Impact of the choice of biomarkers and equations to estimate kidney function on the epidemiology of chronic kidney disease

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Purpose of review
The CKD-EPI equations were updated in 2021 to remove the race variable from eGFR estimation. In the same year, the creatinine-based EKFC equation was published, subsequently supplemented by the cystatin C-based EKFC equation. Recent findings suggest that the prevalence of chronic kidney disease (CKD) can vary depending on the equation, the biomarker, and the population studied.

Recent findings
Using the CKD-EPI$_{2021}$ equation instead of the CKD-EPI$_{2009}$ equation results in an increased prevalence of CKD among Black individuals in the U.S. and a decreased prevalence among non-Blacks. The CKD-EPI equations may underestimate the prevalence of CKD in India and in some sub-Saharan African populations. This is corrected by using the EKFC equation and dedicated Q-values. In general, the prevalence of CKD is slightly higher with EKFC than with the CKD-EPI equations. The CKD-EPI$_{cys}$ equation generally leads to a higher CKD prevalence than the CKD-EPIcrea equations. Few epidemiological data are available for EKFC$_{cys}$.

Summary
The choice of biomarkers and equations has an impact on the prevalence of CKD, with implications that also depend on the characteristics of the population being studied.

Keywords
chronic kidney disease, creatinine, cystatin C, epidemiology, glomerular filtration rate

INTRODUCTION

Serum creatinine has been used to evaluate kidney function for close to one century [1,2]. However, it is well known that its concentration is not only dependent on the glomerular filtration rate (GFR), but on muscular mass and diet [3,4]. This dependency probably explains the difference observed in serum creatinine in healthy men and women. This argument has also been frequently advanced to explain differences between populations [the classical example being the difference between Black and White people from the United States of America (US)], but the scientific proofs sustaining this assertion are lacking [5,6]. This is only one among many other limitations of serum creatinine. We can cite the impact of diet, tubular secretion, and the hyperbolic (non-linear) association between serum creatinine and GFR [3]. For all these reasons, serum creatinine is not used as it is, but in equations including other variables (like sex and age) that are sensed to improve GFR estimation. At least using estimating GFR equations (eGFR), the same thresholds can be used both in men and women and in all populations to define chronic kidney disease (CKD). Recently, cystatin C has gained more and more interest as a variable for eGFR. First, this biomarker (and thus the related eGFR) are less dependent on populations characteristics, including sex [6,10,11]. Second, if the performance of cystatin C-based equations (eGFR$_{cys}$)

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KEY POINTS

- The choice of the creatinine- and/or cystatin C-based eGFR equation has an impact on the epidemiology of chronic kidney disease.
- In non-Black U.S. individuals, the prevalence of CKD is decreased when using the creatinine-based CKD-EPI$_{2021}$ equation instead of the CKD-EPI$_{2009}$ equation or the EKFC equation.
- These results have been confirmed in European and Asian populations.
- The prevalence of CKD is generally higher with the cystatin C-based eGFR equations than with those based on creatinine, but few epidemiological data exist for the cystatin C-based EKFC equation.
- The creatinine-based EKFC equation is adaptable, via a dedicated Q factor, to specific populations for which creatinine-based eGFR is commonly overestimated by the usual equations.

are not obviously better than creatinine-based equations (eGFR$_{crea}$), the equations combining both biomarkers (eGFR$_{crea+cys}$) perform better than equations using either single biomarker [10,11]. Third, the eGFR$_{cys}$ could be of interest in specific populations for whom the eGFR$_{crea}$ are particularly poor [12–18], but this last assertion remains debatable [19]. In the current article about CKD epidemiology, we will focus on the impact of GFR estimation (both the choice of the equation and biomarker) on the prevalence of CKD. We will not discuss the role of cystatin C in its ability to predict outcomes, and notably cardiovascular outcomes [20,21].

HOW CAN THE CHOICE OF AN EQUATION IMPACT THE PREVALENCE OF CHRONIC KIDNEY DISEASE (WHEN THE SAME BIOMARKER IS USED)?

