions: Our findings illustrate participants with 2021 eGFR < 60 compared with those with eGFR > 90 mL/min/1.73 m^2 have higher risk of dementia in both African American and non-African American participants, but not of stroke.

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Approximately 15% of adults in the United States live with chronic kidney disease (CKD).[1] Current estimates suggest that more than half remain unaware of their kidney impairment until the disease progresses to a more symptomatic and pathogenic manifestation.[2] The pathophysiological relationship between kidney dysfunction and neurologic disorders of stroke and dementia is complex but co-occurrence of CKD and neurologic pathologies such as stroke and dementia are common.[3,4] The association does not seem to be limited to CKD but also evident in early stages of kidney function decline.[5,6] Studies have shown that individuals with impaired kidney function have a 43% increased risk of stroke and 53% increased risk of dementia.[5,7] These associations are important because early detection of kidney dysfunction can help with a timely application of appropriate interventions to prevent negative outcomes.

A commonly used marker of kidney function is estimated glomerular filtration rate (eGFR). This rate is calculated from clinical inputs of serum creatinine and/or cystatin C levels and demographic inputs consisting of age, sex, and race.[8] Importantly, these calculations of eGFR have included African American race as a coefficient in the equations and have been shown to overestimate eGFR in African American populations.[8] Systematic overestimation of eGFR by these equations in African American individuals could potentially lead to misclassification, later diagnosis of CKD, and delay in delivery of care. Updated eGFR equations were published in 2021 that estimate GFR without using race, and studies found that these equations more accurately estimated kidney function than previous equations, yielded smaller differences in average eGFR between African American and non-African American populations, and improved classification of CKD diagnosis and staging.[8] This is an important change because although incidence of CKD is similar between African American and non-African American populations, African American individuals are at higher risk of end-stage renal

PLAIN LANGUAGE SUMMARY

Existing research has established that declined kidney function is associated with stroke and dementia. Kidney function is commonly estimated using inputs of blood proteins alongside demographic inputs of age, sex at birth, and race. Inclusion of race to estimate kidney function has gained increased scrutiny given its problematic nature of being a societal construct rather than an inherent biological trait that affects function of the kidneys. Recommendations were recently made to remove race from this estimation, and data were lacking on the relationship between new estimates of kidney function with outcomes such as stroke and dementia. Our research provides updated risk estimates for stroke and dementia using the new estimation for kidney function in a large multiethnic cohort.

disease, which may be partially explained by a systematic overestimation of eGFR using the old equations.[9-11]

The new equations of eGFR have been recommended to be adopted by clinical laboratories across the United States.[12] Information is currently lacking on whether the application of these equations changes the magnitude of relationship between kidney function and neurological outcomes such as stroke and dementia. Therefore, we aimed to investigate these relationships using data from the Multi-Ethnic Study of Atherosclerosis (MESA).

METHODS

Study Population

The MESA cohort consists of participants who had no history of clinical cardiovascular disease (CVD) at enrollment. Details of the study design and data collection methods have been published previously.[13] Briefly, enrollment and the baseline examination (examination 1) of the original cohort including 6,814 participants occurred between 2000 and 2002. The cohort included men and women aged between 45 and 84 years who identified their race/ethnicity as African American, Chinese, Hispanic/Latino, or White. The institutional review boards at all participating sites approved the MESA study protocol and all participants provided written informed consent. Participants were excluded if they had prevalent CVD identified at the baseline examination (n = 5), were missing measures of creatinine or cystatin C (n = 65), missing information on incident stroke and dementia (n = 30), or missing covariates of interest (n = 68), leaving an analytic sample of 6,646 individuals (Fig 1).

Kidney Function Assessment

Blood was collected at the baseline visit after a 12-hour overnight fast. Serum cystatin C level was later measured with a BNII nephelometer (Dade Behring Inc), which had an intra-assay coefficient of variation ranging from 2.0%-2.8%.[14] Serum creatinine level was measured with a Vitros analyzer (Johnson & Johnson Clinical Diagnostics Inc) and calibrated to the Cleveland Clinic Foundation laboratory.[14] The analytical coefficient of variation established by the laboratory was 2.2%.[14] Both cystatin C and creatinine levels at examination 1 were calibrated and scaled to MESA examination 5 (2010-2011) levels to minimize random error and variability between measurements. The eGFR exposure variable was calculated using the following equations: 2021 eGFR calculated from creatinine and cystatin C (2021 eGFRcr-cys), 2012 eGFR calculated from creatinine and cystatin C (2012 eGFRcr-cys), 2021 eGFR calculated from creatinine (2021 eGFRcr), and 2009 eGFR calculated from creatinine (2009 eGFRcr).[8] Table S1 shows the covariates used in eGFR calculation for each of the 4 equations included in this manuscript. In contrast to the 2012 eGFRcr-cys and 2009 eGFRcr equations, the 2021 equations did not use a coefficient for African American race. Primary analyses concentrated on 2021 eGFRcr-cys.

