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A Systematic Review Evaluating Estimated GFR Performance in South Asian Populations

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Introduction: Estimated glomerular filtration rate (eGFR) equations are widely used to measure kidney function; however, their performance in South Asian populations is variable. We performed a systematic review and meta-analysis to assess the performance of creatinine-based ($eGFR_{Cr}$), cystatin-C–based ($eGFR_{CysC}$) and combined ($eGFR_{Cr\text{-}CysC}$) eGFR equations compared with measured GFR (mGFR) in South Asians.

Methods: Pubmed/Medline, Embase (Ovid), Scopus, Web of Science, and Cochrane Library for Systematic Reviews and Clinical Trials were searched for relevant studies between January 1, 1976 and November 30, 2024. Eligible studies compared eGFR to mGFR in South Asian adult populations. Meta-analyses were performed to assess bias (standardized mean difference [SMD]) and 30% accuracy (meta proportion/percentage of eGFR results within 30% of the corresponding mGFR result [P30]) for eGFR equations compared with mGFR with multivariable meta-regression for key moderators.

Results: Thirty-five cohorts ($n = 4725$) were included. $eGFR_{Cr}$ equations overestimated mGFR with the Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI\text{-}2009_{Cr}$) equation showing the highest standardised mean difference (0.66; 95% confidence interval [CI]: 0.35–0.97). $eGFR_{CysC}$ had the least standardized mean difference (−0.03 to 0.15). However, accuracy for $eGFR_{Cr}$ and $eGFR_{CysC}$ equations were $< 75\%$. $eGFR_{Cr\text{-}CysC}$ had the best P30, ranging from 79% to 82%. Meta-regression identified age, sex, ethnicity, and cohort type as having significant impacts on bias effect size.

Conclusion: eGFR equation accuracy in South Asians is suboptimal, consistently below the accepted clinical P30 threshold of 75%. $eGFR_{CysC}$ equations had reduced bias compared with $eGFR_{Cr}$ or $eGFR_{Cr\text{-}CysC}$; however, accuracy was better with $eGFR_{Cr\text{-}CysC}$. Emerging equations, such as the CKD-EPI-Pakistan variant and European Kidney Function Consortium (EKFC) equations warrant further investigation in diverse South Asian cohorts with population-specific calibration.

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CKD currently affects 7% to 13% of the population worldwide and is predicted to become the fifth most common chronic disease by 2040.[1,2] South Asian populations have increased risk of developing hypertension and diabetes mellitus, which are common causes of CKD.[3] Therefore, accurate measurement of kidney function is vital to diagnose and classify CKD, monitor progression, guide medication dosing, and signpost for advanced care, such as transplantation workup.

Creatinine, an endogenous filtration marker, is widely used to estimate GFR (i.e. eGFR) because it is readily available, inexpensive, and has a rapid turnaround time. However, performance is affected by

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non-GFR determinants, including muscle mass and diet. $eGFR_{Cr}$ equations, such as the CKD-EPI-2009_{Cr} and the Modified Diet in Renal Disease 4-variable (MDRD-4v) remain routine measures of kidney function worldwide.[4-6] However, the accuracy of eGFR equations in non-White populations is under increased scrutiny worldwide, following recent recommendations for removal of the Black ethnicity coefficient in international guidelines such as Kidney Disease: Improving Global Outcomes CKD 2024 Guidelines.[7,8]

In South Asian populations, multiple studies have reported $eGFR_{Cr}$ overestimating mGFR,[9,10] which is presumed to be related to differences in muscle mass and diet. Reports that $eGFR_{CysC}$ equations have reduced bias support this notion, because cystatin-C is unaffected by muscle mass, diet, or biological sex.[11] However, uncertainty remains over the optimal eGFR equation and biomarker, because of the substantial variability in mGFR measurement methodologies and differences in reported eGFR bias and accuracy among South Asian cohorts.

Therefore, this systematic review and meta-analysis aimed to:

1. Review existing studies that assess accuracy of $eGFR_{Cr}$, $eGFR_{CysC,}$ and $eGFR_{Cr-CysC}$ equations compared with mGFR in South Asian populations.
2. Describe and compare the accuracy of eGFR equations in population cohorts across different geographics, ethnicities and demographics.

METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines registered on Prospero (registration ID: CRD42022368442).[12]

Inclusion and Exclusion Criteria

Peer-reviewed and gray literature were searched for randomized controlled trials, observational studies, systematic reviews, meta-analyses, and conference abstracts with language limited to English. Inclusion criteria were adults (aged $\geq$ 18 years), studies comparing eGFR with mGFR with data reported for South Asian populations. eGFR equations included the Cockcroft-Gault equation with correction for body surface area (i.e., ml/min per 1.73 m^2).

Studies were excluded if an ineligible intervention or outcome was assessed; non-English language; ethnicities not stated; ineligible study design or report (e.g., narrative review, case report, editorial, books, and news media).

Search Strategy

The following databases were searched from January 1, 1976 to November 30, 2024: Pubmed, Embase (Ovid), Scopus, Web of Science, and The Cochrane Library for Systematic Reviews and Clinical Trials (Supplementary Materials - Search Strategy). All search results were processed using Rayyan.[13]

Study Screening and Data Extraction

Two researchers (RG and ASi) independently screened titles and abstracts and subsequently full-text articles of selected studies. Discrepancies were discussed between researchers. If no agreement was found, a third independent researcher (KB) was consulted. Full-text articles were screened for eligibility. For studies where data were missing or unclear, authors were approached for aggregate data.

Extracted data included citation details, study design, study population characteristics including ethnicity and study country, study aims, primary and secondary outcomes, demographic characteristics (age, sex, and body mass index [BMI]), creatinine, cystatin-C, biochemistry assays, eGFR equations, mGFR filtration markers (iohexol, inulin, Technetium-99m-diethylenetriaminepentaacetate or chromium-51 ethyldiaminetetraacetate, mGFR method (plasma clearance, urinary clearance, gates method, or not stated), eGFR and mGFR result, bias (eGFR minus mGFR), precision and accuracy (i.e., P30). Studies typically reported participants as "male" or "female" but did not always specify whether this was gender or biological sex. For the purpose of this review, we interpreted these categories as biological sex and have referred to them as such throughout. Where applicable, weighted aggregate mean and SDs were calculated using the formula described in Supplementary Figure S1.

Statistical Meta-Analysis

Data are presented as counts and percentages and mean $\pm$ SD. Bias and P30 were included in the meta-analysis. Because of the variety of metrics used to report precision across the studies, it was not possible to combine these into a pooled dataset for meta-analysis. Therefore, the precision metrics used have been described in the results but have not been assessed.

SMD was calculated for bias using mean eGFR, mGFR, sample size, and pooled SDs. Standardization was required because of different metrics being used for study aggregate data (e.g., mean or median) and the variability in methodology. Meta-analyses were stratified by eGFR equation using a random-effects model with Hartung-Knapp adjustment. Bias was assessed using mean difference (using reported mean bias, SD of

the bias, and sample size) for clinical utility. P30 was assessed using proportions (events vs. observations) using logit transformation. Forest plots were generated for both outcomes and stratified by eGFR equation. The proportion of total variance attributable to true interstudy differences, as opposed to sampling error, was assessed using the I^2 statistic. The magnitude of heterogeneity was assessed using 95% prediction intervals (PIs), which represents the dispersion of true effect sizes across comparable studies.[14] For brevity, these measures are referred to henceforth as between-study variability (I^2) and heterogeneity (95% PIs).

A series of meta-regression analyses were performed adjusting for potential moderators including patient cohort type (CKD vs. control / prospective kidney donors), ethnicity, age, sex (proportion of male sex), BMI, and creatinine assay. Further sensitivity analyses were performed excluding studies using the mGFR Gates method (because it is considered inferior to plasma or urinary clearance methods[15,16]) and conference abstracts because of increased risk of bias. All statistical analyses were performed using R Software version 4.4.1.[17]

Assessment of Bias

Risk of bias and applicability for the included studies were assessed by RG and ASa independently using the Quality Assessment of Diagnostic Accuracy Studies–2 tool.[18] Discordant results were reviewed and discussed internally. If no resolution was found, a third reviewer (KB) was consulted (Supplementary Materials -Assessment of Bias).

