Cardiovascular Diabetology

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Prognostic impact of switching to the 2021 chronic kidney disease epidemiology collaboration creatinine-based equation in Caucasian patients with type 2 diabetes: the Renal Insufficiency and Cardiovascular events (RIACE) Italian Multicenter Study

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Abstract

Background A Chronic Kidney Disease (CKD) Epidemiology Collaboration (EPI) formula not including a Black race coefficient has been recently developed and is now recommended in the US. The new (2021) equation was shown to yield higher estimated glomerular filtration rate (eGFR) values than the old (2009) one in a non-Black general population sample, thus reclassifying a significant number of individuals to a better eGFR category. However, reclassified individuals were previously shown to have a lower risk of progression to end-stage kidney disease, but higher adjusted risks for all-cause death and morbidity and mortality from cardiovascular disease than those not reclassified. This study evaluated the prognostic impact of switching from the 2009 to the 2021 CKD-EPI equation in non-Black individuals with type 2 diabetes.

Methods The Renal Insufficiency And Cardiovascular Events (RIACE) was a prospective cohort study enrolling 15,773 Caucasian patients in 19 Italian centers in 2006–2008. Cardiometabolic risk profile, treatments, complications, and comorbidities were assessed at baseline and eGFR was calculated with the two equations. Vital status was retrieved on 31 October 2015 for 15,656 participants (99.3%).

Results With the 2021 equation, the eGFR value increased in all patients, except for 293 individuals with a 2009 eGFR ≥ 105 ml·min^{-1}·1.73 m^{-2}. The median difference was 4.10 ml·min^{-1}·1.73 m^{-2} and was higher in males, older individuals and those in the G2 category. Reclassification decreased the percentage of patients with reduced eGFR from 17.28 to 13.96% and with any CKD from 36.23 to 34.03%. Reclassified individuals had better cardiometabolic risk

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profile and lower prevalence of complications and use of medications than non-reclassified individuals. Risk of death versus the 2009 G1 category was lower for reclassified than non-reclassified participants in all eGFR categories and, particularly, in each 2009 eGFR category, though difference was significant only in the G4-G5 category. The Receiver Operator Characteristic curves were statistically, but not clinically different with the two equations.

Conclusion Changing from the 2009 to the 2021 CKD-EPI equation results in higher eGFR and lower CKD prevalence, with a lower risk of death in reclassified patients with an eGFR < 30 ml·min^{-1}·1.73 m^{-2}, but virtually no impact on mortality prediction.

Trial registration: ClinicalTrials.gov, NCT00715481, retrospectively registered 15 July, 2008.

Keywords All-cause mortality, Chronic kidney disease epidemiology collaboration equation, Estimated glomerular filtration rate, Race, Type 2 diabetes

Background

Glomerular filtration rate (GFR) is widely used for diagnostic, prognostic, and therapeutic purposes [1]. A GFR cut-off of 60 ml·min^{-1}·1.73 m^{-2} is in fact a criterion for diagnosing chronic kidney disease (CKD) and, on a population level, for calculating CKD incidence and prevalence. Moreover, GFR thresholds are used for nephrologist referral and dialysis or transplant planning as well as for clinical trial eligibility. The level of eGFR is also used for predicting risk of CKD progression to end-stage kidney disease (ESKD) and, in epidemiological studies, to assess the association with adverse renal and cardiovascular outcomes. Finally, GFR serves as a guide for medication initiation, discontinuation, and dosing as well as for utilization of contrast media for imaging procedures.

The gold standard for measuring GFR is plasma or urinary clearance of an exogenous filtration marker [2, 3], which however is a cumbersome procedure that cannot be routinely performed [4]. For this reason, several equations have been developed for estimating GFR from serum levels of endogenous filtration markers such a creatinine and cystatin C [5]. The currently recommended creatinine-based equation is the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [6], which estimates GFR using the variables age, sex, and race (Black versus non-Black), in addition to creatinine [7]. However, the evidence supporting the introduction of race as a correction factor for muscle mass has been questioned [8], and it is now widely accepted that race is a social, not a biological construct [9]. Therefore, the inclusion of this variable has been recently questioned [10, 11], leading to the development of a new (2021) CKD-EPI formula that does not include a race coefficient and includes refitted coefficients for age, sex and creatinine [12]. The 2021 CKD-EPI equation was shown to underestimate measured GFR in Blacks and to overestimate it in non-Blacks; moreover, in non-Blacks, bias versus measured GFR was larger than with the 2009 CKD-EPI equation [12]. Nevertheless, due to issues with inequities, the 2021 CKD-EPI equation has been recommended for immediate implementation in the US [13]. With the exception of UK [14], this has not yet been the case in Europe, where a much greater proportion of the population is non-Black, though the percentage of Black individuals is increasing due to the increasing migration flows [15].

A recent report from a Swedish general population sample, mostly consisting of non-black people, showed that changing from the 2009 to the 2021 CKD-EPI equation increased estimated GFR (eGFR), thus reclassifying a significant number of individuals to a better eGFR category and decreasing the prevalence of eGFR categories G3a-G5 from 5.1 to 3.8% [16]. However, reclassified individuals had a lower risk of progression to end-stage kidney disease (ESKD), but higher adjusted risks for all-cause death and morbidity and mortality from cardiovascular disease (CVD) than those who were not reclassified [16]. This might be a matter of concern as people reclassified to a better eGFR category would receive a less aggressive treatment despite a worse prognosis.

In the present analysis, we focused on people with type 2 diabetes, because there are virtually no data on this population that is at high risk for CKD and mortality. To this end, we used the Renal Insufficiency And Cardiovascular Events (RIACE) cohort of Caucasian individuals with type 2 diabetes for assessing the prognostic impact of estimating GFR with the 2021 CKD-EPI equation in a non-Black population. In particular, we evaluated the effect on CKD prevalence and staging, risk of death from any cause, and mortality prediction.

Methods

Design

The RIACE Italian Multicenter Study was an observational, prospective, cohort study on the impact of eGFR on morbidity and mortality in individuals with type 2 diabetes [17]. The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the ethics committees of participating centers. Participants provided an informed consent.

Participants

The RIACE enrolled 15,773 Caucasian patients with type 2 diabetes, consecutively attending 19 hospital-based, tertiary referral Diabetes Clinics of the National Health Service throughout Italy, most of them in the years 2006–2008 (first patients 6 October 2005 - last patient 17 December 2008). Exclusion criteria were dialysis or renal transplantation.

Baseline data

Baseline data were collected using a standardized protocol across participating centers; results from different laboratories/methods were standardized by comparison with values detected in test samples at the reference laboratory of the Coordinating Center [17].

Participants underwent a structured interview to collect the following information: current age, smoking status, known diabetes duration, severe co-morbidities, and current treatments including glucose-, lipid-, and blood pressure (BP)-lowering therapies.