Bias of an equation and its impact on chronic kidney disease prevalence

In this paragraph, we will discuss how a different eGFR$_{crea}$ can impact the CKD epidemiology. To assess the performance of an equation to estimate GFR, studies are comparing eGFR with measured GFR (mGFR) by a reference method. Then, classically, three metrics are used: bias, precision and accuracy [22–24]. Bias is the systematic difference between eGFR and mGFR and is calculated as the median difference between eGFR and mGFR. Precision is the interquartile range around the bias and represents the spread of the results around the bias. Precision conceptualized the random error between eGFR and mGFR (Fig. 1). Accuracy is a metric specifically used in the little world of eGFR. This metric is dependent on both the systematic and random error and is calculated as the proportion of estimated results (eGFR) within plus or minus 30% of the paired measured results (mGFR). Even if not free from criticisms [24], this concept has the advantage to be easy to interpret for clinicians. The relationship of bias, precision and accuracy is illustrated in Figure 1, where in 1A imprecision with no bias, leads to suboptimal accuracy, yet the prevalence of eGFR < 60 ml/min/1.73 m^2 is identical to that of mGFR $<$ 60 ml/min/1.73 m^2. In 1B, positive bias with the same imprecision illustrates what may be seen when using an eGFR equation in a population that would on average have lower muscle mass and/or protein intakes than the population in which the eGFR equation was initially developed. Finally in 1C, no bias and improved precision leads to accuracy approaching 100%. This may be achieved through improvement in the GFR estimation method (combining several endogenous markers, for example) and/or to the application of the eGFR equation to a population that is highly homogeneous for the non-GFR determinants of the endogenous GFR marker(s) used (Fig. 1).

At the individual level, the performance of an equation will be, above all, dependent on its precision (random error). At the population level, and thus in the context of epidemiology, the impact of bias (systematic error) will be crucial on the CKD epidemiology, as positive bias (overestimation of mGFR), would likely result in a reduced estimated population prevalence of CKD and *vice versa*. The consequences of moving from one eGFR$_{crea}$ to another one on the CKD prevalence can be easily anticipated by analyzing the bias of the respective equations (Table 1).

Moving from Modified Diet in Renal Disease study to CKD-EPI$_{2009}$ equation

In 2009, the Chronic Kidney Disease Epidemiology consortium proposed to move from the Modified Diet in Renal Disease study (MDRD) equation to the Chronic Kidney Disease Epidemiology (CKD-EPI) equation [25,26]. The CKD-EPI equation had comparable precision to the MDRD equation (IQR 16.6 [15.9–17.3] versus 18.3 [17.4–19.3] ml/min/1.73 m^2, respectively) [26], and thus, the added value of the CKD-EPI equation at the individual was moderate [22]. However, at the population level, the impact was huge. Indeed, the MDRD study equation underestimated mGFR in healthy subjects (thus MDRD had a systematic negative bias). The CKD-EPI equation had a better bias (-3.5 ml/min.1.73 m^2) than MDRD (−10.6 ml/min/1.73 m^2) in individuals with

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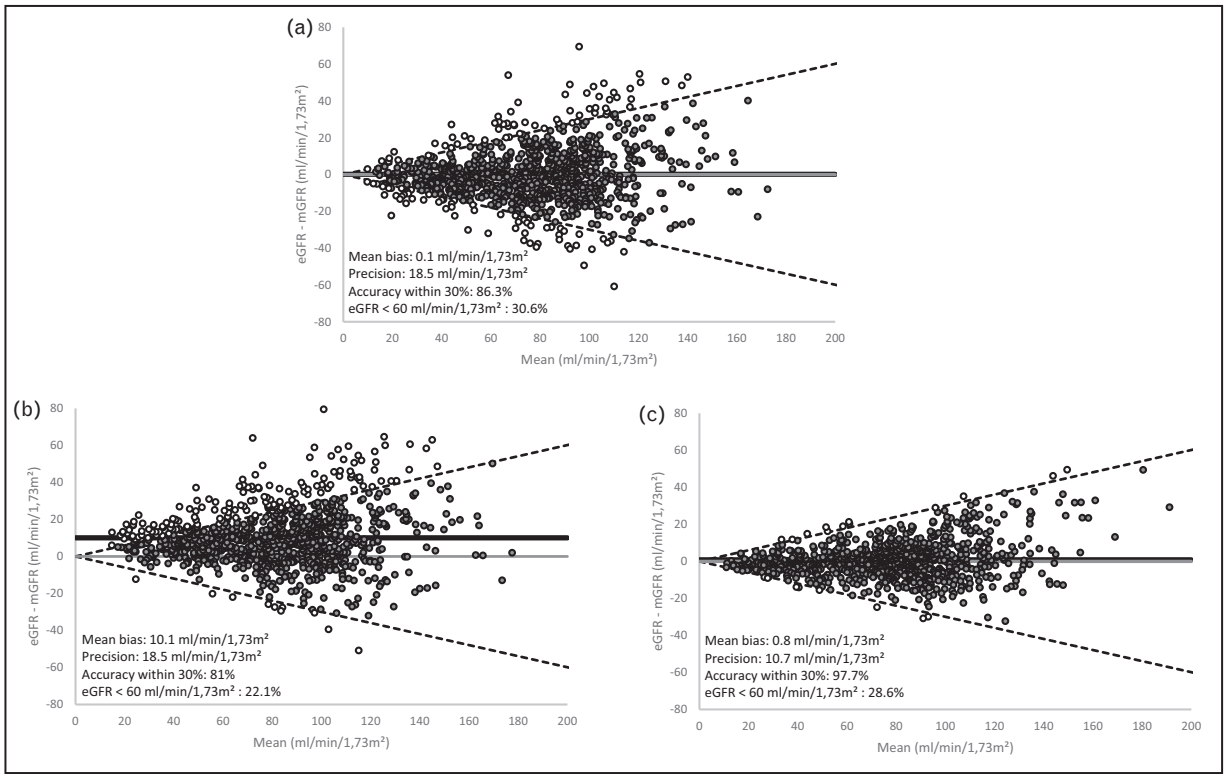