Certainty of outcomes (bias and P30) were determined using the GRADE criteria and stratified by $eGFR_{Cr}$, $eGFR_{CysC}$, and $eGFR_{Cr\text{-}CysC}$. Funnel plot and Egger's test, using a mixed-effects meta-regression model, were used to evaluate publication bias / small study effect for SMD and P30.

RESULTS

Search Strategy Results

A total of 4858 records were identified, with 3567 after deduplication; 135 required detailed evaluation, of which 8 were unretrievable. Following full-text review. 90 records were excluded, leaving 37 studies. Studies by Wang *et al.*[11] and Safdar *et al.*[19] included additional analysis from a previous cohort (Jessani *et al.*[10] and Safdar *et al.*[20] respectively), resulting in 35 cohorts (Figure 1).[10,19-53] All studies were cross-sectional observational cohort design published between 2008 to 2024. There were 28 peer-reviewed publications, 8 conference abstracts, and 1 abstract only.

Study Population Characteristics

Study populations were described in 32 of 35 cohorts (Supplementary Table S1). The majority included people with CKD ($n = 14$, 40.0%) or prospective kidney donors ($n = 16$, 45.7%). Two studies had participants with chronic liver disease ($n = 79$), 2 were nonspecific (participants who had a mGFR test in the past; $n = 190$) and 1 study included participants with a unilateral single kidney ($n = 47$).

Study sample sizes ranged from 19 to 599 participants, with a median of 88 (interquartile range: 53.5–121) per study and 4725 in total, with comparable numbers of males ($n = 2289$, 48.4%) and females ($n = 2204$, 46.7%); no transgender participants were reported. Most participants were Indian ($n = 2389$, 50.6%), Pakistani ($n = 1198$, 25.4%) or reported as "South Asian" ($n = 1026$, 21.7%), as summarized in Table 1.

Weighted mean age was 46.8 ± 14.6 (range: 31.3–62.0) years, with 7 cohorts having individuals with a mean age > 50 years. BMI was reported in 15 of 35 cohorts (42.9%), with a weighted mean of 25.6 ± 5.3 kg/m^2, ranging from 21.6 to 28.6 kg/m^2.

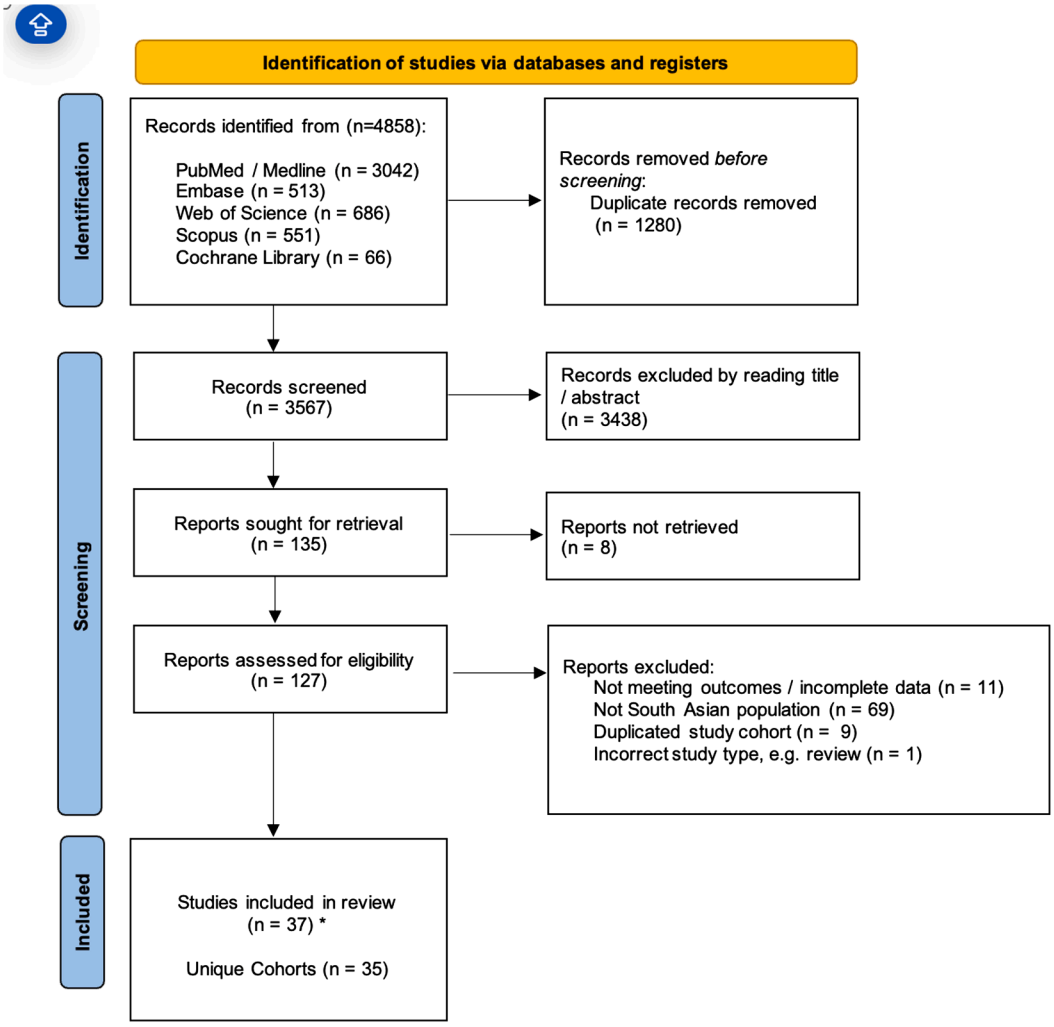
Renal Characteristics

Technetium-99m-diethylenetriaminepentaacetate was used in 25 cohorts (Gates method = 14). Other filtration markers used were iohexol (4 cohorts), inulin (2 cohorts) and chromium-51 ethyldiaminetetraacetate (1 cohort). mGFR was most commonly calculated using plasma clearance (17 cohorts); methods were not stated in 4 cohorts. The weighted mean mGFR was 66 ± 35 ml/min per 1.73 m^2, ranging from 16 to 104 ml/min per 1.73 m^2 (31 cohorts; Table 2).

Precision was recorded in 18 of 35 cohorts (51%). Interquartile range of bias or relative bias was most commonly used ($n = 6$; 17%). Other metrics were 95% limits of agreement ($n = 4$; 11%), SD of bias or relative bias ($n = 4$; 11%), 95% CIs ($n = 2$; 6%) or r-squared statistic ($n = 2$; 6%).

Creatinine-Based Equations ($eGFR_{Cr}$)

$eGFR_{Cr}$ equations were used in every cohort (Supplementary Table S2). Creatinine assays included Jaffe method (18 cohorts), enzymatic method (4 cohorts), and multiple methods (1 cohort). Assays were not stated in 12 cohorts. Isotope-dilution mass spectrometry reference was only explicitly stated in 9 of 35 (25.7%) cohorts. The most commonly assessed equations were the MDRD-4v ($n = 30$), CKD-EPI-2009$_{Cr}$ ($n = 21$), and Cockcroft-Gault ($n = 17$). In most cases, $eGFR_{Cr}$ equations largely overestimated mGFR (Figure 2) with positive SMD observed in all $eGFR_{Cr}$ (Figure 3a). For example, following meta-analysis,



*Two studies have the same cohort but have different eGFR equations in the analysis (Jessani et al. and Wang et al.; Safdar et al. and Safdar et al.). Therefore in each case, both will be included, however, the population data will only be taken from the originally published study.

Figure 1. PRISMA flow diagram illustrating the selection process of studies included in the systematic review and meta-analysis. eGFR, estimated glomerular filtration rate; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

CKD-EPI-2009$_{Cr}$ (n = 17) demonstrated positive SMD in 15 cohorts (Figure 4a). However, there was a greater range of SMD observed with MDRD-4v (n = 25) with negative SMD reported in 7 cohorts (Figure 4b).

SMD was lowest with the Cockcroft-Gault equation (0.18; 95% CI: −0.15 to 0.51) and highest with the CKD-EPI-2009$_{Cr}$ (0.66; 95% CI: 0.35–0.97) and MDRD-6v equations (0.64; 95% CI: 0.39–0.89). P30 was low except with MDRD-6v and Cockcroft-Gault equations (Figure 5a).