Urinary albumin and creatinine levels collected at baseline were measured at the Clinical Chemistry Laboratory at Fletcher Allen Health Care in Burlington, VT using nephelometry and rate Jaffe reaction, respectively.[15] The urinary albumin-creatinine ratio (UACR) (mg/g) was calculated for all participants with available data (n = 6618).

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines consider both eGFR and UACR measures for CKD risk; therefore, we combined eGFR and UACR to establish risk categories of CKD using the 2012 KDIGO guidelines comparing risk of CKD of participants between 2012 eGFRcr-cys to 2021 eGFRcr-cys.[16] For UACR, the 2012 KDIGO guidelines considers <30 mg/g normal to mildly increased, 30-299 moderately increased, and ≥300 severely increased.[16] For eGFR, the 2012 KDIGO guidelines considers >90 mL/min/1.73 m^2 normal or high, 60-90 mildly decreased, and <60 moderately decreased to kidney failure.[16]

Follow-up and Ascertainment of Outcomes

Incident stroke was defined as a rapid onset of a documented neurologic deficit with imaging showing an infarct or lasting at least 24 hours including both ischemic and hemorrhagic stroke. Incident stroke was adjudicated by a MESA committee comprised of vascular neurologist reviewing medical records.[17,18] Incident dementia was ascertained through International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10, respectively) codes in medical records for hospitalizations reported during follow-up interviews and dementia death certificates. The relevant codes used for dementia abstraction are listed in Table S2. A validation study of dementia events ascertained through ICD-9 and ICD-10 codes found that this method had a true positive rate of at least 73% in MESA.[19] Cognitive function was measured in a clinical setting at examination 5 and was used as a secondary

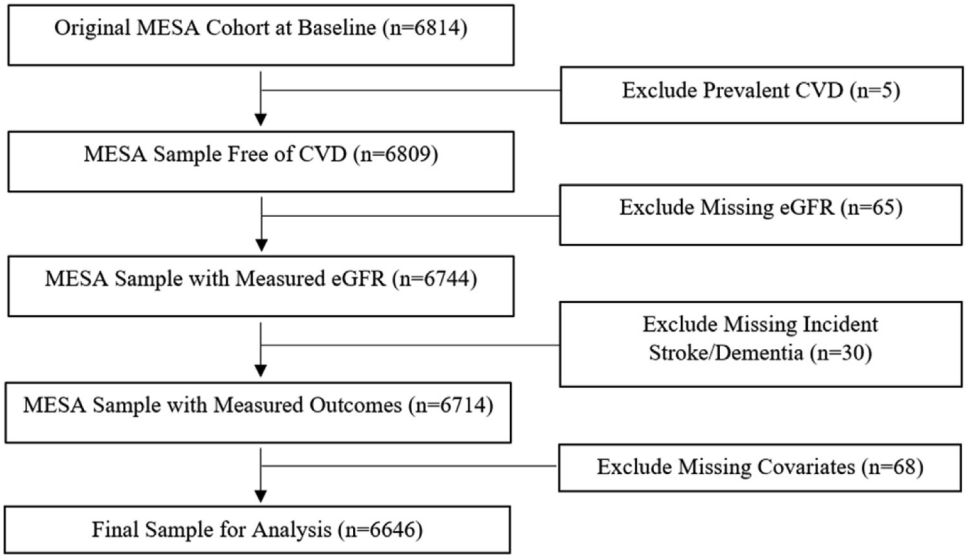

Figure 1. Flowchart of exclusions in analytic sample. Exclusion on missing covariates include variables listed in Table 1. Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

outcome for dementia to assess the association with 2021 eGFRcr-cys at baseline with cognition.

Follow-up time was defined as the number of days from participant baseline visit to date of incident stroke or dementia event, loss to follow up, death from another cause, or end of follow-up (December 31, 2018), whichever occurred first.