FIGURE 1. Bland Altman plots of the different metrics used to assess the performance of glomerular filtration rate estimation equations, based on a hypothetical sample of 975 patients, of whom 29% have an mGFR $<$ 60 ml/min/1.73 m_2. using Bland Altman plots. The y-axis represents the difference between eGFR and mGFR and the x-axis the mean of eGFR and mGFR. Mean or median bias is represented by the thick black line. Precision of eGFR is the distance between the third and the first quartile of the bias and corresponds to the dispersion of the scatterplot. Accuracy is represented by the black dots located between the dotted lines. eGFR is unbiased, but because of imperfect precision, accuracy is nonoptimal. eGFR significantly overestimates mGFR (positive bias), precision is the same as in example A, and accuracy is reduced due to the bias, with eGFR prevalence $<$ 60 ml/min/1.73 m_2 being underestimated. There is no bias, and the precision is significantly better than in the previous examples, leading to an accuracy approaching 100%.

GFR more than 60 ml/min/1.73 m^2. It can thus be expected that the CKD prevalence would be lower with the CKD-EPI study equation compared to the MDRD study equation. This has been already illustrated in the seminal article about the CKD-EPI equations, using the epidemiological data from National Health and Nutrition Examination Survey (NHANES): the CKD prevalence (defined as eGFR$<$60 ml/min/1.73 m^2) was 11.5 versus 13.1% with the CKD-EPI and MDRD equations, respectively. This observation has been thoroughly confirmed by other authors [27–29].

Moving from CKD-EPI$_{2009}$ to race-free CKD-EPI$_{2021}$

Recently, the racial coefficient, present both in the MDRD and original CKD-EPI equation, has been criticized and considered as a source of discrimination in USA [5,30,31]. The criticisms were mainly driven by US nephrologists, as the coefficient into question should not be used in Africa and Europe [9,30–33]. This led the authors of the CKD-EPI equation to propose a new equation without the race variable in 2021 (CKD-EPI$_{2021}$ versus CKD-EPI$_{2009}$). Focusing on bias, the CKD-EPI$_{2021}$ equation overestimated GFR in non-Black populations, whereas the 2009 version was unbiased. In Black US populations, the new equation underestimated GFR whereas the 2009 version with the race coefficient was overestimating GFR [11]. What could be the impact of moving from the 2009 to 2021 CKD-EPI equation? Once again, the results on CKD epidemiology can be anticipated. In Black US populations, the CKD prevalence should increase and, in non-Black population, the prevalence should decrease [34]. This has been illustrated and confirmed in several studies and we consider here only some illustrative examples. In the seminal article where the CKD-EPI$_{2021}$ equation has been developed, the

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Table 1. Summary of bias, precision, P30, and the potential impact on estimating chronic kidney disease population prevalence for the CKD-EPI$_{2009}$, CKD-EPI$_{2021}$, and EKFC equations (creatinine only, cystatin-C, and combined)