Cystatin-C Based Equations (eGFR$_{CysC}$)

eGFR$_{CysC}$ was analyzed in 10 cohorts. The most commonly used equation was CKD-EPI-2012$_{CysC}$ equation (n = 8; 53.3%). Most studies involved Indian participants (8 cohorts; n = 1203), followed by Pakistani participants (1 cohort; n = 557). mGFR was calculated using plasma clearance in 6 studies and Gates methods in the remaining 4. eGFR$_{CysC}$ tended to underestimate mGFR (e.g., CKD-EPI-2012$_{CysC}$ underestimated mGFR in 66.7% of cohorts).

Compared with the other equations, eGFR$_{CysC}$ had smaller SMD, with the CKD-EPI-2012$_{CysC}$ performing best (−0.03; 95% CI: −0.18 to 0.12). Per study (n = 6), SMD ranged from −0.35 to 0.27 with negative and positive SMD observed in 3 studies each respectively (Figure 4c). P30 was only available for the CKD-EPI-2012$_{CysC}$ equation (Figure 5a), which remained suboptimal at 0.72 (0.63–0.80).

Combined Creatinine and Cystatin-c based Equations (eGFR$_{Cr\text{-}CysC}$)

eGFR$_{Cr\text{-}CysC}$ equations were used in 6 cohorts (n = 1630). The CKD-EPI-2012$_{Cr\text{-}CysC}$ equation was

Table 1. Summary of study-level aggregate baseline characteristics

Variable	Number of study populations included, *n* (%)	Number of participants included, *n* (%)	Weighted mean ± SD
Total population	35 (100)	4725 (100)	-
Age, yrs	31 (88.6)	4554 (96.4)	46.8 ± 14.6
BMI, kg/m^2	15 (42.9)	2250 (47.6)	25.6 ± 5.3
Study cohort			
CKD	13 (37.1)	1523 (32.2)	
Transplant	1 (2.9)	30 (0.6)	
Prospective kidney donor	16 (45.7)	1909 (40.4)	
Control / healthy volunteers	6 (17.1)	660 (14.0)	
Other / not stated	5 (14.3)	603 (12.8)	
Sex			
Male	31 (88.6)	2289 (48.4)	
Female	31 (88.6)	2204 (46.7)	
Sex not stated	4 (11.4)	232 (4.9)	
Ethnicity			
Bangladeshi	1 (2.9)	61 (1.3)	
Indian	26 (74.3)	2389 (50.6)	
Nepali	1 (2.9)	51 (1.1)	
Pakistani	4 (11.4)	1198 (25.4)	
South Asian	3 (8.6)	1026 (21.7)	
Study location (country)			
Bangladesh	1 (2.9)	61 (1.3)	
India	22 (62.9)	2144 (45.4)	
Nepal	1 (2.9)	51 (1.1)	
Pakistan	4 (11.4)	1198 (25.4)	
Singapore	1 (2.9)	34 (0.7)	
South Africa	2 (5.7)	156 (3.3)	
United Kingdom	2 (5.7)	157 (3.3)	
South Asia (countries not specified)	2 (5.7)	935 (19.8)	

BMI, body mass index; CKD, chronic kidney disease.
Includes (1) the number and proportion of studies reporting each variable and (2) the aggregate number and proportion of participants from the respective studies for each variable. The weighted mean and SDs calculated from aggregate study data is also included where available.

most commonly used ($n = 6$); eGFR mostly overestimated mGFR (3/4; 75%). SMD was superior, with $eGFR_{Cr\text{-}CysC}$ compared with $eGFR_{Cr}$, ranging from −0.15 to 0.09 (Figure 3a). At study level, SMD of CKD-EPI-$2021_{Cr\text{-}CysC}$ ($n = 4$) was negative in 3 cohorts ranging from −0.31 to 0.03 (Figure 4d). P30 was superior to $eGFR_{Cr}$ and $eGFR_{CysC}$ ranging from 0.79 to 0.82 for the CKD-EPI-$2021_{Cr\text{-}CysC}$ and CKD-EPI-$2012_{Cr\text{-}CysC}$ equations.

Meta-analysis and Regressions

SMD was significantly different between eGFR equations ($P < 0.001$) ranging from −0.03 (95% CI: −0.18 to 0.12; CKD-EPI-2012_{CysC}) to 0.66 (95% CI: 0.35–0.97; CKD-EPI-2009_{Cr}). Between-study variability for SMD was substantial ($I^2 = 84.5\%$) and heterogeneity was high (95% PI: −0.30 to 0.82), with wide 95% PI ranges reported across each eGFR equation (Figure 3a). Repeating the analysis at study level with stratification for eGFR equation (Supplementary Figure S2) showed similar findings between equations but higher between-study variability ($I^2 = 97.1\%$) and greater heterogeneity (95% PI: −0.79 to 1.44). The analysis was repeated using mean difference as illustrated in Supplementary Figure S3.

P30 also identified significant differences between eGFR equations ($P = 0.006$) with proportions ranging from 0.41 (95% CI: 0.16–0.72; CKD-EPI-2021_{Cr}) to 0.82 (95% CI: 0.61–0.93; CKD-EPI-$2012_{Cr\text{-}CysC}$). Between-study variability ($I^2 = 60.9\%$) and heterogeneity (95% PI: 0.46–0.78) were moderate; however, heterogeneity was substantially greater within each equation, except for EKFC (Figure 5a). This was illustrated when repeating the analysis at study level with an overall 95% PI of 0.18 to 0.93, demonstrating substantial heterogeneity (Supplementary Figure S4). Similar to SMD, between-study variability was also greater at 95.9%.

For SMD, the meta-regression demographics model (14 cohorts) explained 78.6% of the between-study variance (R^2) but retained a high-residual between-study variability of 88.4% (I^2). Heterogeneity demonstrated substantial improvement with narrower 95% PIs ranging from 0.01 to 0.83. Mean age was inversely associated with SMD ($\beta = -0.06 \pm 0.01$, $P < 0.001$), whereas BMI ($\beta = 0.40 \pm 0.10$, $P < 0.001$) and male sex ($\beta = 2.01 \pm 0.50$, $P < 0.001$) were associated with greater SMD. Furthermore, Bangladeshi ethnicity differed significantly from the Indian reference group ($\beta = -0.98 \pm 0.22$, $P < 0.001$).

By comparison, the methods model (28 cohorts) accounted for only 17.5% of variance, with high between-study variability ($I^2 = 97.7\%$) and only modest improvement in heterogeneity (95% PI: −0.69 to 1.32). Cohort type (control vs. CKD) was the sole significant moderator for SMD ($\beta = 0.33 \pm 0.14$, $P = 0.024$). Multivariable regression models are described in Table 3.

In the univariable regression analyses, factors which affected SMD were mean age, ethnicity, cohort type, article type, not stated creatinine methods, Gates method for mGFR, and conference abstracts (Supplementary Table S3).

Sensitivity Analyses

In a subgroup analysis excluding the Gates clearance method, 21 of 35 cohorts ($n = 2811$; mean age 50.3 ± 14.4 years; 1282 men [45.6%], 1297 women [46.1%], 232 unspecified [8.3%]) were retained (Supplementary Table S4). Pooled SMDs and P30 for $eGFR_{Cr}$, $eGFR_{CysC}$, and $eGFR_{Cr\text{-}CysC}$ were essentially unchanged compared with the full dataset.