Body mass index (BMI) was calculated from weight and height, whereas estimated waist circumference (eWC) was calculated from log-transformed BMI values [18]. Then, BP was measured with a sphygmomanometer with the patients seated with the arm at the heart level.

Hemoglobin A_{1c} (HbA_{1c}) was measured by HPLC using DCCT-aligned methods, whereas triglycerides and total and HDL cholesterol were determined in fasting blood samples by standard colorimetric enzymatic methods. Then, LDL cholesterol concentration was estimated using the Friedewald formula.

The presence of CKD was assessed by measuring albuminuria and serum creatinine, as previously detailed [17, 19]. Briefly, albumin excretion rate (AER) was obtained from 24-hour urine collections or calculated from albumin-to-creatinine ratio in early-morning, first-voided urine samples; albumin concentration in urines was measured by immunonephelometry or immunoturbidimetry, in the absence of interfering clinical conditions. Serum (and urine) creatinine was measured by the modified Jaffe method, traceable to IDMS, and GFR was estimated using both the 2009 [7] and the 2021 [12] CKD-EPI equations (Table S1). Based on albuminuria and eGFR values, participants were then stratified according to the Kidney Disease Improving Global Outcomes (KDIGO) classification [6, 20].

The presence of diabetic retinopathy (DR) was assessed in each center by an expert ophthalmologist by dilated fundoscopy [21]. Patients were then classified as having no DR, non-advanced DR (including mild or moderate non-proliferative DR), or advanced DR (including severe non-proliferative DR, proliferative DR, or diabetic macular edema). DR grade was assigned based on the worse eye.

Previous major adverse CVD events, including myocardial infarction, stroke, foot ulcer, gangrene and non-traumatic amputation, and cerebrovascular, carotid, and lower limb revascularization, were adjudicated based on hospital discharge records by an ad hoc committee in each center [22].

All-cause mortality

The vital status of study participants on 31 October 2015 was verified by interrogating the Italian Health Card database (http://sistemats1.sanita.finanze.it/wps/portal/), which provides updated and reliable information on all current Italian residents [23].

Statistical analysis

Data are expressed as mean ± SD or median (interquartile range) for continuous variables, and number of cases (percentage) for categorical variables. For continuous variables, the Kolmogorov-Smirnov test was used to determine if variables were normally distributed; if not, logarithmic conversion was performed before regression analyses. Continuous variables were compared using the Student's t-test (or one-way ANOVA) and Mann-Whitney test (or Kruskal-Wallis's test) for parametric and non-parametric data, respectively, whereas the χ^2 test was applied to categorical variables. None of the variables had missing values.

The eGFR distributions for the two equations were calculated in the whole cohort and in pre-specified subgroups using kernel density estimation, a nonparametric technique that provides a better estimation of the probability density function than traditional histogram [24]. Since the coefficients of age, sex and creatinine differ between the two equations, their influence on eGFR increase was assessed by calculating for each individual the eGFR change (ΔeGFR) from the 2009 to the 2021 CKD-EPI equation and plotting it against age, sex and the 2009 eGFR level. The level of agreement between the two equations were estimated using Bland-Altman plots, Lin's concordance correlation, and linear weighted Cohen's kappa.

The number and percentage of participants in each eGFR and KDIGO category with the 2009 CKD-EPI equation that were reclassified with the 2021 CKD-EPI equation to another rGFR category were then calculated. As nobody was reclassified to a worse eGFR category, the term "reclassified" is hereinafter used for "reclassified to a better eGFR category. The baseline clinical features of reclassified versus non-reclassified participants were compared either in the whole cohort (excluding individuals falling in the G1 category, who could not be reclassified to a better eGFR category) or separately in those with a 2009 eGFR 60–90 or <60 ml·min^{-1}·1.73m^{-2}.

For survival analysis, the index date was the date of the baseline visit when participants were enrolled into the study and the end of follow-up was the date of the census (31 October 2015) or, for those who died, the date of death. Kaplan-Meier survival probabilities for all-cause mortality were estimated for reclassified and non-reclassified participants in each eGFR category and differences were analyzed with the Log rank statistic. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated by Cox proportional hazards regression with backward selection of variables, separately for reclassified and non-reclassified participants in each eGFR category, using the 2009 G1 category as reference. The backward variable selection method was chosen to reduce the chances of overfitting the data and make the linear regression model more interpretable. These analyses were unadjusted (model 1) or adjusted for baseline age (model 2) or age and other CVD risk factors (i.e., sex, smoking status, diabetes duration, HbA_{1c}, BMI, triglycerides, total and HDL cholesterol, systolic and diastolic BP, anti-hyperglycemic, lipid-lowering, and anti-hypertensive treatment) and complications/comorbidities (albuminuria, DR grade, any CVD, and any comorbidity) (model 3). The analyses were repeated for reclassified versus non-reclassified participants in each eGFR category and further adjusted for the 2009 CKD-EPI eGFR level on top of model 2 (model 2a) and 3 (model 3a). Finally, Cox proportional hazards regression analyses according to KDIGO categories were run separately for the 2009 and 2021 CKD-EPI equations, using the category G1A1a as reference and adjusting as in models 1–3 (except for albuminuria); the G2 category was split in G2a and G2b (75–89 and 60–74 $ml{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$, respectively), as previously reported [20].

Receiver Operator Characteristic (ROC) curves were plotted and areas under ROC curves were calculated, using all-cause mortality at the end of follow-up as dependent variable and the CKD-EPI 2009 or 2021 eGFR values (as continuous variables) as predictors. Moreover, the Youden's J statistic was used to assess the cut-off point with the maximum "J" index, where J = sensitivity + specificity – 100.

Tests were two sided, and a p value < 0.05 was considered statistically significant. Data entry and statistical analyses were performed using SPSS version 26.0 (SPSS, Chicago, IL, USA) and MedCalc version 22.014 (MedCalc Software Ltd, Ostend, Belgium).

Results

Level and distribution of eGFR

The distributions of eGFR using the 2009 and 2021 CKD-EPI creatinine-based equations are shown in Figure S1; values with both equations were not normally distributed (Kolmogorov-Smirnov test, $p < 0.0001$). The use of the 2021 equation resulted in a statistically significant higher eGFR compared with the 2009 equation, with a median ΔeGFR of 4.1 $ml{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ (Table S2), and a correlation coefficient r of 0.998 ($p < 0.0001$). With the 2021 equation, all participants with a 2009 eGFR level $< 105\ ml{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ had a higher eGFR value, whereas among the 1,373 with a 2009 eGFR level $\geq 105\ ml{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$, 293 (21.3%) had a lower eGFR value (Fig. 1). Density distributions were similar in males and females, with larger ΔeGFR in males; moreover, ΔeGFR was smallest in younger individuals and those with a 2009 eGFR $< 30\ ml{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ (G4-5) and largest for older individuals and those with a 2009 eGFR of 60–89 $ml{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ (G2) (Table S2). Limits of agreement with Bland-Altman analysis were 1.14–6.54 $ml{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ and varied according to sex and age and eGFR categories; moreover, rho and κ were 0.98, and 0.83, indicating a substantial and strong agreement, respectively, and remained in these ranges in most subgroups (not shown).