Published article	Population cohort and size	Measured GFR (ml/min/1.73 m^2) (Mean ± SD or Median (IQR)	eGFR equation	Bias (ml/min/1.73 m^2) (Median difference with 95% CI)	Precision (ml/min/1.73 m^2) (IQR with IQR range)	P30, % (95% CI)	Predicted impact of CKD prevalence estimate
Pottel *et al.* [10]	EKFC cohort (White European patients), *N* = 7727	70.8 (43.4–90.6)	CKD-EPI$_{2009\ crea}$	4.0 (3.7–4.3)	15.5 (−3.0 to 12.5)	81.6 (80.8–82.5)	↑
			CKD-EPI$_{2021\ crea}$	7.4 (7.0–7.8)	16.3 (0.0–16.3)	75.7 (74.8–76.7)	↑
			EKFC$_{crea}$	0.6 (0.3–0.9)	14.5 (−6.5 to 8.0)	85.8 (85.0–86.5)	↑
			CKD-EPI$_{cys}$	0.3 (−0.0 to 0.6)	19.1 (−7.9 to 11.2)	80.8 (79.9–81.7)	↑
			EKFC$_{cys}$	0.0 (−0.4 to 0.3)	14.4 (−7.9 to 6.5)	86.2 (85.4–87.0)	↑
			CKD-EPI$_{crea\text{-}cys}$	2.5 (2.2 to 2.8)	14.8 (−3.6 to 11.2)	88.3 (87.6–89.0)	↑
			EKFC$_{crea\text{-}cys}$	0.4 (0.1–0.7)	12.0 (−5.9 to 6.1)	90.4 (89.8–91.1)	↑
	US Cohort (White patients from Rochester, Minnesota), N = 1093	80.0 (66.0–93.0)	CKD-EPI$_{2009\ crea}$	2.8 (1.7–3.6)	18.8 (−6.6 to 12.2)	86.0 (83.9–88.1)	↑
			CKD-EPI$_{2021\ crea}$	7.1 (6.2–8.0)	18.7 (−2.2 to 16.5)	81.0 (78.6–83.3)	↑
			EKFC$_{crea}$	−2.7 (−3.7 to −1.8)	18.5 (−11.9 to 6.6)	89.3 (87.5–91.1)	↓
			CKD-EPI$_{cys}$	12.1 (11.1–13.3)	21.5 (1.5–23.0)	72.9 (70.3–75.6)	↑↑
			EKFC$_{cys}$	4.3 (3.3– 5.1)	18.3 (−5.3 to 13.0)	83.9 (81.7–86.1)	↑
			CKD-EPI$_{crea\text{-}cys}$	9.2 (8.5–10.1)	18.4 (0.5–18.8)	79.5 (77.1–81.9)	↑
			EKFC$_{crea\text{-}cys}$	1.0 (0.0–2.1)	17.4 (−8.2 to 9.2)	88.7 (86.9–90.6)	↑
	Paris cohort (Black patients), *N* = 858	64.3 (45.9–81.7)	CKD-EPI$_{2009\ crea}$	0.2 (−0.6 to 0.8)	19.3 (−12.7 to 4.1)	79.8 (77.1–82.5)	↑
			CKD-EPI$_{2021\ crea}$	−5.1 (−5.7 to −4.1)	16.8 (−12.7 to 4.1)	82.3 (79.7–84.8)	↓
			EKFC$_{crea}$	−2.6 (−3.5 to −1.7)	14.9 (−9.9 to 5.1)	85.5 (83.2 to 87.9)	↓
			CKD-EPI$_{cys}$	−0.6 (−1.7 to 0.3)	17.9 (−8.1 to 9.8)	81.5 (78.9–84.1)	↓
			EKFC$_{cys}$	−0.8 (−1.3 to −0.3)	15.3 (−8.5 to 6.7)	87.6 (86.3–88.9)	↓
			CKD-EPI$_{crea\text{-}cys}$	−2.1 (−2.7 to −1.3)	14.0 (−7.9 to 6.1)	89.0 (87.0–91.1)	↓
			EKFC$_{crea\text{-}cys}$	−0.7 (−1.2 to 0.1)	12.4 (−6.2 to 6.2)	92.0 (90.1–93.8)	↓

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Table 1 (*Continued*)