Following removal of Gates method, between-study variability fell moderately for SMD from 84.5% to 65.6% (Figure 3b) and modestly for P30 from 60.9% to

Table 2. Summary of weighted mean mGFR, eGFR, reported bias and aggregate P30 for each eGFR equation. Number of studies included for each set of calculations is also included

Biomarker	eGFR equation	Weighted mGFR & eGFR, no. studies (*n*)	Weighted mGFR (ml/min per 1.73 m^2)	Weighted eGFR (ml/min per 1.73 m^2)	Reported bias range, no. studies (*n*)	Reported bias range (ml/min/1.73 m^2)	P30, no. studies (*n*)	P30 (95% CI)
$eGFR_{Cr}$	CKD-EPI 2009	14	68 ± 33	71 ± 38	19	−10.3 to 39.1	12	59.1 (56.7–61.3)
	CKD-EPI 2021	4	57 ± 30	72 ± 37	4	5.7 to 19.2	5	32.1 (29.3–34.9)
	CKD-EPI Pakistan	2	61 ± 43	-	1	1.3	2	50.0 (46.9–53.2)
	CKD-EPI Asian	1	16 ± 11	21. ± 13	1	5.6	1	40.8 (35.9 – 45.7)
	MDRD 4-variable	21	73 ± 32	76 ± 38	25	−20.4 to 39.2	15	65.3 (63.3–67.2)
	MDRD 6-variable	6	91 ± 16	104 ± 24	6	−2.3 to 31.3	5	74.9 (72.0–77.8)
	Cockcroft Gault	13	86 ± 26	90 ± 33	11	−18.8 to 31.5	5	73.6 (70.7–76.5)
	EKFC	3	58 ± 31	72 ± 35	3	2.7 to 15.0	3	54.8 (51.5–58.1)
	LMR	2	27 ± 28	31 ± 28	1	6.9	2	58.4 (54.0–62.8)
	Cr Mayo clinic	1	96 ± 12	119 ± 17	1	23.4	1	63.4 (59.5–67.3)
$eGFR_{CysC}$	CKD-EPI 2012	6	63 ± 36	61 ± 34	7	−2.1 to 9.5	6	68.2 (65.8–70.6)
	Le Bricon	2	48 ± 33	51 ± 35	1	2.8	0	-
	EKFC	1	54 ± 30	55 ± 26	1	0.2	1	60.0 (55.3–64.7)
$eGFR_{Cr\text{-}CysC}$	Combined Cr-CysC CKD-EPI 2012	5	65 ± 36	63 ± 34	4	−6.2 to 0.9	3	74.8 (72.2–77.4)
	Combined Cr-CysC CKD-EPI 2021	2	52 ± 29	58 ± 32	2	1.6 to 6.6	2	60.2 (55.8–64.6)
	Combined Cr-CysC EKFC	1	54 ± 30	62 ± 30	1	7.6	1	54.0 (49.2–58.8)

CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; EKFC, European Kidney Function Consortium; MDRD, Modified Diet in Renal Disease; mGFR, measured glomerular filtration rate; P30, aggregate percentage of eGFR results within 30% of their corresponding mGFR result.
Data are reported as counts, mean ± SD, range and P30 with 95% confidence intervals.

55.4% (Figure 5b). Heterogeneity decreased in magnitude following removal of the Gates method for SMD from 1.12 (95% PI: −0.30 to 0.82) in all cohorts to 0.88 (95% PI: −0.18 to 0.70) in cohorts excluding Gates method. For P30, there was minimal change in heterogeneity from 0.32 (95% PI: 0.46–0.78) in all cohorts to 0.30 (95% PI: 0.45–0.75) in cohorts without Gates method.

However, when reestimating at the study level, residual I^2 remained > 90% in both SMD and P30 meta-analyses and Cochran's Q tests for subgroup differences were similar (Supplementary Figures S5 and S6). This indicated that exclusion of the Gates method did not significantly alter between-study variability or the ranking of equations.

A further sensitivity analysis was performed with additional exclusion of non–peer-reviewed publications, because of its significant impact on bias identified in the meta-regression (Figures 3c and 5c). For SMD, between-study variability and heterogeneity were only modestly reduced compared with all studies (I^2: 76.5%; 95% PI: −0.35 to 0.69). For P30, between-study variability and heterogeneity were greater (I^2 = 66.8%; 95% PI: 0.39–0.84). In addition, eGFR equation performance rankings for both SMD and P30 were like previous analyses, with minimal changes in between-study variability (I^2 = 96.3% and 96.6%, respectively) and heterogeneity (95% PI: 0.17–0.94), as illustrated in Supplementary Figures S7 and S8.

Assessments of Bias

Using the Quality Assessment of Diagnostic Accuracy Studies–2 tool, patient selection bias and applicability was low in 16 studies (43.2%) for both domains. For the index test (i.e., eGFR), bias and applicability were low in 29 (78.4%) and 11 studies (29.7%) , respectively. The latter was high because of studies not stating if isotope-dilution mass spectrometry–traceable creatinine assays were performed. Bias and applicability for the reference test (i.e., mGFR) were low in 18 studies (48.7%). For flow and timing, it was low in 21 cases (56.8%) and was unclear in 14 cases (37.8%). Bias assessment is summarized in Table 4. Certainty of the outcomes for bias and P30 were largely affected by the heterogeneity of the studies, including differences in methodology (Table 5). Egger's test was significant for both SMD of bias (P = 0.002), and logit-transformed P30 proportions (P = 0.003). Funnel plots are illustrated in Supplementary Figure S9.

DISCUSSION

This study is the first systematic review and meta-analysis to assess the performance of creatinine- and/or cystatin-C–based eGFR equations, compared with mGFR

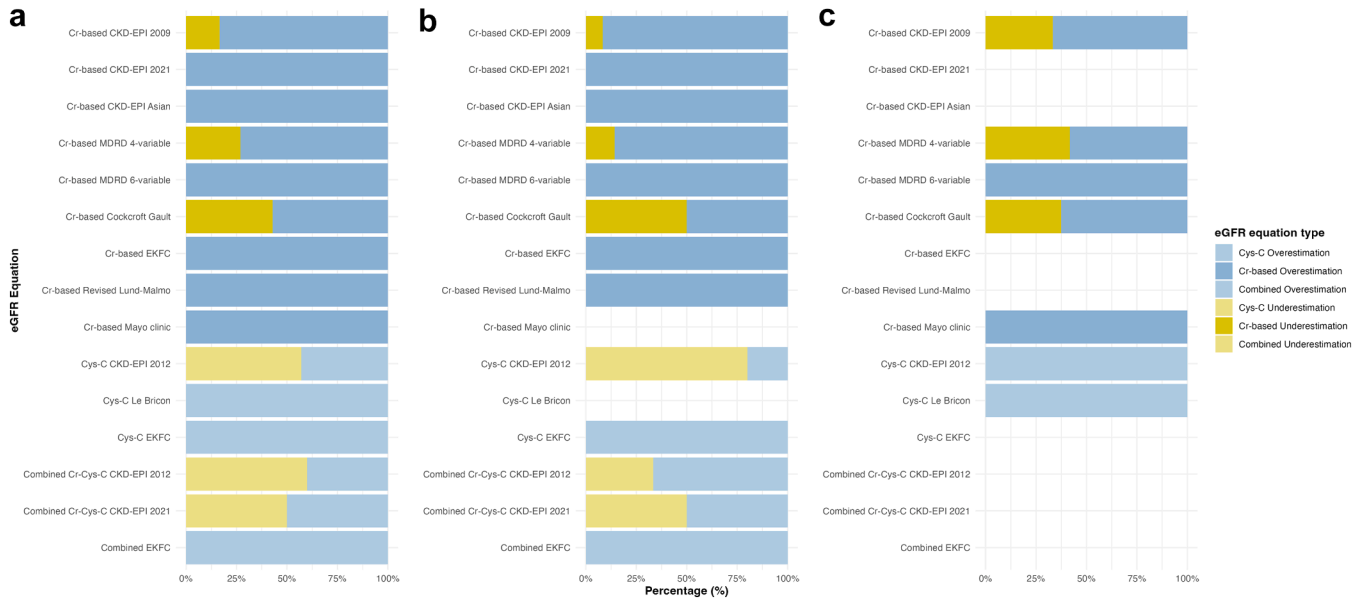


Figure 2. Illustrates the proportion of overestimation (blue) and underestimation (yellow) of eGFR compared with mGFR for each eGFR equation grouped by endogenous filtration markers ($eGFR_{CysC}$, $eGFR_{Cr}$, and $eGFR_{Cr\text{-}CysC}$). (a) All Cohorts; (b) includes cohorts using the Gates method for mGFR only; (c) includes cohorts using plasma or urinary clearance for mGFR. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated GFR; $eGFR_{Cr}$, creatinine-based eGFR; $eGFR_{Cr\text{-}CysC}$, combined eGFR; $eGFR_{CysC}$, cystatin-C–based eGFR; GFR, glomerular filtration rate; MDRD, Modified Diet in Renal Disease; mGFR, measured GFR.

in South Asians. The study included 35 cohorts (4725 participants), which to our knowledge is the largest pooled eGFR analysis in South Asian populations.