CKD prevalence and staging

A total of 2,431 individuals (15.5%) in the whole cohort and 753 individuals (27.8%) among those with an eGFR $< 60\ ml{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ (G3a-5) were reclassified with the 2021 CKD-EPI equation (Table 1). The extent of reclassification was lowest from G4-5 to G3b category (19.7%) and highest from G3a to G2 category (31.3%). As 521 individuals were upgraded to G2, the number of participants with an eGFR $< 60\ ml{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$ decreased from 2,706 (17.28%) to 2,185 (13.96%). Reclassified participants were only slightly younger, more frequently males, and had shorter diabetes duration, lower HbA_{1c}, BMI, eWC, triglycerides, non-HDL cholesterol, albuminuria, and prevalence of dyslipidemia, hypertension, insulin, lipid lowering, anti-hypertensive, anti-coagulant, and anti-platelet treatment, advanced DR, CVD (any and by vascular bed), and higher HDL cholesterol and, by definition, eGFR (Table 2). Distribution of participants with the two equations and reclassification with the 2021 formula across KDIGO categories are shown in Fig. 2 and Table S3, respectively. The extent of reclassification was lowest from G4-5A1b to G3bA1b (11.9%) and highest from G3aA1b to G2A1b (37.1%). Since 344 individuals were upgraded from G3aA1 to G2A1, the number of participants with any CKD decreased from 5,672 (36.23%) to 5,328 (34.03%) and that of participants at very high risk from 794 (5.1%) to 678 (4.3%).

Risk of death from any cause and mortality prediction

As previously reported, valid information on vital status was retrieved for 15,656 participants (99.3%); of these individuals, 12,054 (76.99%) were alive, whereas 3,602 (23.01%) had deceased (follow-up duration: 7.42 ± 2.05

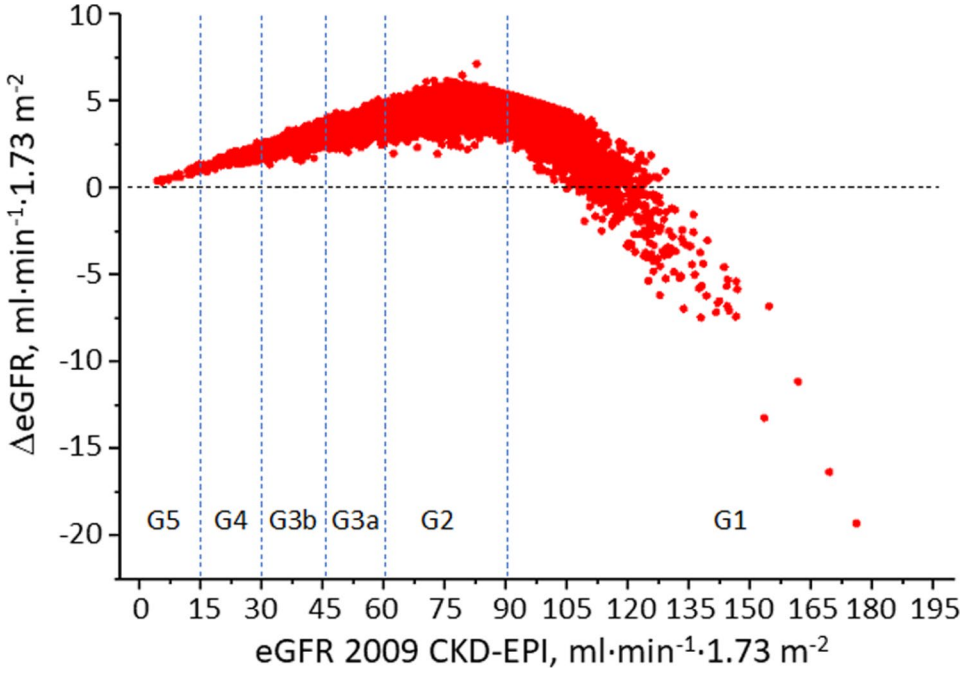


Fig. 1 ΔeGFR between the 2009 to the 2021 CKD-EPI equation in each participant. ΔeGFR = eGFR change

Table 1 Reclassification of participants across eGFR categories with the 2021 CKD-EPI eGFR equation

eGFR categories with the 2009 CKD-EPI equation (ml·min^{-1}·1.73 m^{-2})	eGFR categories with the 2021 CKD-EPI equation (ml·min^{-1}·1.73 m^{-2})					Total
	G1 ≥ 90	G2 60–89	G3a 45–59	G3b 30–44	G4-5 < 30	
G1 ≥ 90	5,776 (100)					5,776 (36.9)
G2 60–89	**1,678 (23.4)**	5,496 (76.5)				7,174 (45.8)
G3a 45–59		**521 (31.3)**	1,146 (68.8)			1,667 (10.6)
G3b 30–44			**177 (23.3)**	583 (76.7)		760 (4.9)
G4-5 < 30				**55 (19.7)**	224 (80.3)	279 (1.8)
Total	7,454 (47.6)	6,017 (38.4)	1,323 (8.5)	638 (4.1)	224 (1.4)	15,656 (100)
Reclassifed		1,678 (23.4)	753 (27.8)	753 (27.8)		

Data are expressed as number of cases (percentage) of reclassified (black cells) and non-reclassified (white cells) participants in each 2009 eGFR category and among individuals with a 2009 eGFR 60–89 and < 60 ml·min^{-1}·1.73 m^{-2}. eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

years; death rate: 31.02 per 1,000 person-years [20, 25]. When using the 2009 G1 category as reference, the HR for reclassified participants was lower than that for non-reclassified participants in each 2009 eGFR category (Table S4). When using each 2009 eGFR category as reference, risk of death was lower for reclassified versus non-reclassified individuals in all categories, though difference was significant only in the G4-G5 category (Table 3). When mortality risk was analyzed according to KDIGO categories, a significantly higher risk was observed in patients with normal or mildly increased albuminuria (A1a and A1b, respectively) only for a 2009 eGFR < 60 ml·min^{-1}·1.73 m^{-2}. In contrast, when using the 2021 CKD-EPI equation, the HR was significantly higher also in the G2bA1b category, i.e., in participants with an eGFR < 75 ml·min^{-1}·1.73 m^{-2} and an AER 10–29 mg/24 h (Fig. 3). There was a statistically, but not clinically significant difference between the areas under the curve with the two equations, with similar Jouden's J statistic (Fig. 4).