Published article	Population cohort and size	Measured GFR (ml/min/1.73 m^2) (Mean ± SD or Median (IQR)	eGFR equation	Bias (ml/min/1.73 m^2) (Median difference with 95% CI)	Precision (ml/min/1.73 m^2) (IQR with IQR range)	P30, % (95% CI)	Predicted impact of CKD prevalence estimate
	African cohort (Black patients from Ivory Coast ($N=285$) and Democratic Republic of Congo ($N=223$)), $N=508$	86.8 (71.7–99.2)	CKD-EPI$_{2009\ crea}$	12.2 (10.7–15.0)	30.0 (−3.2 to 26.8)	63.6 (59.4–67.8)	↑↑
			CKD-EPI$_{2021\ crea}$	2.5 (0.7–4.2)	23.3 (−9.0 to 14.3)	74.4 (70.6–78.2)	↑
			EKFC$_{crea}$	−1.5 (−2.8 to 0.6)	20.4 (−10.6 to 9.9)	78.9 (75.4–82.5)	↔
			CKD-EPI$_{cys}$	2.8 (1.4–4.5)	23.7 (−7.7 to 16.0)	77.4 (73.7–81.0)	↑
			EKFC$_{cys}$	1.7 (0.3–3.3)	19.5 (−7.4 to 12.1)	83.5 (80.2–86.7)	↑
			CKD-EPI$_{crea\text{-}cys}$	8.6 (6.9–10.3)	24.7 (−4.5 to 20.1)	75.0 (71.2–78.8)	↑
			EKFC$_{crea\text{-}cys}$	0.4 (−1.0 to 1.5)	17.1 (−7.2 to 10.0)	84.3 (81.1–87.4)	↔
Fabian *et al.* [37]	ARK Consortium (Uganda, Malawi, and South Africa), $N=2578$	81 (64–97)	CKD-EPI$_{2009\ crea}$	12 (11–13)	0.33 (0.31–0.35)[a]	65 (63–67)	↑↑
			CKD-EPI$_{2021\ crea}$	15 (14–16)	0.33 (0.31–0.34)[a]	60 (58–62)	↑↑
			EKFC$_{crea}$	7 (6–8)	0.32 (0.31–0.34)[a]	71 (69 to 73)	↑
			CKD-EPI$_{cys}$	−2 (−3 to −1)	0.35 (0.34–0.37)[a]	70 (69 to 73)	↓
			EKFC$_{cys}$	–	–	–	↔
			CKD-EPI$_{crea\text{-}cys}$	7 (6 to 8)	0.32 (0.30–0.33)[a]	70 (68–72)	↑
			EKFC$_{crea\text{-}cys}$	–	–	–	↔

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Table 1 (*Continued*)

Published article	Population cohort and size	Measured GFR (ml/min/1.73 m^2) (Mean ± SD or Median (IQR)	eGFR equation	Bias (ml/min/1.73 m^2) (Median difference with 95% CI)	Precision (ml/min/ 1.73 m^2) (IQR with IQR range)	P30, % (95% CI)	Predicted impact of CKD prevalence estimate
Yadav *et al.* [44] KI Reports 2024	North Indian cohort (Potential kidney donors and CKD participants), N = 412	54.2 ± 30.2	CKD-EPI$_{2009\ crea}$	17.0 (15.0–19.1)[b]	29.0 (25.6–33.0)[c]	43	↑↑
			CKD-EPI$_{2021\ crea}$	19.2 (17.0–21.3)[b]	30.3 (25.8–34.3)[c]	41	↑↑
			EKFC$_{crea}$	15.0 (13.0–16.8)[b]	25.6 (22.0–28.6)[c]	47	↑↑
			CKD-EPI$_{cys}$	−3.7 (−5.5 to −1.7)[b]	20.4 (17.9–23.4)[c]	61	↓
			EKFC$_{cys}$	0.2 (−1.8 to 2.0)[b]	20.4 (18.2–23.6)[c]	60	↔
			CKD-EPI$_{crea\text{-}cys}$	6.6 (4.6–8.4)[b]	22.3 (19.5–25.7)[c]	55	↑
			EKFC$_{crea\text{-}cys}$	7.6 (5.8–9.3)[b]	21.1 (18.8–23.6)[c]	54	↔