Assessment of Covariates

All participants completed standardized interviews by trained research staff to gather demographic characteristics, medical history, and medication use. Furthermore, trained clinical staff performed anthropometric measurements and collected 12-hour fasting blood samples at each visit. Sociodemographic variables such as age (years), sex (male/female), self-identified race/ethnicity (African American, Chinese, Hispanic/Latino, and White), center (New York, Baltimore, Chicago, Los Angeles, Twin Cities, and Winston-Salem), and education (< high school graduate, high school graduate/some college, and college graduate/graduate school) were collected at baseline, along with lifestyle variables such as physical activity (based on total moderate and vigorous activity minutes per week), smoking status (current, former, and never), and alcohol use (current, former, and never). Clinical variables included prevalent diabetes mellitus (defined as fasting plasma glucose levels > 126 mg/dL or use of antidiabetic medication) (yes/no), total cholesterol (collected after a 12-hour overnight fast and measured from venous samples) (mg/dL), body mass index (BMI, calculated by weight in kilograms divided by height in meters squared [kg/ m^2]), and resting systolic blood pressure (SBP) and diastolic blood pressure (DBP), which were based on the average of the last 2 of 3 total measurements recorded in a seated position and reported in mm Hg.[14] Antihypertension medication use and statin medication use were collected through participants bringing their medications for ascertainment during the clinical examination and was reported as yes/no. DNA was extracted from peripheral blood using a DNA isolation kit (Puregene, Qiagen Instrument Service). *APOE* isoforms were estimated from rs7412 and rs429358 single nucleotide polymorphisms and were analyzed as *APOE* e4 carrier status yes/no.[20]

Statistical Analyses

Baseline characteristics of the study sample were examined overall and in the 2021 eGFRcr-cys group. Primary analyses involved CKD-EPI 2021 eGFRcr-cys. Secondary and sensitivity analysis incorporated three other eGFR equations of 2009 eGFRcr, 2012 eGFRcr-cys, and 2021 eGFRcr. The analysis investigated eGFR in two formats. The first was a continuous variable, per 15 mL/min/1.73 m^2 lower eGFR. Second, eGFR was categorized into 3 groups based on the cutoffs established by the KDIGO group (2012) and consisted of the following: <60, 60-90, and >90 mL/min/1.73 m^2 (reference).[16] Kaplan-Meier survival curve plots were constructed examining the crude association of categorical 2021 eGFRcr-cys with incident stroke and dementia. Four Cox proportional hazards regression models of eGFR's relationship with incident stroke and dementia were created to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for incident stroke and dementia events for eGFR. Model 1 was an unadjusted crude model. Model 2 adjusted for sex, age, race/ethnicity, and center. Model 3 added diabetes mellitus status, total cholesterol, BMI, SBP, DBP, antihypertensive medication use, and statin use. Model 4 added highest obtained education, physical activity, smoking status, and alcohol use. We further

Table 1. Baseline Characteristics of Participants Overall and by 2021 eGFR (Based on Cystatin C and Creatinine) group, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2002

		2021 eGFRcr-cys, mL/min/1.73 m²[a]		
	Total (n = 6,646)	<60 (n = 160)	60-90 (n = 1,312)	>90 (n = 5,174)
Age, years	62.1 ± 10.2	72.4 ± 8.4	69.3 ± 8.8	60.0 ± 9.6
Female, %	3,505 (52.7)	90 (56.2)	757 (57.7)	2,658 (51.4)
Race/ethnicity, %				
African American	1,820 (27.4)	58 (36.3)	444 (33.8)	1,318 (25.5)
Chinese	792 (11.9)	17 (10.6)	105 (8.0)	670 (12.9)
Hispanic/Latino	1,475 (22.2)	32 (20.0)	212 (16.2)	1,231 (23.8)
White	2,559 (38.5)	53 (33.1)	551 (42.0)	1,955 (37.8)
Body mass index, kg/m²	28.3 ± 5.4	29.8 ± 6.1	29.3 ± 5.8	28.0 ± 5.3
Systolic blood pressure, mm Hg	126.6 ± 21.5	140.1 ± 27.9	133.3 ± 22.4	124.4 ± 20.5
Diastolic blood pressure, mm Hg	71.9 ± 10.3	71.6 ± 12.4	71.6 ± 10.4	72.0 ± 10.2
Total cholesterol, mg/dL	194.1 ± 35.7	192.6 ± 48.2	192.8 ± 34.9	194.5 ± 35.5
Diabetes, %	823 (12.4)	45 (28.1)	185 (14.1)	593 (11.5)
Hypertension medication use, %	2,471 (37.2)	129 (80.6)	717 (54.6)	1,625 (31.4)
Statin use, %	991 (14.9)	41 (25.6)	257 (19.6)	693 (13.4)
[b]APOE e4 carrier, %	1,677 (26.9)	46 (30.1)	336 (27.4)	1,295 (26.7)
Education level, %				
<High school graduate	1,203 (18.1)	50 (31.2)	250 (19.0)	903 (17.4)
High school graduate/some college	2,291 (34.5)	58 (36.3)	497 (37.9)	1,736 (33.6)
College graduate/graduate school	3,152 (47.4)	52 (32.5)	565 (43.1)	2,535 (49.0)
Physical activity, MET-MIN/WK M-SU	4,020 [1,980- 7,515]	2,880 [1,095- 5,059]	3,450 [1,590-6,146]	4,260 [2,100-7915]
Smoking status, %				
Never	3,345 (50.3)	87 (54.4)	656 (50.0)	2,602 (50.3)
Former	2,433 (36.6)	55 (34.4)	506 (38.6)	1,872 (36.2)
Current	868 (13.1)	18 (11.2)	150 (11.4)	700 (13.5)
Alcohol status, %				
Never	1,370 (20.6)	50 (31.2)	311 (23.7)	1,009 (19.5)
Former	1,586 (23.9)	43 (26.9)	370 (28.2)	1,173 (22.7)
Current	3,690 (55.5)	67 (41.9)	631 (48.1)	2,992 (57.8)
2021 eGFRcr-cys, mL/min/1.73 m²	101.1 ± 17.0	47.5 ± 11.3	79.7 ± 7.6	108.2 ± 9.9
Urinary albumin to creatinine ratio (mg/g)	5.3 [3.3-10.9]	18.7 [6.6-131.5]	6.6 [3.6-15.2]	5.0 [3.2-9.7]