Table 2 Clinical features of reclassified and non-reclassified individuals with the 2021 CKD-EPI eGFR equation

Variable	eGFR with the 2009 CKD-EPI equation								
	< 90 ml·min^{-1}·1.73 m^{-2} (G2-G5; *n* = 9,880)			60–89 ml·min^{-1}·1.73 m^{-2} (G2; *n* = 7,174)			< 60 ml·min^{-1}·1.73 m^{-2} (G3a-G5; *n* = 2,706)		
	Reclassified	Non-reclassified	*p*	Reclassified	Non-reclassified	*p*	Reclassified	Non-reclassified	*p*
n (%)	2,431 (24.6)	7,449 (75.4)		1,678 (23.4)	5,496 (76.6)		753 (27.8)	1,953 (72.2)	
Age, years	70.2 ± 8.2	70.6 ± 9.1	< 0.0001	68.6 ± 7.5	69.5 ± 8.9	< 0.0001	74.0 ± 8.30	73.8 ± 8.7	0.586
Gender, n (%)			0.005			0.041			0.007
Females	1,008 (41.5)	3,334 (44.8)		663 (39.5)	2,326 (42.3)		345 (45.8)	1,008 (51.6)	
Males	1,423 (58.5)	4,115 (55.2)		1,015 (60.5)	3,170 (57.7)		408 (54.2)	945 (48.4)	
Smoking status, n (%)			0.270			0.335			0.452
Never	1,378 (56.7)	4,317 (58.0)		949 (56.6)	3,156 (57.4)		429 (57.0)	1,161 (59.4)	
Former	731 (30.1)	2,234 (30.0)		491 (29.3)	1,637 (29.8)		240 (31,9)	597 (30.6)	
Current	322 (13.2)	808 (12.0)		238 (14.2)	703 (12.8)		84 (11.2)	105 (10.0)	
Diabetes duration, years	14.6 ± 10.6	15.1 ± 10.7	0.032	13.4 ± 10.0	14.3 ± 10.4	0.001	17.1 ± 11.3	17.3 ± 11.1	0.788
HbA_{1c}, %	7.47 ± 1.41	7.58 ± 1.48	0.002	7.40 ± 1.36	7.53 ± 1.45	0.001	7.65 ± 1.51	7,72 ± 1.56	0.242
(mmol·mol^{-1})	(58.2 ± 15.5)	(59.4 ± 16.2)		(57.3 ± 14.9)	(58.8 ± 15.8)		(60.1 ± 16.5)	(60.9 ± 17.1)	
BMI, kg 2^{-2}	28.5 ± 4.7	28.9 ± 5.0	< 0.0001	28.40 ± 4.70	28.81 ± 4.91	0.002	28.68 ± 4.78	29.29 ± 5.19	0.006
eWC, cm	101.6 ± 9.6	102.4 ± 10.0	< 0.0001	101.4 ± 9.7	102.2 ± 9.9	0.006	101.8 ± 9.6	102.9 ± 10.4	0.011
Triglycerides, mmol·l^{-1}	1.29 (0.93–1.79)	1.37 (1.00-1.94)	< 0.0001	1.22 (0.89–1.70)	1.33 (0.96–1.84)	< 0.0001	1.45 (1.07–2.01)	1.53 (1.14–2.17)	0.005
Total cholesterol, mmol·l^{-1}	4.74 ± 0.97	4.77 ± 0.99	0.145	4.72 ± 0.95	4.77 ± 0.97	0.063	4.78 ± 1.02	4.78 ± 1.06	0.968
HDL cholesterol, mmol·l^{-1}	1.30 ± 0.35	1.28 ± 0.35	0.041	1.32 ± 0.35	1.30 ± 0.35	0.016	1.25 ± 0.36	1.23 ± 0.36	0.420
Non-HDL cholesterol, mmol·l^{-1}	3.44 ± 0.93	3.49 ± 0.95	0.020	3.40 ± 0.92	3.47 ± 0.93	0.004	2.77 ± 0.84	2.74 ± 0.84	0.409
LDL cholesterol, mmol·l^{-1}	2.76 ± 0.85	2.77 ± 0.85	0.878	2.76 ± 0.84	2.78 ± 0.84	0.518	3.53 ± 0.96	3.55 ± 1.00	0.752
Dyslipidaemia, n (%)	1,955 (80.4)	6,241 (83.8)	< 0.0001	1,331 (79.3)	4,605 (83.8)	< 0.0001	624 (82.9)	1,636 (83.8)	0.572
Systolic BP, mmHg	139.4 ± 17.9	139.5 ± 18.5	0.864	139.2 ± 17.4	139.5 ± 18.2	0.570	139.9 ± 19.0	139.5 ± 19.3	0.636
Diastolic BP, mmHg	78.3 ± 9.4	78.4 ± 9.5	0.679	78.6 ± 9.2	78.7 ± 9.4	0.752	77.6 ± 9.7	77.5 ± 10.0	0.855
Pulse pressure, mmHg	61.1 ± 15.7	61.1 ± 16.3	0.961	60.6 ± 15.2	60.8 ± 15.9	0.635	62.4 ± 16.9	62.1 ± 17.2	0.671
Hypertension, n (%)	2,110 (86.8)	6,648 (89.2)	0.001	1,417 (84.4)	4,801 (87.4)	0.002	693 (92.0)	1,847 (94.6)	0.014
Anti-hyperglycaemic treatment, n (%)			0.001			0.036			< 0.0001
Lifestyle only	317 (13.0)	948 (12.7)		232 (13.8)	780 (14.2)		85 (11.3)	168 (8.6)	
Non-insulin	1,526 (62.8)	4,412 (59.2)		1,097 (65.4)	3,418 (62.2)		429 (57.0)	994 (50.9)	
Insulin	588 (22.5)	2,089 (28.0)		349 (20.8)	1,298 (23.6)		239 (31.7)	791 (40.5)	
Lipid-lowering treatment, n (%)	1,142 (47.0)	3,749 (50.3)	0.004	741 (44.2)	2,673 (48.6)	0.001	401 (53.3)	1,076 (55.1)	0.389
Anti-hypertensive treatment, n (%)	1,806 (74.3)	5,856 (78.6)	< 0.0001	1,177 (70.1)	4,099 (74.6)	< 0.0001	629 (83.5)	1757 (90.0)	< 0.0001
Anti-platelet treatment, n (%)	1,052 (43.3)	3,432 (46.1)	0.016	667 (39.7)	2,336 (42.5)	0.045	385 (51.1)	1,096 (56.1)	0.019
Anti-coagulant treatment, n (%)	116 (4.8)	439 (5.9)	0.037	48 (2.9)	263 (4.8)	0.001	68 (9.0)	176 (9.0)	0.988
Albuminuria, mg/24 hours	14.0 (7.0-34.6)	15.0 (6.9–42.3)	0.020	12.3 (6.5–27.0)	12.9 (6.2–30.0)	0.204	20.6 (9.5–77.5)	27.0 (9.8-119.6)	0.002

Table 2 (continued)