Data are presented from cohorts in Europe, Africa, Asia, and USA.
Bias defined as eGFR minus mGFR. P30 is the proportion of eGFR results within 30% of the corresponding mGFR result.
CKD-EPI$_{2009\ crea}$ = CKD-EPI$_{2009}$ equation with black race coefficient.
EKFC$_{crea}$ rescaled Q-values :
- Men, aged ≤ 25: ln(Q) = 3.200 + 0.259 × age - 0.543 × log(age) - 0.00763 × age^2 + 0.0000790 × age
- Women, aged ≤ 25 ln(Q) = 3.080 + 0.177 × age - 0.223 × log(age) - 0.00596 × age^2 + 0.0000686 × age
- Adults > 25 years old: Men = 0.9 mg/dl; Women = 0.7 mg/dl
- Rescaled Cr/Q where available: EKFC Cohort = 1.13 (0.94–1.65); US Cohort = 1.04 (0.92–1.17); Paris Cohort = 1.46 (1.19–1.94); African Cohort = 1.16 (1.02–1.41).
EKFC$_{cys}$ sex-specific Q-values for adults > 25 years old: Men = 0.86 mg/dl; Women = 0.79 mg/dl
ARK Consortium and North Indian cohort used the standard sex-specific Q values for creatinine and cystatin C (based on a White European cohort).
ARK, African Research on Kidney Disease; CI, confidence intervals; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium using the Q-values derived from a White European cohort.
[a]Precision reported as the log of the root mean square error, with 95% confidence intervals.
[b]Mean bias with 95% confidence intervals.
[c]IQR value with 95% confidence intervals.

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authors used once again the NHANES database. The prevalence of CKD (defined as eGFR below 60 ml/min/1.73 m^2) was decreasing from 6.9 to 5.3% in non-Black populations and increasing from 6.5 to 8.5% in Black populations when the CKD-EPI 2009 or 2021 equations were considered, respectively (Table S16 in [11]). From a large nationwide Danish database (predominantly non-Black population), moving from CKD-EPI_{2009} to CKD-EPI_{2021} was associated a 25% lower CKD prevalence (from 5.5 to 4.2%, CKD being defined as two eGFR below 60 ml/min/1.73 m^2 at least 90 days apart) [35]. These results have been confirmed in a recent analysis from Sweden [the Stockholm CREAtinine Measurements (SCREAM)] showing that 9.9% of the participants were reclassified to a higher CKD stage with the CKD-EPI_{2021} equation. Among patients with eGFR below 60 ml/min/1.73 m^2, 36.2% were reclassified to a higher stage and CKD prevalence decreased from 5.1 to 3.8% [36▪]. Data from the US Veteran cohort were also analyzed. The authors studied the prevalence of CKD (defined as GFR between 15 and 60 ml/min/1.73 m^2 at least 90 days apart). As expected, the CKD-EPI_{2021} equation identified an increase in CKD among Black patients and a decrease among non-Black individuals [37]. In another publication using US Military Health System, the number of Black individuals diagnosed as having CKD (defined as eGFR below 60 ml/min/1.73 m^2 90 days apart) increased by 58.1% (from 1.47 to 2.32%) and the number of non-Black CKD patients decreased by 30.4% (from 2.26 to 1.58%) when moving from CKD-EPI_{2009} to CKD-EPI_{2021} [38]. In a joint analysis of the US NHANES database including self-reported Asian individuals and the Korean Health and Nutrition Examination Survey, the authors showed that 32.8% of patients originally classified with eGFR below 60 ml/min/1.73 m^2 using the CKD-EPI_{2009} equation in the Korean population and 30.1% in the US Asian population were reclassified as healthy with CKD-EPI_{2021} [39]. Interestingly, a multicenter African study (Uganda, Malawi, and South Africa) found that the CKD-EPI_{2009} without ethnicity coefficient and the CKD-EPI_{2021} equations both overestimated iohexol-derived mGFR (median bias 12 [IQR 11–13] and 15 [IQR 14–16] ml/min/1.73 m^2) [33]. Similar findings were reported in an Indian cohort ($n = 492$), with substantial overestimation of iohexol-derived mGFR reported from both equations (17.0 ± 21.4 and 19.2 ± 21.6 ml/min/1.73 m^2) [40]. The findings from both studies, also illustrated in other data in Africa and Asia [9,41–43], would predict an underestimate of the true population prevalence of CKD and highlight the limitations of the CKD-EPI equation in non-White non-American populations. The last example comes from Australia. In a large cohort of individuals older than 70 years (99% of European ancestry), using the CKD-EPI_{2021} instead of CKD-EPI_{2009} was associated with a lower prevalence of eGFR values below 60 ml/min/1.73 m^2 (12 and 17%, respectively). Twenty percent of the population considered were classified in a higher CKD stage with the CKD-EPI_{2021} equation [44].