Accuracy of eGFR Equations in South Asian Populations

P30 for all equations was low regardless of the biomarker used. For most eGFR equations (creatinine or cystatin-C), accuracy was substantially below the recommended acceptable P30 threshold of 75% (or 0.75) for clinical decision-making.[54] When weighting for sample size and variance, P30 was better for $eGFR_{CysC}$ (0.72) and $eGFR_{Cr\text{-}CysC}$ (0.79–0.82). However, reported P30 remained lower in this pooled South Asian cohort, compared with landmark studies in other ethnic groups, including European (75.7%–86.2%) American (85.9%–91.5%), and African cohorts (60%–71%) reporting CKD-EPI and EKFC equation outcomes.[55–57] eGFR was typically overestimated and the real-world impact of this would be underestimation of CKD population prevalence, delayed diagnosis, and inappropriate prescribing practices based on eGFR thresholds.

Creatinine ($eGFR_{Cr}$)

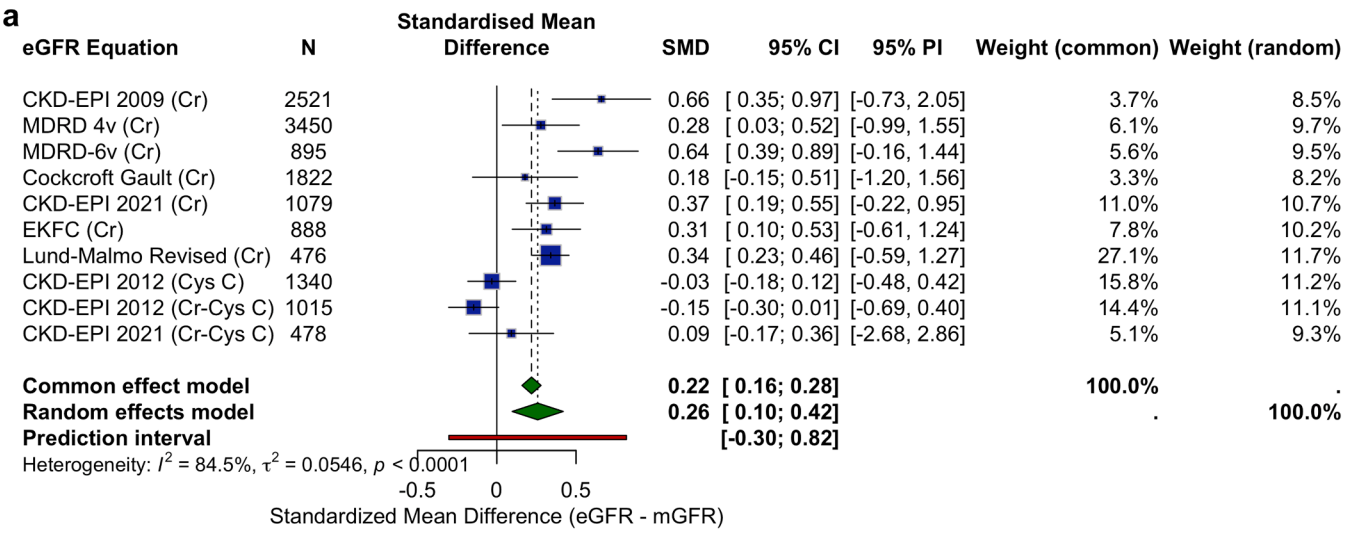
$eGFR_{Cr}$ overestimated mGFR in South Asian populations. This outcome is predictable because non-GFR determinants such as diet and muscle mass may differ in South Asian groups when compared with US populations. This is likely to be significant given that the MDRD and CKD-EPI equations were derived and validated using US cohorts.[6,55,58,59]

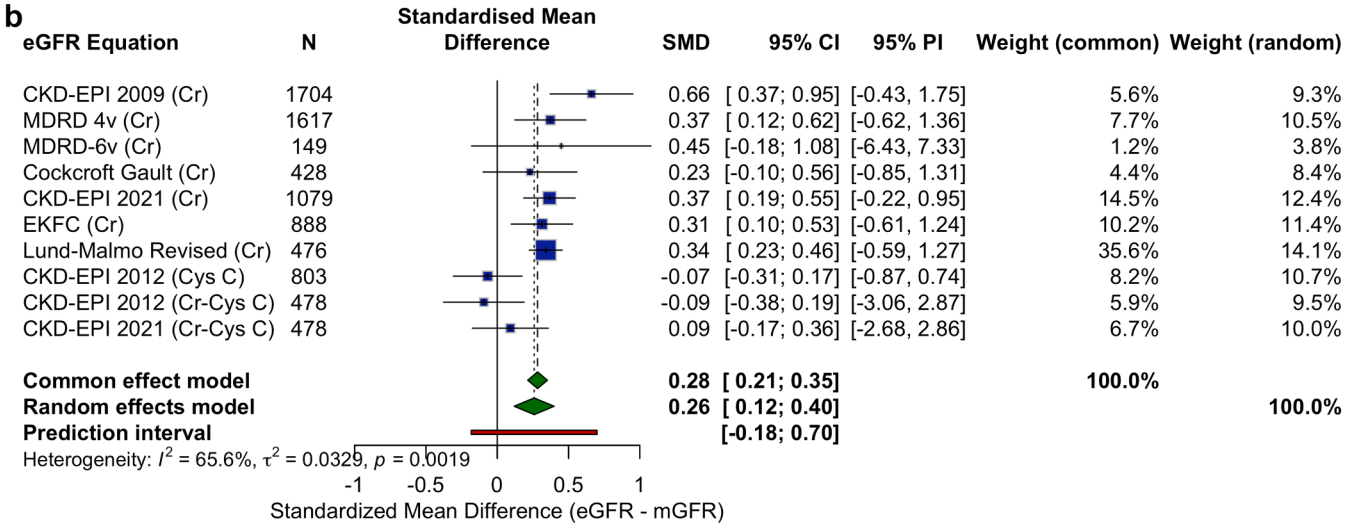
The more recent CKD-EPI-2021 (race-free) equation, which was developed to reduce the gap between Black and White ethnic groups in the USA had minimal South Asian representation and therefore was unlikely to address eGFR performance in South Asian cohorts. However, it performed worse than in predecessors. The reasons for this remain unclear but similar performance has been reflected in other cohorts in Europe and Africa.[40,56]

Cockcroft-Gault and MDRD-4v had the lowest SMD out of the $eGFR_{Cr}$ equations. For Cockcroft-Gault, this may be partly explained by the inclusion of weight as a variable in the equation, because inaccuracy in $eGFR_{Cr}$ is related to differences in weight as a crude surrogate for muscle mass.[60] However, variability in the cohorts and methodology for endogenous and exogenous filtration marker concentration calculation may contribute to the variable performance of $eGFR_{Cr}$, highlighted by the wide 95% CIs for both equations.

Aside from Cockcroft-Gault, the EKFC and Lund-Malmo Revised equations had the smallest SMD for $eGFR_{Cr}$. Interestingly, both equations have been derived from White European populations; however, both have demonstrated improved performance compared with other $eGFR_{Cr}$ equations in non-White populations worldwide.[38,40,56,61] This highlights that factors other than ethnicity are likely to be driving the differences in eGFR performance.

Equally, ethnicity could be seen as a surrogate marker for differences in non-GFR determinants. Therefore, deriving an eGFR equation from a local





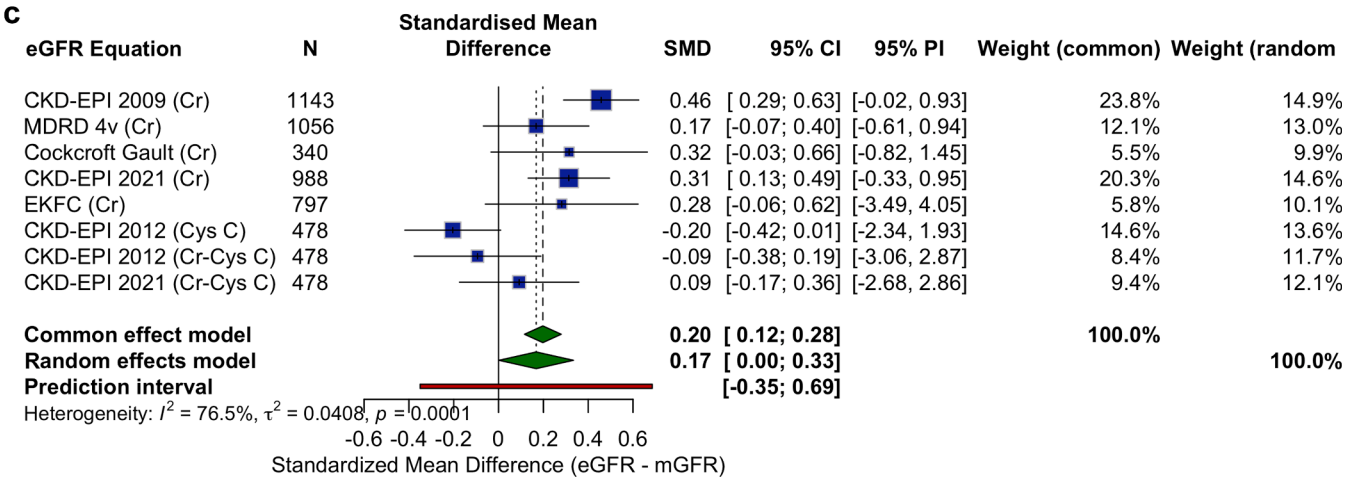


Figure 3. Forest plots for standardized mean difference of eGFR compared with mGFR for the (a) whole cohort, (b) cohort excluding Gates method for mGFR, and (c) cohort excluding Gates method and non–peer-reviewed publications. CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium; MDRD, Modified Diet in Renal Disease; PI, prediction interval; SMD, standardized mean difference.