Variable	eGFR with the 2009 CKD-EPI equation								
	< 90 ml·min^{-1}·1.73 m^{-2} (G2-G5; *n* = 9,880)			60–89 ml·min^{-1}·1.73 m^{-2} (G2; *n* = 7,174)			< 60 ml·min^{-1}·1.73 m^{-2} (G3a-G5; *n* = 2,706)		
	Reclassified	Non-reclassified	*p*	Reclassified	Non-reclassified	*p*	Reclassified	Non-reclassified	*p*
Serum creatinine, µmol/l	87.0 ± 34.1	98.8 ± 37.9	< 0.0001	74.7 ± 10.2	86.0 ± 12.3	< 0.0001	112.2 ± 38.4	134.5 ± 57.5	< 0.0001
eGFR (2009 CKD-EPI), ml·min^{-1}·1.73 m^{-2}	76.7 ± 17.0	65.9 ± 15.8	< 0.0001	87.5 ± 1.5	73.9 ± 7.12	< 0.0001	52.6 ± 9.0	43.4 ± 10.9	< 0.0001
eGFR (2021 CKD-EPI), ml·min^{-1}·1.73 m^{-2}	81.2 ± 17.6	70.0 ± 16.6	< 0.0001	92.4 ± 1.4	78.4 ± 7.4	< 0.0001	56.2 ± 9.6	46.4 ± 11.6	< 0.0001
DR, n (%)			0.021			0.512			0.001
No	1,871 (77.0)	5,591 (75.1)		1,324 (78.9)	4,294 (78.1)		547 (72.64)	1,297 (66.41)	
Non-advanced	333 (13.7)	1,013 (13.6)		215 (12.8)	696 (12.7)		118 (15.67)	317 (16.23)	
Advanced	227 (9.3)	845 (11.3)		139 (8.3)	506 (9.2)		88 (11.69)	339 (17.36)	
CVD, n (%)									
Any	585 (24.1)	2,160 (29.0)	< 0.0001	325 (19.4)	1,363 (24.8)	< 0.0001	260 (34.5)	797 (40.8)	0.003
Acute myocardial infarction	281 (11.6)	1,047 (14.1)	0.002	152 (9.1)	658 (12.0)	0.001	129 (17.1)	389 (19.9)	0.099
Coronary revascularization	238 (9.8)	930 (12.5)	< 0.0001	130 (7.7)	588 (10.7)	< 0.0001	108 (14.3)	342 (17.5)	0.047
Any coronary event	381 (15.7)	1,424 (19.1)	< 0.0001	210 (12.5)	895 (16.3)	< 0.0001	171 (22.7)	529 (27.1)	0.020
Stroke	88 (3.6)	326 (4.4)	0.106	48 (2.9)	207 (3.8)	0.079	40 (5.3)	119 (6.1)	0.439
Carotid revascularization	134 (5.5)	543 (7.3)	0.003	57 (3.4)	325 (5.9)	< 0.0001	77 (10.2)	218 (11.2)	0.484
Any cerebrovascular event	210 (8.6)	815 (10.9)	0.001	102 (6.1)	500 (9.1)	< 0.0001	108 (14.3)	315 (16.1)	0.251
Ulcer/gangrene/amputation	84 (3.5)	343 (4.6)	0.021	42 (2.5)	190 (3.5)	0.053	42 (5.6)	153 (7.8)	0.042
Lower limb revascularization	81 (3.3)	293 (3.9)	0.177	37 (2.2)	167 (3.0)	0.072	44 (5.8)	126 (6.5)	0.559
Any peripheral event	151 (6.2)	559 (7.5)	0.032	74 (4.4)	325 (5.9)	0.019	77 (10.2)	234 (12.0)	0.199
Comorbidities, n (%)									
Any	456 (18.8)	1,398 (18.8)	0.991	297 (17.7)	953 (17.3)	0.734	159 (21.1)	445 (22.8)	0.350
COPD	110 (4.5)	365 (4.9)	0.453	63 (3.8)	213 (3.9)	0.821	47 (6.2)	152 (7.8)	0.169
Liver disease	209 (8.6)	646 (8.7)	0.909	139 (8.3)	455 (8.3)	0.995	70 (9.3)	191 (9.8)	0.702
Cancer	177 (7.3)	554 (7.4)	0.798	120 (7.2)	390 (7.1)	0.938	57 (7.6)	164 (8.4)	0.481

Data are expressed as mean ± SD or median (interquartile range), for continuous variables, and number of cases (percentage), for categorical variables. eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; HbA_{1c} = haemoglobin A_{1c}; BMI = body mass index; eWC = estimated waist circumference; BP = blood pressure; DR = diabetic retinopathy; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease

Discussion

This study analyzed the impact of switching from the 2009 to the 2021 CDK-EPI equation for estimating GFR in the non-Black cohort of people with type 2 diabetes from the RIACE Italian Multicenter Study. On the one hand, it confirmed that, in these individuals, the new, no-race formula yield higher eGFR values than the old one and, hence, reclassifies a significant number of them to a better eGFR category with consequent reduction of the proportion of those with impaired eGFR or any CKD. On the other hand, this analysis provided important new information on the prognostic implications of using the new CKD-EPI equation in a non-Black population of individuals with type 2 diabetes.

The 4.1 ml·min^{-1}·1.73 m^{-2} median increase in eGFR, with higher increments in males, older individuals and those in the G2 category, is consistent with the 3.9 ml·min^{-1}·1.73 m^{-2} median increase, with similar differences across subgroups, reported in a Swedish, predominantly White general population sample [16].

A

eGFR, ml/min/1.73 m²			AER, mg/24h			
			A1a	A1b	A2	A3
			<10	10-29	30-299	≥300
G1	≥90		2,410 (15.4)	2,154 (13.8)	1,072 (6.8)	140 (0.9)
G2	60-89		2,889 (18.5)	2,531 (16.2)	1,527 (9.8)	227 (1.4)
G3a	45-59		513 (3.3)	523 (3.3)	504 (3.2)	127 (0.8)
G3b	30-44		152 (1.0)	220 (1.4)	261 (1.7)	127 (0.8)
G4-5	<30		26 (0.2)	42 (0.3)	101 (0.6)	110 (0.7)

KDIGO risk categories	
Low	9,984 (63.8)
Moderate	3,635 (23.2)
High	1,243 (7.9)
Very high	794 (5.1)

B

eGFR, ml/min/1.73 m²			AER, mg/24h			
			A1a	A1b	A2	A3
			<10	10-29	30-299	≥300
G1	≥90		3,092 (19.7)	2,769 (17.7)	1,416 (9.0)	177 (1.1)
G2	60-89		2,357 (15.1)	2,110 (13.5)	1,317 (8.4)	233 (1.5)
G3a	45-59		401 (2.6)	388 (2.5)	429 (2.7)	105 (0.7)
G3b	30-44		123 (0.8)	166 (1.1)	228 (1.5)	121 (0.8)
G4-5	<30		17 (0.1)	37 (0.2)	75 (0.5)	95 (0.6)