Moving from CKD-EPI to European Kidney Function Consortium

In 2019, a new equation has been proposed by the European Kidney Function Consortium (EKFC). This equation is based on the ratio of serum creatinine on the Q value which is the median serum creatinine concentration of a healthy population. This equation better conceptualizes the age variable [7,8,45,46] and allows a continuum in eGFR results between children, adolescents and adults [46,47]. This equation is very flexible and can be used in different populations, including with a concept of race-free Q values [7,9,48]. Focusing once gain on the bias, this equation was shown to have a better performance than the CKD-EPI (both 2009 and 2021) equations. This was especially the case in European and US populations younger than 30 years and in patients older than 70 years in which the CKD-EPI equations overestimate GFR (the overestimation is particularly relevant in young healthy people) [9,33,40,46,48,49▪]. Accordingly, one can expect that using the EKFC equation instead of the CKD-EPI equation would lead to a higher CKD prevalence in young people, and maybe in elderly people. This has been well illustrated in a mathematical model [34]. Until now, only some studies are available about the impact of moving from CKD-EPI to EKFC equations on epidemiological results. In a large adult cohort from the Korean Health and Nutrition Examination Survey, the authors showed that the prevalence of eGFR below 60 ml/min/1.73 m^2 was higher with the EKFC equation (5.3%) than with CKD-EPI_{2009} (3.8%) or CKD-EPI_{2021} (3%) equations [50]. Another publication using laboratory data from Korea also compared the three equations. The percentage of eGFR below 60 ml/min/1.73 m^2 was 26.2, 22.9, and 30.3% with the CKD-EPI_{2009}, CKD-EPI_{2021}, and EKFC equations, respectively [51]. Lu *et al.* [52] analyzed the results of the US NHANES study but restricting the analysis to non-Black people and considering only the CKD-EPI_{2009}. They found that the prevalence of CKD was higher with the EKFC equation (11.9%) compared to the CKD-EPI 2009 equation (9.2%) [52]. Unfortunately, the results of the CKD prevalence in these studies were not analyzed according to age. Moreover, they all used the European-Q values,

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which is questionable in non-European cohorts [7,48]. Using data from SCREAM (but limited to 6174 individuals with mGFR available), the authors showed and compared the density of eGFR values in a Swedish population with the different equations used (Supplement Figure 3 in [53]). Once again, the prevalence of CKD was higher with the EKFC equation compared to the CKD-EPI$_{2009}$ equation and still more the CKD-EPI$_{2021}$ [53]. Further epidemiological studies are necessary to illustrate the potential impact of using the EKFC equation instead of the CKD-EPI equations on the prevalence of CKD in diverse populations (notably in Africa and Asia) and in different ages ranges.

IMPACT OF USING CYSTATIN C INSTEAD OF CREATININE TO ESTIMATE GLOMERULAR FILTRATION RATE ON THE CHRONIC KIDNEY DISEASE PREVALENCE

Cystatin C, as a renal biomarker, has been discovered in 1985 by Anders Grubb [54]. Since then, many cystatin C-based equations (eGFR$_{cys}$) have been proposed. Among them, the cystatin C-based equation proposed by the CKD-EPI consortium in 2012 (CKD-EPI$_{cys}$) has been the most studied [55]. In the seminal article about the race-free CKD-EPI$_{2021}$ equation, the authors have compared the impact of using the CKD-EPI$_{2021}$ equation versus CKD-EPI$_{cys}$ or the equation combining the two biomarkers (eGFR$_{crea+cys}$) on the CKD prevalence in the NHANES cohort (Table S16 in [11]). The prevalence of eGFR less than 60 ml/min/1.73 m^2 in the overall population was 5.6, 8.7, and 6.2% for CKD-EPI$_{2021}$, CKD-EPI$_{cys}$, and CKD-EPI$_{crea+cys}$, respectively. In non-Black populations, the prevalence was 5.3%, 8.9%, and 6.2%, respectively. In Black populations, the prevalence was 8.5%, 6.8%, and 6.3%, respectively [11]. In the whole population, using the CKD-EPI$_{cys}$ could thus lead to a higher CKD prevalence. This has been recently illustrated in the Atherosclerosis Risk in Communities Study (ARIC) in a US community-based cohort with a mean age of 75.8 $\pm$5.3 years. Moving from CKD-EPI$_{2021}$ to the CKD-EPI$_{cys}$ is associated with a huge increase in CKD prevalence (eGFR below 60 ml/min/1.73 m^2): from 25.7 to 48.7% (using the CKD-EPI$_{crea+cys}$, the prevalence is 32.5%) [56]. The assertion that CKD prevalence is higher with eGFR$_{cys}$ could however not be true for Black populations in which the CKD-EPI$_{2021}$ equation could lead to a higher prevalence of CKD than CKD-EPI$_{cys}$ (unfortunately, this has not been analyzed in the ARIC study). Further studies are needed.