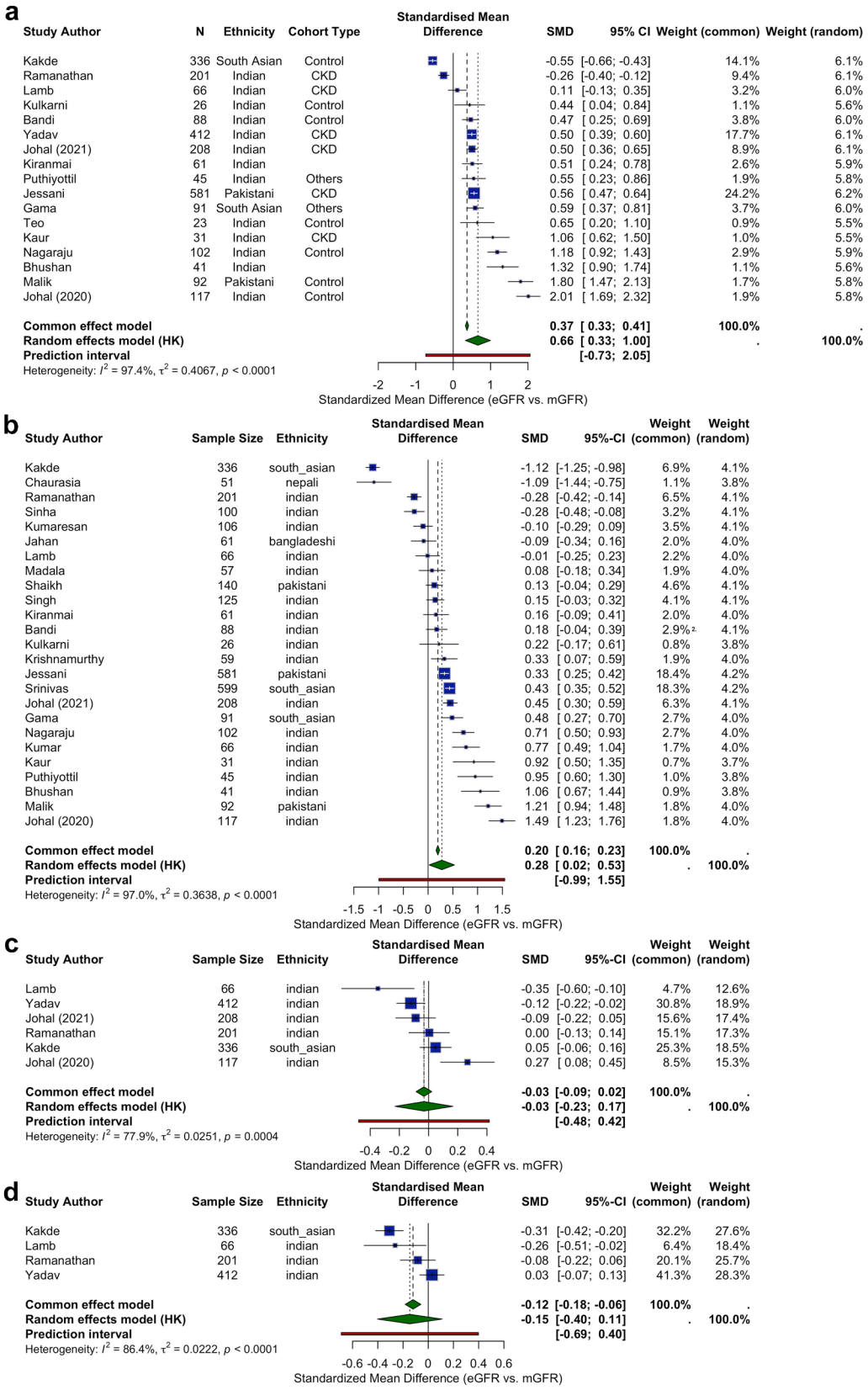


Figure 4. Forest plots demonstrating the treatment effect size (SMD) for (a) CKD-EPI-2009$_{Cr}$, (b) MDRD-4v, (c) CKD-EPI-2012$_{CysC}$, and (d) CKD-EPI-2012$_{Cr\text{-}CysC}$ equations. CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; MDRD, Modified Diet in Renal Disease; SMD, standardized mean difference.

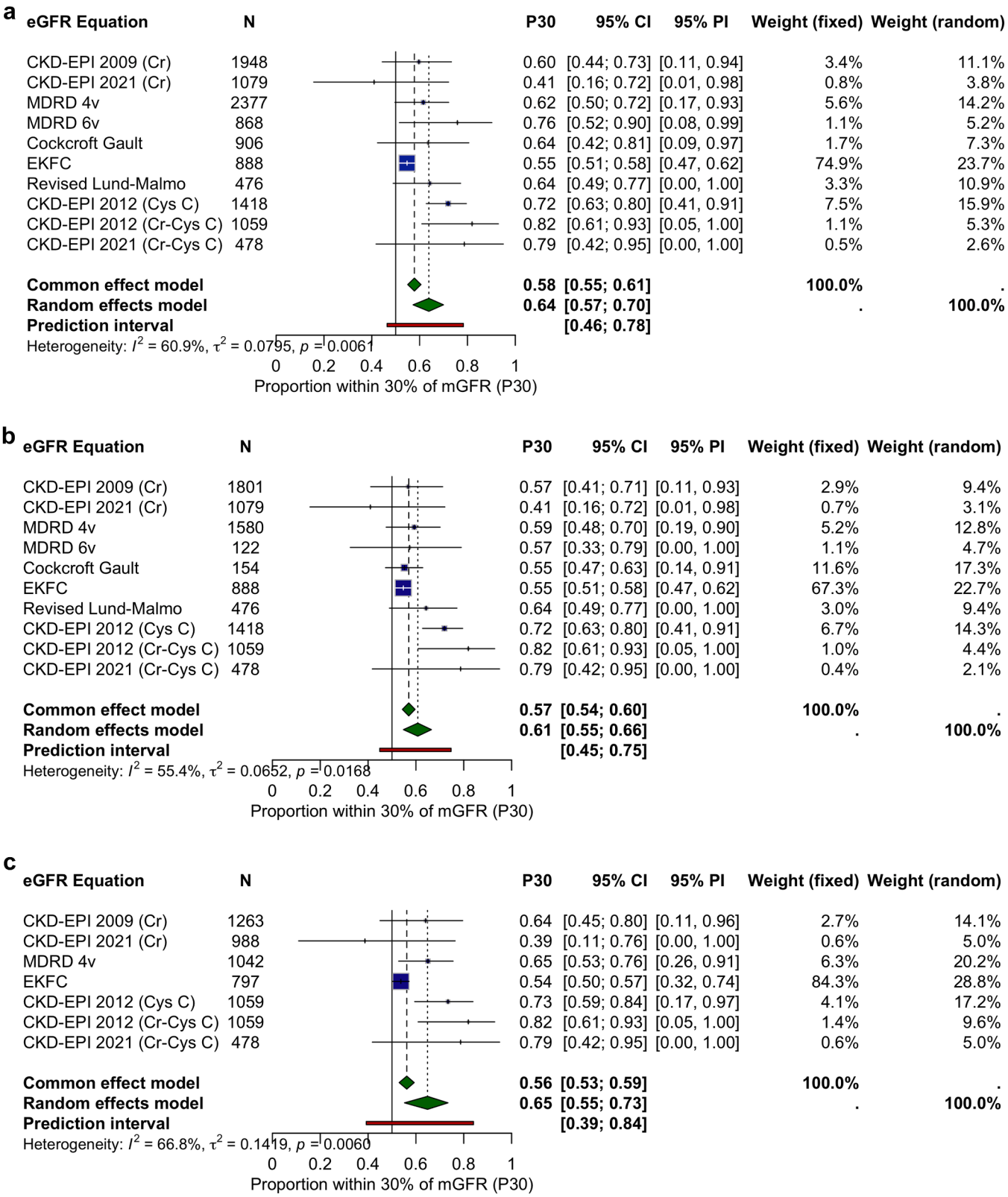


Figure 5. Forest Plots illustrating P30 with logit transformation for the (a) whole cohort, (b) cohort excluding Gates method for mGFR, and (c) cohort excluding Gates method and non-peer reviewed publications. CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EKFC, European Kidney Function Consortium; MDRD, Modified Diet in Renal Disease; PI, prediction interval.