Abbreviations: *APOE,* apolipoprotein E; eGFR, estimated glomerular filtration rate; MET-MIN/WK M-SU, moderate and vigorous physical activity total minutes per week metabolic equivalent of task.
Note: Continuous variables are presented as mean ± SD for normally distributed variables and median [25th percentile, 75th percentile] for skewed variables, whereas categorical variables are presented as n (percentage).
[a]Estimated glomerular filtration rate.
[b]Missing *APOE* data (n = 415).

adjusted model 4 by urinary UACR in model 5 to check its effect on the results.

Restricted cubic spline (RCS) plots were created with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles to visualize the relationship of 2021 eGFRcr-cys with incident stroke and dementia. We assessed linearity of the relationships including a quadratic term for 2021 eGFRcr-cys with no significant relationship found. The proportional hazards assumption was checked in the primary analysis using an interaction term between 2021 eGFRcr-cys and log follow-up time, with no violation detected. Effect-measure modification on the multiplicative scale was evaluated by testing interaction between 2021 eGFRcr-cys and age, race/ethnicity, sex, diabetes, hypertension, and *APOE* e4 carrier status (only for dementia) in model 4. An interaction *P* value of <0.05 was considered significant.

We performed several sensitivity checks to validate our analysis including repeated analyses for stratified outcomes of dementia hospitalization and mortality to check whether the associations differed between the 2 outcomes. Incidence rates and HRs for African American and non-African American participants were compared between the older and newer equations of eGFR. We used multiple linear regression adjusted for age, sex, and race/ethnicity to analyze the association of 2021 eGFRcr-cys and cognitive function as a secondary outcome to dementia. Cognitive function was calculated using principal component analysis combining different cognitive tests collected in MESA including standardized digit symbol coding, forward digit span, and backward digit span as a secondary endpoint to dementia. Cognitive function was log-transformed as the distribution was not normal.

All statistical analyses were performed using SAS v 9.4 (SAS Inc).

RESULTS

Description of participants

Table 1 summarizes baseline characteristics of the analytic sample. The mean age was 62.1 years, and 53% were women. The self-identified race/ethnicity of the sample was 27% African American, 12% Chinese, 22% Hispanic/Latino, and 39% White. The mean (standard deviation [SD]) 2021 eGFRcr-cys was 101.1 (17.0) mL/min/1.73 m^2. The prevalence of 2021 eGFRcr-cys <60 mL/min/1.73 m^2 was 2.4% and 19.7% were between 60 and 90.

Comparing eGFR equations in African American and non-African American participants

Fig 2 depicts eGFR distributions in African American and non-African American participants comparing 2012 eGFRcr-cys and 2021 eGFRcr-cys. African American participants had a slightly lower median eGFR in the new 2021 eGFR equation than the old 2012 eGFR, whereas non-African American participants had a slightly higher median eGFR in the 2021 eGFRcr-cys equations. Table S3 shows the classification of kidney function according to older and newer eGFR equations, overall and by African American and non-African American race. In African American participants, reclassification was almost always from a better to worse kidney function category (eg, from >90 to 60-90 mL/min/1.73 m^2). By contrast, reclassification was always from a worse to better kidney function category in non-African American participants. The extent of reclassification in the new equations was greater in African American participants.

Fig S1 compares risk of CKD by the 2012 KDIGO nomenclature for 2012 eGFRcr-cys and 2021 eGFRcr-cys in conjunction with UACR.[16] In general, movement was limited for participants identified as having a higher risk of CKD in the 2012 eGFRcr-cys equation to lower risk categories in the 2021 eGFRcr-cys equation.