Other cystatin C-based equations are considered as 'valid' by the recent Kidney Disease-Improving Global Outcomes (KDIGO) guidelines [57]. Among them, we would like to evoke the new cystatin C-based EKFC equation (EKFC$_{cys}$) [10]. Of interest, this equation has the same mathematical form as the creatinine-based EKFC (EKFC$_{crea}$) equation, but using a Q value dedicated to cystatin C. Like CKD-EPI$_{cys}$, EKFC$_{cys}$ is totally race-free, but additionally, EKFC$_{cys}$ is also gender or sex-free (as the cystatin C Q value is independent of this variable) [10].

In the seminal article validating the EKFC$_{cys}$ against mGFR (and in comparison to the respective CKD-EPI equations), it can be deducted that the difference between CKD-EPI$_{crea}$ and EKFC$_{crea}$ is much important than between CKD-EPI$_{cys}$ and EKFC$_{cys}$ (Fig. 1 in [10]), at least in the main European cohort. It can thus be anticipated that using either EKFC$_{cys}$ or CKD-EPI$_{cys}$ could have relatively few (or fewer impact) on the CKD prevalence in comparison to differences observed when respective creatinine-based equations are considered. If an impact is still seen, it should be theoretically higher eGFR results with EKFC$_{cys}$ than with CKD-EPI$_{cys}$ in the majority of scenarios [58]. From the SCREAM cohort limiting to older individuals (mean age of 77 years), the authors calculated the number of patients re-classified in a different CKD stage if the CKD-EPI$_{2021}$ versus the CKD-EPI$_{crea+cys}$ are used. They found that using the combined equation would lead to a reclassification to a more severe category in 31.2% of cases (older the individual is and more the rate of reclassification is high). Moreover, the authors showed that the density of low eGFR was still higher when GFR is estimated with cystatin C than with creatinine [the density being in middle of the two for the combined equations (Supplement Figure 2)]. Interestingly, the authors also considered the EKFC equations. A direct comparison between CKD-EPI and EKFC equations is difficult because only density figures are available (density of eGFR according to EKFC equations is shown in Supplement Figure 8), but two observations can be made. First, in this specific population of old European individuals, the prevalence of individuals with eGFR below 60 ml/min/1.73 m^2 is larger with EKFC$_{cys}$ than with EKFC$_{crea}$ (the EKFC combining both biomarkers being in the middle of two). Second, it seems interesting to underline that the difference in CKD prevalence seems much less important between EKFC$_{crea}$ and EKFC$_{cys}$ than between CKD-EPI$_{2021}$ and CKD-EPI$_{cys}$ [59▪▪]. Accordingly, the rate of discordant results between eGFR$_{crea}$ and eGFR$_{cys}$ could be much lower with the EKFC than CKD-EPI equations, which has also been suggested by other authors [53,60,61]. Further studies are, however, needed to compare these four equations and their impact on CKD epidemiology in other age-ranges and populations.

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CONCLUSION

In the current article, we showed that the choice of both the biomarkers and the equations has a real and important impact on the CKD prevalence, and thus on CKD epidemiology. Most of the consequences of using one or another equation or biomarker can be anticipated knowing the bias of these equations with mGFR. We must however keep in mind that we only show the consequences of moving from one equation to another one in large cohorts in "general populations". Because the bias of all eGFR equations can vary according to age, co-morbidities, and CKD category, the impact of moving from one equation to another one (or one biomarker to another) can be different in more selected populations. In the same way, both creatinine and cystatin C concentrations are influenced by non-GFR determinants [62]. In selected populations, moving from one biomarker to another one can thus have different consequences on CKD prevalence than in the general population.

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Conflicts of interest

Pierre Delanaye is a consultant for Nephrolyx.

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