KDIGO risk categories	
Low	10,328 (66.0)
Moderate	3,522 (22.5)
High	1,128 (7.2)
Very high	678 (4.3)

Fig. 2 Distribution of participants across KDIGO categories with eGFR calculated with the 2009 (**A**) and the 2021 (**B**) CKD-EPI equations. KDIGO = Kidney Disease Improving Global Outcomes; eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

Table 3 Numbers and percentages of deaths, Kaplan-Meier estimates, and hazard ratios for all-cause mortality for non-reclassified and reclassified participants with the 2021 CKD-EPI eGFR equation by Cox proportional hazards regression with backward selection of variables using the by Cox proportional hazards regression with backward selection of variables for all-cause mortality for non-reclassified versus reclassified participants with the 2021 CKD-EPI eGFR equation using the corresponding 2009 CKD-EPI eGFR category as reference

eGFR category	*n*	Deaths *n* (%)	Kaplan-Meier log rank, *p*	Cox proportional hazards regression with backward selection of variables Hazard ratio (95% confidence interval) and *p* value				
				Model 1	Model 2	Model 2a	Model 3	Model 3a
G2	1,678 vs. 5,496	341 (20.3%) vs. 1312 (23.9%)	9.009 $p=0.003$	0.83 (0.74–0.94) $p=0.003$	0.96 (0.85–1.09) $p=0.524$	1.08 (0.92–1.26) $p=0.362$	0.98 (0.87–1.11) $p=0.796$	1.04 (0.89–1.22) $p=0.616$
G3a	521 vs. 1,146	186 (35.7%) vs. 466 (41.7%)	3.881 $p=0.049$	0.84 (0.71–0.99) $p=0.049$	0.84 (0.71–0.99) $p=0.049$	1.23 (0.94–1.61) $p=0.136$	0.89 (0.75–1.06) $p=0.190$	1.18 (0.90–1.56) $p=0.229$
G3b	177 vs. 583	95 (53.7%) vs. 339 (58.1%)	0.666 $p=0.414$	0.91 (0.72–1.14) $p=415$	0.86 (0.68–1.07) $p=0.177$	0.99 (0.73–1.35) $p=0.945$	0.95 (0.75–1.20) $p=0.661$	1.03 (0.75–1.43) $p=0.836$
G4-5	55 vs. 224	24 (43.6%) vs. 163 (72.8%)	11.604 $p<0.0001$	0.48 (0.31–0.74) $p<0.0001$	0.45 (0.29–0.69) $p<0.0001$	0.60 (0.37–0.97) $p=0.039$	0.44 (0.28–0.71) $p<0.0001$	0.56 (0.33–0.95) $p=0.031$

Model 1: not adjusted; model 2: adjusted for age; model 3: further adjusted for CVD risk factors and complications/comorbidities, i.e., age, sex, smoking status, diabetes duration, HbA_{1c}, BMI, triglycerides, total cholesterol and HDL-cholesterol, systolic and diastolic BP, anti-hyperglycemic, lipid-lowering, and anti-hypertensive treatment, albuminuria categories, DR grade, any CVD, and any comorbidity; model 2a: adjusted as in model 2 plus the 2009 CKD-EPI eGFR level; model 3a: adjusted as in model 3 plus 2009 CKD-EPI eGFR level. CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; HbA_{1c} = haemoglobin A_{1c}; BMI = body mass index; BP = blood pressure; DR = diabetic retinopathy; CVD = cardiovascular disease

Another study in adult people with CKD from British Columbia, Canada reported a lower increase in eGFR (2.7 ml·min^{-1}·1.73 m^{-2}) [26], which however is similar to that observed in Jordanian individuals with type 2 diabetes (2.1 ml·min^{-1}·1.73 m^{-2}) [27] and in the RIACE participants with CKD. The extent of reclassification is also similar to that reported in individuals with diabetes in the Jordanian (20%) and the Swedish study (15.5% and 27.8% versus 15.3% and 32.4% of all participants and those with an eGFR < 60 ml·min^{-1}·1.73 m^{-2}, respectively), though different from that observed in the whole Swedish cohort (9.9% and 36.2%, respectively) [16] and in Jordanian individuals with type 2 diabetes (2.1 ml·min^{-1}·1.73 m^{-2}) [27]. Likewise, the 3.3% reduction in the prevalence of eGFR < 60 ml·min^{-1}·1.73 m^{-2} is almost identical to that reported in the diabetic subgroup in the Swedish study (3.2%) [16], but higher than that observed in non-Black individuals from the general population, ranging from 1.3% [16, 28] to 1.6% [12], likely due to the higher burden from CKD in people with diabetes.