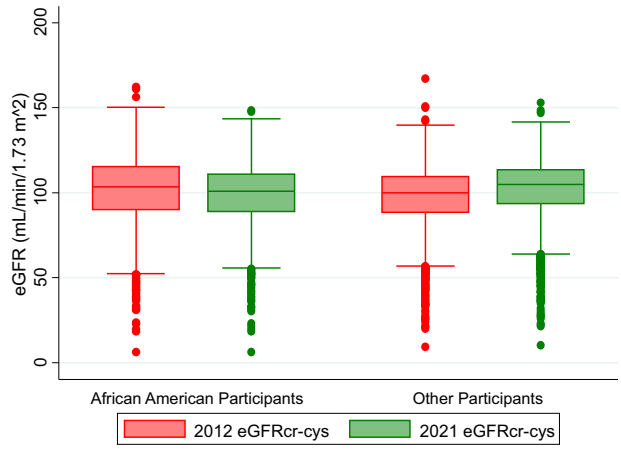

Figure 2. Box and whisker plots of old and new eGFRcr-cys equations stratified by race, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2002.

2021 eGFRcr-cys and incident stroke

Over a mean (SD) follow-up time of 14.1 (4.9) years, 349 incident strokes occurred with an incidence rate of 3.7 per 1,000 person years. Kaplan-Meier curves modeling stroke survival by 2021 eGFRcr-cys category are depicted in Fig S2a. All 3 2021 eGFRcr-cys groups had similar cumulative incidence of stroke until approximately 3 years of follow-up, after which the <60 and 60-90 mL/min/1.73 m^2 groups diverged away from the >90 group with greater incident stroke. Fig S3a shows the RCS plot assessing the linearity between 2021 eGFRcr-cys and incident stroke.

The crude association of 2021 eGFRcr-cys group and rate of incident stroke was significant (Table 2, model 1). However, this association was attenuated and no longer significant after additional adjustment. In the fully adjusted model 4, all *P* values were >0.05 in both continuous and categorical eGFR and incident stroke. Adjusting for UACR in model 5 did not change the findings from model 4; however, the effect estimates attenuated for eGFR < 60 mL/min/1.73 m^2 in comparison with eGFR > 90 mL/min/1.73 m^2.

2021 eGFRcr-cys and incident dementia

In total, 574 incident cases of dementia occurred during a mean (SD) follow-up time of 14.2 (4.8) years with an incidence rate of 6.08 per 1,000 person years. Kaplan-Meier curves for incident dementia by 2021 eGFRcr-cys category are shown in Fig S2b. All 3 eGFR groups had similar cumulative incidence of dementia until approximately 3 years of follow-up, after which the <60 and 60-90 mL/min/1.73 m^2 eGFR groups diverged from the >90 group. There was a higher range of dementia incidence by eGFR category than stroke at the end of follow-up. Fig S3b shows the RCS plot assessing the linearity between 2021 eGFRcr-cys and incident dementia.

In a crude model, participants with a 2021 eGFRcr-cys <60 mL/min/1.73 m^2 had a higher risk of incident dementia (HR [95% CI]: 7.41 [5.33-10.30]) (Table 2, model 1). The HRs were substantially attenuated after adjustment of covariates, but the HR for eGFR < 60 mL/min/1.73 m^2 remained statistically significant (HR [95% CI]: 1.73 [1.21-2.45]) in model 4. Each 15 mL/min/1.73 m^2 lower eGFR was associated with a modestly higher incidence of dementia (HR [95% CI]: 1.08 [1.00-1.18]) in model 4. Adjusting for UACR in model 5 did not change the findings from model 4; however, the effect estimates were attenuated for eGFR < 60 mL/min/1.73 m^2 in comparison with eGFR > 90 mL/min/1.73 m^2.

Dementia hospitalizations (n = 445) were more common than dementia deaths (n = 236) (Table S4). A significantly higher risk of dementia hospitalization for eGFR < 60 mL/min/1.73 m^2 (HR [95% CI]: 1.77 [1.20-

Table 2. The Association of 2021 eGFRcr-cys With Stroke and Dementia Incidence, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2018

	n/case	Crude Incidence Rate (95% CI) per 1,000 pyrs	Hazard Ratio (95% CI)				
			Model 1	Model 2	Model 3	Model 4	Model 5[a]
Stroke incidence							
eGFR, mL/min/1.73 m^2							
<60	160/15	9.35 (4.64-14.05)	3.27 (1.94-5.51)	1.59 (0.93-2.72)	1.32 (0.77-2.28)	1.30 (0.75-2.24)	1.11 (0.64-1.92)
60-90	1312/98	5.85 (4.70-7.01)	1.93 (1.52-2.44)	1.11 (0.86-1.43)	1.09 (0.85-1.41)	1.09 (0.84-1.40)	1.09 (0.84-1.41)
>90	5,174/236	3.13 (2.73-3.53)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
per 15-Unit lower	6,646/349	3.72 (3.33-4.11)	1.38 (1.27-1.51)	1.04 (0.94-1.16)	1.02 (0.91-1.13)	1.01 (0.91-1.13)	1.00 (0.90-1.11)
Dementia incidence							
eGFR, mL/min/1.73 m^2							
<60	160/40	24.86 (17.25-32.46)	7.41 (5.33-10.30)	2.06 (1.46-2.89)	1.85 (1.31-2.62)	1.73 (1.21-2.45)	1.65 (1.16-2.35)
60-90	1,312/206	12.27 (10.60-13.93)	3.09 (2.60-3.68)	1.11 (0.92-1.34)	1.09 (0.91-1.32)	1.08 (0.89-1.30)	1.08 (0.89-1.30)
>90	5,174/328	4.31 (3.85-4.78)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
per 15-Unit lower	6,646/574	6.08 (5.58-6.57)	1.79 (1.69-1.90)	1.13 (1.04-1.22)	1.10 (1.01-1.19)	1.08 (1.00-1.18)	1.08 (0.99-1.17)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate, mL/min/1.73 m^2; pyrs, person-years.
Notes: Cox regression survival models with time to stroke and dementia hospitalization and death were used for calculation of HR and corresponding 95% CI by 15-unit lower eGFR and eGFR groups. Model 1 was the crude model. Model 2 was adjusted for age, sex, race/ethnicity, and center. Model 3 further adjusted for diabetes, cholesterol, BMI, SBP, DBP, hypertension medication, and statin medication. Model 4 further adjusted for education, physical activity, cigarette use, and alcohol use. Model 5 further adjusted for UACR.
[a]Slight loss in sample size due n = 28 missing UACR information.

2.63]) but not dementia death (HR [95% CI]: 1.12 [0.63-2.01]) was detected in model 4 (Table S4).

Comparing old and new eGFR equations in association with stroke and dementia

Incidence rates and HRs adjusted for age, sex, and center for stroke and dementia using older equations of 2009 eGFRcr and 2012 eGFRcr-cys in African American and non-African American participants were compared with newer equations of 2021 eGFRcr and 2021 eGFRcr-cys in Table 3. We did not observe a meaningful difference between African American and non-African American participants across different eGFR equations. The difference of HRs for both stroke and dementia in the old compared with new equation of eGFRcr was larger than the difference in HRs in old and new calculations of eGFRcr-cys in African American participants. Both stroke and dementia HRs for 2021 eGFRcr < 60 mL/min/1.73 m^2 of African American participants trended toward non-African American participant HRs, which remained relatively constant. Although we found these differences in point estimates, confidence intervals were overlapping.

Table S5 compares stroke and dementia incidence in African American participants based on joint classification of older and new eGFR equations. In general, those who were reclassified into a worse category of kidney function by the 2021 eGFRcr equation had higher incidence rates than those who remained in the same category by both equations.

Sensitivity Analysis

Effect modification was not identified on the multiplicative scale for eGFR and stroke adjusting for age, race/ethnicity, sex, diabetes, and hypertension status. Effect modification on the multiplicative scale was identified for 2021 eGFRcr-cys with diabetes status and *APOE* e4 carrier status for incident dementia with results stratified accordingly in Table S6. No other effect modification for dementia was identified.

Table S7 examines the relationship between per 15 mL/min/1.73 m^2 lower 2021 eGFRcr-cys and eGFR category with cognitive function as a secondary endpoint to dementia. Significant associations were lacking between 15 mL/min/1.73 m^2 lower eGFRcr-cys and cognitive function. However, eGFRcr-cys of 60-90 mL/min/1.73 m^2 had a significant negative association with cognitive function with a parameter estimate of -0.11 and a *P* value of 0.04, suggesting that participants in this group had significantly worse cognitive function than those with eGFR > 90. The 2021 eGFRcr-cys < 60 mL/min/1.73 m^2 category had no significant relationship with cognitive function.