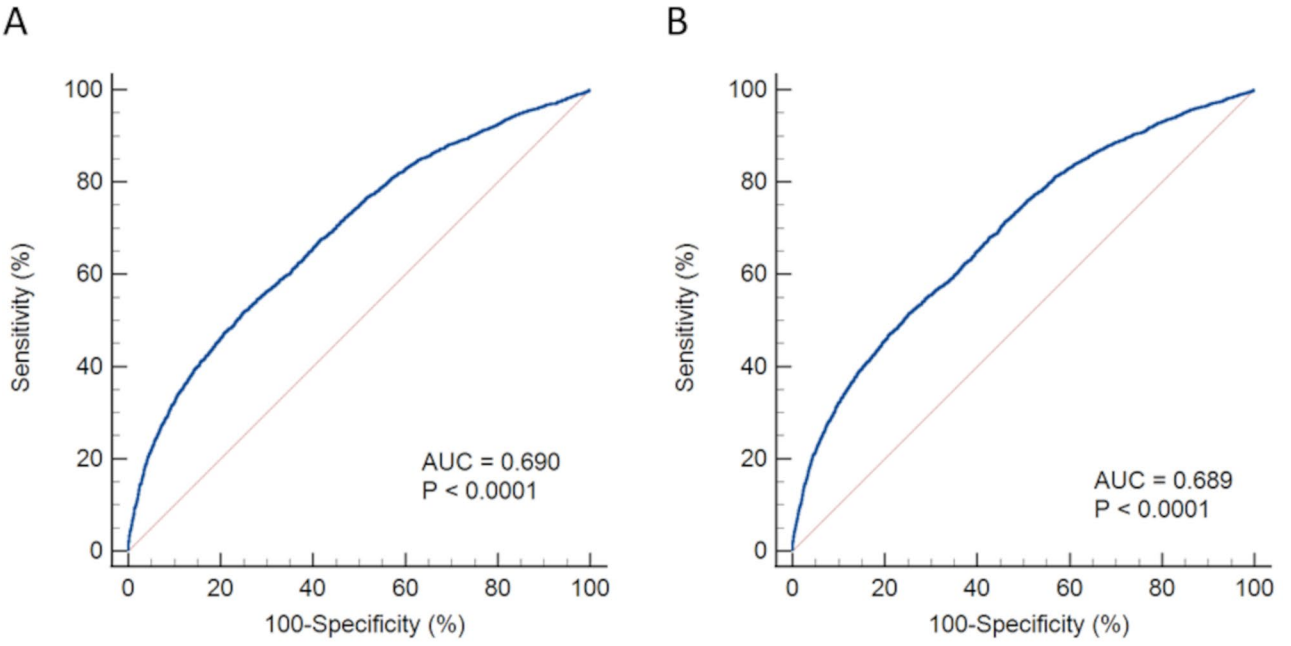
A

eGFR, ml/min/1.73 m²			AER, mg/24h			
			A1a	A1b	A2	A3
			<10	10-29	30-299	≥300
	G1	≥90	1 (Ref)	0.943 (0.785 – 1.132) p=0.527	1.293 (1.062 – 1.574) p=0.010	2.240 (1.580 – 3.175) p<0.0001
	G2	75-89	0.797 (0.666 – 0.954) p=0.013	1.058 (0.891 – 1.256) p=0.520	1.331 (1.106 – 1.600) p=0.002	2.307 (1.690 – 3.149) p<0.0001
	G2b	60-74	1.005 (0.834 – 1.212) p=0.955	1.070 (0.889 – 1.289) p=0.472	1.403 (1.160 – 1.696) p<0.0001	1.733 (1.251 – 2.401) p<0.0001
	G3a	45-59	1.331 (1.084 – 1.636) p=0.006	1.378 (1.129 – 1.681) p=0.002	1.409 (1.157 – 1.716) p<0.0001	2.130 (1.606 – 2.826) p<0.0001
	G3b	30-44	1.791 (1.357 – 2.362) p<0.0001	2.193 (1747 – 2.754) p<0.0001	2.048 (1.652 – 2.539) p<0.0001	2.726 (2.092 – 3.551) p<0.0001
	G4-5	<30	1.615 (0.878 – 2.973) p=0.123	2.116 (1.408 – 3.180) p<0.0001	2.680 (2.015 – 3.566) p<0.0001	4.647 (3.578 – 6.036) p<0.0001

B

eGFR, ml/min/1.73 m²			AER, mg/24h			
			A1a	A1b	A2	A3
			<10	10-29	30-299	≥300
	G1	≥90	1 (Ref)	1.068 (0.919 – 1.241) p=0.390	1.425 (1.212 – 1.675) p<0.0001	2.340 (1.746 – 3.137) p<0.0001
	G2	75-89	0.906 (0.766 – 1.072) p=0.252	1.155 (0.983 – 1.357) p=0.079	1.445 (1.214 – 1.718) p<0.0001	2.175 (1.603 – 2.951) p<0.0001
	G2b	60-74	1.169 (0.976 – 1.401) p=0.091	1.215 (1.022 – 1.445) p=0.028	1.472 (1.228 – 1.764) p<0.0001	2.220 (1.642 – 3.003) p<0.0001
	G3a	45-59	1.539 (1.257 – 1.884) p<0.0001	1.608 (1318 – 1.967) p<0.0001	1.737 (1.445 – 2.088) p<0.0001	2.275 (1.697 – 3,049) p<0.0001
	G3b	30-44	1.865 (1.395 – 2.493) p<0.0001	2.507 (1.989 – 3.161) p<0.0001	1.984 (1.600 – 2.459) p<0.0001	3.294 (2.558 – 4.242) p<0.0001
	G4-5	<30	3.274 (1.683 – 6.368) p<0.0001	2.261 (1.483 – 3.448) p<0.0001	4.183 (3.125 – 5.598) p<0.0001	5.006 (3.850– 6.507) p<0.0001

Fig. 3 Survival analysis by Cox proportional hazard regression, adjusted for multiple confounders, according to KDIGO risk categories and subcategories using the eGFR values calculated with the 2009 (**A**) and the 2021 (**B**) CKD-EPI equations. KDIGO = Kidney Disease Improving Global Outcomes; eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration



ROC curve parameters	2009 CKD-EPI eGFR	2021 CKD-EPI eGFR
Area under the ROC curve, AUC (95% CI)	0.690 (0.683–0.697), p<0.0001	0.689 (0.682–0.696), p<0.0001
Youden's J index	0.2682 (0.2493–0.2831)	0.2630 (0.2452–0.2781)
Sensitivity (true positive rate)	52.0%	51.7%
100 – Specificity (false positive rate)	25.2%	25.4%
eGFR cut-off point with the maximum "J" index, ml/min/1.73 m^2 (95% CI)	72.1 (68-7–82.6)	76.6 (73.2–92.1)
Comparison between ROC curves	Difference between AUCs: 0.00089 (95% CI: 0.00051–0.00127); p<0.0001	

Fig. 4 ROC curves for prediction of all-cause mortality according to the eGFR values calculated with the 2009 (**A**) and 2021 (**B**) CKD-EPI equations. ROC = Receiver Operator Characteristic; eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration. e Epidemiology Collaboration

More importantly, in the Swedish study, risks for ESKD, all-cause death, and morbidity and mortality from CVD were lower in reclassified versus non-reclassified individuals in the unadjusted analysis, but became higher, except for ESKD, when adjusting for the 2009 eGFR level and remained significantly, though modestly higher (+4–11%) in individuals with a 2009 eGFR ≥ 30 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ when further adjusting for age [16]. Furthermore, an analysis of the predominantly Caucasian Northeastern Italian general population from the Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical End-points (INCIPE) study showed that the mortality risk of individuals reclassified to non-CKD was more similar to non-reclassified confirmed CKD than to confirmed non-CKD individuals [29]. These findings would imply that reclassification to a better eGFR category might be "harmful" by causing delayed care, less aggressive treatment and late referral of individuals with a risk of death that is not lower, if anything, than that of people remaining in the lower eGFR category [8]. However, in the INCIPE study, reclassified individuals to non-CKD were compared with n confirmed non-CKD group that included not only people with confirmed G2 category but also the much larger sample of those with confirmed G 1 category, who have at low risk of death [29]. Moreover, in the Swedish study, the increased mortality risk of reclassified individuals was attributed to the fact that, despite higher eGFR values, they were older and, consequently, had a higher prevalence of comorbidities and use of medications than non-reclassified individuals. However, these differences were likely due to the fact that the non-reclassified group inappropriately included individuals falling in the G1 category with the 2009 equation, who cannot be reclassified to a better eGFR category and were not considered when comparing the two groups for outcomes [16]. Conversely, our study showed that individuals reclassified to a better eGFR category with the 2021 equation had lower mortality risk across all eGFR categories than

those who were not reclassified, though the difference was statistically significant only in those with a 2009 eGFR < 30 ml·min^{-1}·1.73 m^{-2}. The lower risk of death of reclassified individuals was in keeping with the better cardiometabolic risk profile and the lower prevalence of complications and treatments, indicating that reclassification with the new equation is appropriate and "safe" by moving to a better eGFR category those who are relatively healthier and leaving in the lower eGFR category those who are relatively sicker. These findings are consistent with those of a recent report form the Danish general population showing that people in the CKD range with the new equation had a higher mortality rate than those with the old Eq. (8.8% versus 7.9%), likely due to reclassification to the G2 category of 24.2% of individuals who were at lower risk [28].