DISCUSSION

This analysis of a large multiethnic cohort using a new eGFRcr-cys equation from 2021, which does not include a

Table 3. Association of eGFR with Stroke and Dementia Incidence using Different eGFR Equations Stratified by Race, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2018

Equation	Race	N (N events)	Crude Incidence Rate (95% CI) per 1,000 pyrs	Adjusted Hazard Ratio (95% CI)			
				per 15-Unit Lower eGFR	eGFR < 60	eGFR 60-90	eGFR > 90
Stroke							
2009 eGFRcr	African American	1,820 (96)	3.89 (3.11-4.67)	1.10 (0.93-1.31)	1.50 (0.67-3.36)	1.28 (0.82-2.00)	1 (Reference)
2021 eGFRcr	African American	1,820 (96)	3.89 (3.11-4.67)	1.12 (0.92-1.36)	1.26 (0.59-2.67)	1.22 (0.77-1.93)	1 (Reference)
2009 eGFRcr	Non-African American	4,826 (253)	3.66 (3.21-4.11)	0.88 (0.75-1.03)	0.69 (0.41-1.16)	0.56 (0.42-0.76)	1 (Reference)
2021 eGFRcr	Non-African American	4,826 (253)	3.66 (3.21-4.11)	0.89 (0.76-1.04)	1.09 (0.63-1.89)	0.73 (0.55-0.97)	1 (Reference)
2012 eGFRcr-cys	African American	1,820 (96)	3.89 (3.11-4.67)	1.17 (0.98-1.39)	3.10 (1.40-6.84)	1.33 (0.81-2.17)	1 (Reference)
2021 eGFRcr-cys	African American	1,820 (96)	3.89 (3.11-4.67)	1.19 (0.99-1.43)	2.96 (1.35-6.49)	1.25 (0.77-2.02)	1 (Reference)
2012 eGFRcr-cys	Non-African American	4,826 (253)	3.66 (3.21-4.11)	0.95 (0.83-1.09)	1.18 (0.64-2.16)	0.80 (0.59-1.06)	1 (Reference)
2021 eGFRcr-cys	Non-African American	4,826 (253)	3.66 (3.21-4.11)	0.96 (0.84-1.10)	1.05 (0.49-2.26)	1.04 (0.77-1.41)	1 (Reference)
Dementia							
2009 eGFRcr	African American	1,820 (162)	6.50 (5.50-7.50)	1.07 (0.94-1.23)	1.55 (0.95-2.55)	0.89 (0.63-1.27)	1 (Reference)
2021 eGFRcr	African American	1,820 (162)	6.50 (5.50-7.50)	1.09 (0.94-1.26)	1.46 (0.88-2.41)	0.98 (0.66-1.45)	1 (Reference)
2009 eGFRcr	Non-African American	4,826 (412)	5.92 (5.35-6.49)	0.97 (0.86-1.10)	1.00 (0.68-1.46)	0.76 (0.58-0.99)	1 (Reference)
2021 eGFRcr	Non-African American	4,826 (412)	5.92 (5.35-6.49)	0.98 (0.97-1.10)	1.31 (0.89-1.94)	0.83 (0.67-1.03)	1 (Reference)
2012 eGFRcr-cys	African American	1,820 (162)	6.50 (5.50-7.50)	1.16 (1.02-1.32)	2.57 (1.51-4.38)	1.08 (0.76-1.55)	1 (Reference)
2021 eGFRcr-cys	African American	1,820 (162)	6.50 (5.50-7.50)	1.18 (1.03-1.35)	2.51 (1.48-4.26)	0.96 (0.67-1.38)	1 (Reference)
2012 eGFRcr-cys	Non-African American	4,826 (412)	5.92 (5.35-6.49)	1.10 (0.99-1.22)	1.65 (1.09-2.51)	1.12 (0.90-1.38)	1 (Reference)
2021 eGFRcr-cys	Non-African American	4,826 (412)	5.92 (5.35-6.49)	1.11 (1.00-1.23)	1.79 (1.13-2.83)	1.20 (0.97-1.49)	1 (Reference)

Abbreviations: CI, confidence interval; eGFRcr, estimated glomerular filtration rate using creatinine input; eGFRcr-cys, estimated glomerular filtration rate using creatinine and cystatin C inputs; pyrs, person-years.
Note: Models are adjusted for age, sex, and center.

coefficient for race, found that middle aged and older adults with eGFR < 60 mL/min/1.73 m^2 had a significant increased risk of incident dementia but not increased risk of incident stroke compared with adults with normal eGFR. HRs for stroke and dementia outcomes depend on a variety of factors including specific cut points used for classifying eGFR and covariates adjusted in the models. This study corroborates prior research that decreased eGFR is a risk factor for incident dementia with an eGFR < 60 mL/min/1.73 m^2 associated with a 73% increased risk of dementia compared with previous estimates which are around 50%.[5,6] Our analysis did not find a significant association between eGFR and stroke, which was an unexpected result. This contradicts recent research which has found that impaired eGFR is a risk factor for incident stroke; however, risk estimates of stroke can vary in significance and magnitude depending on sample size, eGFR measure used, and stroke subtype.[7]