Due to differences in risk profile between reclassified and non-reclassified individuals, differences in mortality among KDIGO categories were more marked with the new formula compared with the old one. This was particularly relevant for participants with mildly elevated albuminuria falling in the G2b category with the 2021 equation, who showed a significantly increased risk of death, at variance with the 2009 equation. This finding is in keeping with a large body of epidemiological surveys showing that risk for all-cause and CVD mortality, CVD events and ESKD starts to increase for an eGFR < 75 ml·min^{-1}·1.73 m^{-2} [30–33]. This is also consistent with the 78 ml·min^{-1}·1.73 m^{-2} eGFR threshold below which the CVD prevalence was found to increase in the RIACE cohort [22].

Strength of our study include the large sample size, the completeness of baseline and follow-up data and the assessment of a wide range of clinical parameters which allowed accounting for several confounders. However, there are several limitations. First, the lack of information on the causes of death did not allow detecting differences in CVD versus non-CVD deaths. Second, the lack of cystatin C measurements did not allow comparing the performance of the creatinine-based and the combined creatinine-cystatin C 2021 CKD-EPI equations. Third, the new anti-hyperglycemic drugs reducing mortality by providing cardiorenal protection [34] were not available at the time of enrolment and their use was very limited during the follow-up. Fourth, results may have been affected by unmeasured confounders that can affect mortality. Fifth, the study findings may not be applicable to the general ambulatory population with type 2 diabetes, but only to individuals attending outpatients diabetes clinics in Italy. Finally, potential limitations concerning non-centralized measurements have been extensively addressed in previous publication [17, 18, 22].

In conclusion, using the new CKD-EPI equation in non-Black individuals with type 2 diabetes resulted in higher eGFR values and, hence, lower CKD prevalence, due to reclassification of a significant proportion of them to a better eGFR category. Reclassification appears appropriate as reclassified people showed a lower risk of death than those who were not reclassified, especially if they were in the low eGFR range, and differences in mortality among eGFR and KDIGO categories were more marked using the new formula, though mortality prediction was similar with the two equations. These findings suggest that the 2021 CKD-EPI formula can be safely implemented also in predominantly non-Black populations, though further studies are needed to evaluate the effect of switching to the new formula on prognostic, diagnostic, and therapeutic issues either in the general population or in people with type 2 diabetes.

Abbreviations

AER	Albumin excretion
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CVD	Cardiovascular disease
DR	Diabetic retinopathy
eGFR	Estimated glomerular filtration rate
ΔeGFR	Estimated glomerular filtration rate change
ESKD	End-stage kidney disease
eWC	Estimated waist circumference
GFR	Glomerular filtration rate
HbA_{1c}	Hemoglobin A_{1c}
HR	Hazard ratio
KDIGO	Kidney disease improving global outcomes
RIACE	Renal Insufficiency and Cardiovascular events
ROC	Receiver operator characteristic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02450-5.

Additional file 1. The RIACE Study Group. List of the RIACE Investigators.

Additional file 2: Table S1. The 2009 and 2021 CKD-EPI equations for calculating eGFR.

Additional file 3: Table S2. Comparison of the 2009 and 2021 CKD-EPI equations for calculating eGFR in the whole cohort and in pre-specified subgroups.

Additional file 4: Table S3. Reclassification of participants across KDIGO categories with the 2021 CKD-EPI eGFR equation.

Additional file 5: Table S4. Hazard ratios for all-cause mortality for non-reclassified and reclassified participants with the 2021 CKD-EPI eGFR equation by Cox proportional hazards regression with backward selection of variables using the 2009 CKD-EPI G1 category as reference.

Additional file 6: Figure S1. Distribution of eGFR values using the 2009 and 2021 CKD-EPI equations.

Acknowledgements

The Authors thank the RIACE Investigators for participating in this study (see the complete list in the Additional file 1: The RIACE Study Group).

Author contributions

MG, MVi, GPe, AS, EO, and GPu conceived and designed the study. All authors contributed to data acquisition, analysis, or interpretation. GPu drafted the

article and had full access to all the data and took responsibility for the integrity of data and accuracy of the data analysis in this study. MG, MVi, GPe, AS, EO, VG, EB, CF, RT, MVe, and AN revised the manuscript critically for essential intellectual content. All authors approved the submitted version of the manuscript and agreed to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding
This research was supported by the Research Foundation of the Italian Diabetes Society (Diabete Ricerca) and the Diabetes, Endocrinology and Metabolism (DEM) Foundation, and by unconditional grants from Eli-Lilly, Sigma-Tau, Takeda, Chiesi Farmaceutici, and Boehringer-Ingelheim. The funding sources had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the ethics committee of the coordinating centre (Sant'Andrea Hospital, Rome, Italy) on 25 September 2006 (number 43/2006) and subsequently by the ethics committee of each participating centre. Participants provided an informed consent.

Consent for publication
Not applicable.

Competing interests
MG reports receiving consultant fees from Eli Lilly, and lecture fees from Eli Lilly, Merck Sharp & Dohme, and Novo Nordisk. MVi reports receiving lecture fees from MundiPharma and Novo Nordisk. GPe reports receiving consultant fees from Bayer and Eli Lilly, and lecture fees from AstraZeneca, Boerhinger Ingelheim, Eli-Lilly, Merck Sharp & Dohme, Mundipharma, Novo Nordisk, and Takeda. AS reports receiving consultant fees from Axxam, Bayer, and Novo Nordisk, and lecture fees from Eli Lilly, Novo Nordisk, and Sanofi-Aventis. EO reports receiving consultant fees from Eli Lilly and Novo Nordisk, and lecture fees from Astellas. VG reports receiving lecture fees from Abbot, Astra-Zeneca, Medtronic, Novo Nordisk, Sanofi-Aventis, Theras, and Vertex. EB reports receiving consultant fees from Abbott, Bayer, Becton Dickinson, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, and Novo Nordisk. CF reports receiving lecture fees from Abbot, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Merck Sharp & Dohme, Mundipharma, and Theras Lifetech. RT reports receiving consultant fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Sanofi-Aventis, and lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, and Novo Nordisk. MVe reports receiving lecture fees from Lifescan and Novo Nordisk. AN reports receiving grants from Artsana, Astra-Zeneca, Eli Lilly, Novo Nordisk, and Sanofi Aventis and personal fees from Eli Lilly and Novo Nordisk. GPu reports receiving consultant fees from Abbot, Bayer, and Novo Nordisk, and lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Mundipharma, and Novo Nordisk.

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Received: 31 July 2024 / Accepted: 19 September 2024
Published online: 24 October 2024

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