We did not observe a sizable difference in eGFR category when comparing older versus newer equations of eGFRcr. Nevertheless, we found African American participants have a wider difference of HRs in both stroke and dementia outcomes in eGFRcr < 60 mL/min/1.73 m^2 compared with non-African American participants. HRs for African American participants with 2012 eGFRcr-cys < 60 mL/min/1.73 m^2 slightly decreased for both stroke and dementia in the new 2021 eGFRcr-cys calculation. Additionally, compared with non-African American participants, reclassification was more common for African American participants from higher categories of eGFR in 2009 eGFRcr and 2012 eGFRcr-cys to lower categories of eGFRcr and eGFRcr-cys in the 2021 equations. This movement in the context of our results highlight the implication that the 2021 eGFRcr and eGFRcr-cys equations (calculated without race) likely better reflect true GFR in African American populations by partially reversing the previous overestimation in the 2009 eGFRcr and 2012 eGFRcr-cys equations and obtain more precise HRs of stroke and dementia outcomes.

Older equations for eGFR have been found to overestimate eGFR in African American populations because of the inclusion of a race coefficient in the calculations, which is problematic because race is a sociation construct, not biological.[5] Its inclusion in old eGFR equations alongside established clinical variables of age, protein measures, and sex reifies race as a biological factor, which is a poor proxy for genetic ancestry and a remnant of racist science. Furthermore, uncertainty typically surrounds how a race coefficient is ascertained, whether it is self-reported, doctor or nurse best guess, or some other factor which results in clinical inconsistency. The overestimation of eGFR in the old calculations is illustrated in the stratified results of Cox regression analysis in Table 3, demonstrating that African American individuals had a higher risk of stroke and dementia outcomes in a categorized eGFR variable using 2009 eGFRcr and 2012 eGFRcr-cys compared with slightly lower HRs of stroke and dementia in the new 2021 eGFRcr and 2021 eGFRcr-cys calculations. These lower HRs are likely attributed to reclassifying participants who were previously above the <60 mL/min/1.73 m^2 cut point to below resulting in more participants with eGFR < 60. Although the new calculations of eGFR have minimal impact on point estimates of kidney function, these changes are imperative for people who are at or above the cut point of a kidney disease diagnosis. Having a lower eGFR, especially in African American individuals, is important for access to treatment. In previous calculations of eGFR, a person may not receive treatment for CKD if they are above the eGFR threshold for diagnosis.

Strengths of this study include a large sample size from a multi-ethnic population with stroke as an adjudicated endpoint enhancing the validity of this outcome. Limitations include ascertainment of dementia using ICD-9 and ICD-10 codes, which were not adjudicated in MESA. This method is known to be particularly problematic in African American populations because of disparities in access to care compared with other ethnic groups and may result in under-reporting of dementia in African American individuals. Furthermore, dementia diagnoses that were not associated with a hospitalization would have been missed which may have underestimated the associations. We found modest reclassification of eGFR comparing the older and newer equations of eGFR which limits the power of these analyses. In addition, only 2.4% of our sample had eGFR < 60 mL/min/1.73 m^2. This limited our ability to fully assess the impact of the newer eGFR equations on prediction of stroke and dementia in participants with impaired kidney function. Lastly, always possible are residual confounding because of errors in measurement of known confounders and omission of unknown confounders in the analyses.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1: Distribution of CKD risk categories using UACR and eGFRcr-cys among African American participants, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2002.

Figure S2: Kaplan-Meier curves for the association of 2021 eGFRcr-cys with stroke and dementia incidence, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2018.

Figure S3: Restricted cubic spline plots showing 2021 eGFRcr-cys and HR (95% CI) of stroke (A) and dementia (B) overlaid with the proportion of the population (%), Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2018.

Table S1: Variables Used in Each Equation to Estimate eGFR, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2018.

Table S2: ICD-9 and ICD-10 Codes Used for Ascertainment of Candidate Dementia Cases, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2018.

Table S3: Cross Tabulation of eGFR Categories According to Older and New Equations, Overall and by Race, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2002.

Table S4: The Association of 2021 eGFRcr-cys with Dementia Hospitalization and Dementia Deaths, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2018.

Table S5: Crude Stroke and Dementia Incidence Rates of African American Participants by eGFR through Joint Classification of Old and New Equations, Multi-Ethnic Study of Atherosclerosis (MESA), 2000-2018.

Table S6: The Association of 2021 eGFRcr-cys with Dementia Hospitalization and Mortality Incidence Stratified by Diabetes Status and Presence of APOE e4 Gene, Multiethnic Study of Atherosclerosis (MESA), 2000-2018.

Table S7: The Association of Baseline 2021 eGFRcr-cys on Cognition Score at Examination 5 Adjusted for Age, Sex, and Race, Multi-Ethnic Study of Atherosclerosis (MESA), eGFR from 2000-2002 and Cognition Scores from 2010-2011.

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