Table 3. Meta-regression multivariable analyses performed grouped by demographic and methodology variables

Variable		Estimate (SE)	*P*-value
Demographics			
Mean age		−0.11 (0.02)	< 0.001
BMI		0.40 (0.10)	< 0.001
Male sex		2.01 (0.50)	< 0.001
Ethnicity[a]: Pakistani		0.08 (0.12)	0.627
Ethnicity: South Asian		−0.08 (0.15)	0.588
Ethnicity: Bangladeshi		−0.93 (0.20)	< 0.001
Demographics model			
Cohorts = 14	R^2 = 78.6%	I^2 = 88.4%	95% PI = 0.01–0.83
Methods			
Reference (enzymatic, gates, CKD)		−0.15 (0.23)	0.513
Creatinine method: Jaffe		−0.04 (0.20)	0.839
Creatinine method: multiple		−0.07 (0.45)	0.869
Creatinine method: not stated		0.34 (0.23)	0.135
Sample size		0.00 (0.00)	0.170
mGFR method: not gates		0.20 (0.15)	0.172
Cohort type: control		0.33 (0.14)	0.024
Cohort type: other		0.43 (0.35)	0.216
Methods model			
Cohorts = 28	R^2 = 17.5%	I^2 = 97.7%	95% PI = −0.69 to 1.32

BMI, body mass index; CKD, chronic kidney disease; mGFR, measured glomerular filtration rate.
[a]Ethnicity reference group = Indian.
Beta-coefficient with standard error and model characteristics (I^2 and R^2) are also recorded for each.

population is likely to result in improved eGFR performance. The CKD-EPI-Pakistan$_{Cr}$ equation is a good example and shows promise for use throughout South Asia, because it outperformed other eGFR$_{Cr}$ equations (as described by Safdar *et al.*[19] and Jessani *et al.*[10]) However, further assessment of this equation in diverse cohorts (with greater representation of CKD) and non-Pakistani populations, is required to determine its utility in other South Asian populations.

Cystatin-C (eGFR$_{CysC}$)

The best performing eGFR equations in South Asians with minimal bias were eGFR$_{CysC}$ equations, which aligns with existing evidence for South Asian groups. Unlike creatinine, cystatin-C is unaffected by muscle mass or sex.[55,62] However, cystatin-C concentrations are higher, independent of kidney function, in the presence of chronic inflammation, smoking, and adiposity.[63,64] Underestimation of mGFR in South Asians using eGFR$_{CysC}$ may therefore be partly explained by adiposity or inflammation from chronic conditions such as diabetes or vascular disease which have been associated with lower eGFR$_{CysC}$; however, confirmation of this association is required with mGFR testing as the reference method.[64,65] Although beyond the scope of this review, similar patterns have been observed in other populations, including different ethnic groups and clinical cohorts, such as oncology patients, where differences in adiposity and/or chronic inflammation may likewise influence eGFR$_{CysC}$.

Combined Creatinine-Cystatin-C (eGFR$_{Cr\text{-}CysC}$)

eGFR$_{Cr\text{-}CysC}$ equations performed better than *eGFR$_{Cr}$*. Potential benefits of using both biomarkers include offsetting limitations of each biomarker (e.g., muscle mass is affected by creatinine, but not cystatin-C) but is dependent on the relative contribution of non-GFR determinants. Bias (SMD) with eGFR$_{Cr\text{-}CysC}$ equations was higher when compared with eGFR$_{CysC}$ equivalents. However, reported P30 was highest with eGFR$_{Cr\text{-}CysC}$ compared with eGFR$_{Cr}$ and eGFR$_{CysC}$ with both CKD-EPI eGFR$_{Cr\text{-}CysC}$ equations surpassing the 75% benchmark.

The improved performance of eGFR in South Asians, when using cystatin-C is important to consider in clinical practice, because smaller positive bias and improved accuracy are likely to improve diagnosis, provide a more accurate representation of CKD prevalence which in turn guides future health policies. Currently, barriers to cystatin-C implementation being included in routine clinical care include a lack of resources within laboratories and higher costs compared with creatinine assays. However, cystatin-C assays have international reference standards and with increased implementation costs, it is possible prices may become more competitive. Therefore, the balance between resource, funding, and clinical performance should be carefully considered by policymakers particularly in regions with significant South Asian representation.

Newer eGFR Equations

Revised Lund-Malmo (Cr) and EKFC (Cr / CysC / Cr-CysC) equations have only been developed recently and therefore were reported in few studies. However, both equations have outperformed CKD-EPI ± MDRD equations in large diverse (non-South Asian) cohorts in Europe and Africa.[20,40,61] The EKFC equation used in the study by Yadav *et al.*[38] used a Q-value (population median Cr/CysC) derived from White Europeans, which is likely to bias the results, because it would not be representative of the Indian cohort being assessed. Therefore, further investigation of newer high performing equations is required to assess performance when "calibrated" for South Asian populations.

Sensitivity Analyses and Meta-regression

After controlling for demographic characteristics, increasing age was associated with a small reduction in SMD, which fits with the existing literature; this highlights increased bias in young adults, particularly with the CKD-EPI and MDRD eGFR$_{Cr}$ equations.[66] Unexpectedly, increasing BMI and male sex (compared

Table 4. Quality assessment of diagnostic accuracy studies–2 table describing the bias of each study based on 4 domains: patient selection, index text (eGFR), reference test (mGFR) and timing and flow (e.g., time between eGFR and mGFR test)

		Patient selection		Index test		Reference test		Flow and timing
#	1st author	Bias	Applicability	Bias	Applicability	Bias	Applicability	Bias
1	Krishnamurthy *et al.*[21]	Low	High	High	High	High	High	Unclear
2	Nagaraju *et al.*[22]	Low	High	Low	Low	High	High	Unclear
3	Washimkar *et al.*[23]	Low	Low	High	High	High	High	Low
4	Hassan *et al.*[24]	High	High	High	High	High	High	Unclear
5	Shaikh *et al.*[25]	High	High	High	High	High	High	Unclear
6	Johal *et al.*[26]	Low	Low	Low	High	Low	Low	Unclear
7	Kakde *et al.*[27]	High	Low	Low	Low	High	High	Unclear
8	Madala *et al.*[28]	Low	Low	Low	High	Low	Low	Unclear
9	Johal *et al.*[29]	Low	Low	Low	High	Low	Low	Low
10	Jessani *et al.*[10]	Low	Low	Low	Low	Low	Low	Low
11	Kaur *et al.*[30]	Low	Low	Low	High	Low	Low	Low
12	Puthiyottil *et al.*[31]	High	High	Low	High	High	High	Unclear
13	Kulkarni *et al.*[32]	High	High	Low	High	Low	Low	Low
14	Teo *et al.*[33]	High	High	Low	Low	Low	Low	Low
15	Malik *et al.*[34]	High	Low	Low	High	High	High	Low
16	Moodley *et al.*[35]	Low	Low	Low	Low	Low	Low	Low
17	Srinivas *et al.*[46]	High	High	Low	High	High	High	Unclear
18	Mulay *et al.*[53]	High	Low	Low	High	High	High	Unclear
19	Lamb *et al.*[36]	Low	High	Low	Low	Low	Low	Low
20	Vinodh *et al.*[37]	Low	Low	Low	High	High	High	Unclear
21	Yadav *et al.*[38]	Low	Low	Low	Low	Low	Low	Low
22	Gama *et al.*[39]	Low	High	Low	High	Unclear	Unclear	High
23	Kumaresan *et al.*[40]	High	High	Low	High	High	High	Unclear
24	Kumar *et al.*[41]	High	High	Low	High	High	High	Low
25	Safdar *et al.*[19]	High	High	Low	Low	Low	Low	Low
26	Ramanathan *et al.*[42]	High	High	Low	High	High	High	Low
27	Chaurasia *et al.*[43]	High	High	Low	High	High	High	Low
28	Jahan *et al.*[44]	High	High	High	High	High	High	Low
29	Nigam *et al.*[45]	Unclear	Low	High	High	Low	Low	Unclear
30	Divyaveer *et al.*[47]	High	High	Low	High	Low	Low	Low
31	Bandi *et al.*[48]	Low	High	Low	High	Unclear	Unclear	Unclear
32	Sinha *et al.*[52]	High	High	Low	High	Low	Low	Low
33	Singh i[49]	High	Low	Low	Low	Low	Low	Low
34	Bhushan *et al.*[50]	High	High	High	High	High	High	High
35	Kiranmai *et al.*[51]	Low	Low	High	High	Low	Low	Low
36	Wang *et al.*[11]	Low	Low	Low	Low	Low	Low	Low
37	Safdar *et al.*[20]	High	High	Low	Low	Low	Low	Low

eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate.

with female sex) had increased SMD. A physiological explanation for this is unclear; however, given that neither variable were significant in the univariable analysis, these findings may reflect residual confounding or collinearity between demographic factors, overfitting of the model, or unaccounted between-study heterogeneity. Nevertheless, this requires further investigation in South Asian cohorts.

There were further statistical differences for Bangladeshi groups (lower estimates) when compared with

Table 5. Assessment of certainty of the meta-analysis outcomes (bias and accuracy) using the GRADE criteria

Outcome	No. of participants (studies)	Effect summary	Overall certainty	Explanation
Bias (Creatinine)	$N = 476 – 3450$ (2–25 studies)	SMD: −0.15 to 0.66	Low / Moderate	Downgraded for inconsistency and indirectness.
P30 (Creatinine)	$N = 476 – 2377$ (2 - 15 studies)	P30: 0.41–0.76	Low	Downgraded for inconsistency, indirectness and imprecision.
Bias (Cystatin-C)	$N = 412 – 1340$ (1–6 studies)	SMD: −0.03–0.14	Moderate	Downgraded for inconsistency
P30 (Cystatin-C)	$N = 412 – 1418$ (1–6 studies)	P30: 0.72	Moderate	Downgraded for inconsistency
Bias (Combined Creatinine and Cystatin-C)	$N = 412 – 1059$ (1–4 studies)	SMD: −0.15 to 0.09	Low	Downgraded for inconsistency and imprecision.
P30 (Combined Creatinine and Cystatin-C)	$N = 412 – 1059$ (1–3 studies)	P30: 0.79–0.82	Low	Downgraded for inconsistency and imprecision.

SMD, Standardized mean difference.
GRADE score based on 5 domains (risk of bias, inconsistency, imprecision, indirectness, and publication bias).

Indian populations. Over half the cohort was defined as Indian; therefore, this is likely to bias the results. However, this highlights the need for population-specific equations (for example, using a calibrated Q-value with the EKFC) to potentially improve performance. It highlights the heterogeneity that exist within high level ethnicity group definitions such as "South Asian" and should encourage subgroup analyses where possible to identify more specific findings, which may be clinically more pertinent. These combined characteristics accounted for 78.6% of the between-study variance in effect sizes, highlighting the importance of these drivers for variation.

In contrast, the methods model—examining factors such as creatinine assay type, mGFR method, sample size, and cohort type—explained only 17.5% of between-study variance by covariates (R^2), with a high I^2 of 97.7% and minimal changes in heterogeneity (95% PIs), suggesting limited explanatory power. None of the creatinine assay methods (e.g., Jaffe vs. enzymatic) or mGFR methods (e.g., clearance vs. Gates) were statistically significant predictors, although control cohorts showed higher SMDs than CKD populations ($\beta = 0.33$; $P = 0.024$). Notably, removing the Gates method, which is recognized as an inferior method for measuring GFR, had only moderate impact pooled SMD and minimal impact on P30, suggesting it was not a major source of heterogeneity in this context. These findings point to the importance of demographic over methodological sources of variation in current evidence and highlight a need for improved standardization and reporting across studies.

Limitations

There was variable reporting of outcomes ranging from mean to median values, which could lead to biased pooled results following a standardized conversion. In addition, some studies lacked detailed reporting on variables such as assay calibration (e.g., isotope-dilution mass spectrometry–traceable standardized creatinine assays), which may inflate heterogeneity.

The Cockcroft-Gault equation was included in the meta-analysis with correction for standardized body surface area. However, 2 out of 14 studies (14.3%) in the meta-analysis did not use this correction but compared the creatinine clearance to absolute mGFR (ml/min).[23,24] We acknowledge that this would introduce bias, particularly with P30 but potentially to a lesser extent with SMD because it is designed to pool different outcomes and units.

Included studies had substantial heterogeneity, with differences in endogenous filtration marker assays, exogenous filtration markers and mGFR methodology (e.g., plasma clearance vs. Gates method). Meta-regression analyses accounted for a substantial portion of between-study variance. However, the persistently high I^2 statistic and wide 95% PIs implies that genetic, environmental, methodological or other unknown factors are likely to have an impact on the study outcomes, which highlights a limitation of the strength of these conclusions.

In addition, precision metrics were variable, and it was not possible to pool these results to include in the meta-analysis. Therefore, although the type of precision metrics were reported, we were unable to assess the precision of eGFR performance across studies.

We included a sensitivity analysis excluding Gates method, but between-study variability and heterogeneity remained high, which suggest that other factors such as study methodologies may contribute. Inclusion criteria were broad, but this has resulted in incomplete or variable datasets between studies (e.g., mean vs. median), thereby impacting the meta-analysis.

There was evidence of publication bias or small study effects from the Egger test and Funnel plots. This could be related to the inclusion of abstracts in the meta-analysis, which have incomplete methodological; and/or outcome reporting or small study populations, which may bias pooled estimates. However, sample size had no significant impact on SMD in the meta-regression and a further sensitivity analysis excluding abstracts showed no meaningful differences in between-study variability or heterogeneity for SMD and P30.

CONCLUSION

Given the growing burden of CKD and the emergence of CKD of unknown etiology in South Asia, accurate GFR estimation is essential not only for individual patient management but also for reliable disease surveillance and longitudinal cohort studies. Despite representing one-fifth of the global population, bias and accuracy of eGFR equations in South Asian populations are currently suboptimal.

$eGFR_{Cr}$ tend to overestimate mGFR, which may lead to underestimation of the true population prevalence of CKD, delayed diagnosis, distorted longitudinal estimates (e.g., time to end-stage kidney failure), and suboptimal medication management for renally excreted drugs. $eGFR_{CysC}$ and $eGFR_{Cr\text{-}CysC}$ equations perform better; however, reported accuracy is variable and clinical implementation is currently limited by the availability and cost of cystatin-C in many settings with substantial South Asian representation. Broader adoption of cystatin C testing may therefore be particularly beneficial for South Asian populations, where body composition, diet, and metabolic factors can introduce creatinine-related bias.

Newer equations such as the Lund-Malmo Revised, EKFC, and CKD-EPI-Pakistan show promise but require further evaluation, calibration, and local validation in South Asian cohorts. Future studies assessing eGFR performance should endeavor to incorporate robust methodological standardization; including the use of plasma or urinary clearance of validated exogenous filtration markers; transparent reporting of biomarker assays and reference standards used (for both creatinine and cystatin-C); and where possible, the inclusion of diverse cohorts across the spectrum of age, body composition, and GFR.

In conclusion, building regionally representative South Asian cohorts, with robust measurement standards, newer eGFR equations and additional biomarkers are required to address eGFR performance in this diverse population, which will be vital to improve CKD detection and ensure more equitable kidney care across this high-risk population.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data supporting this systematic review and meta-analysis were obtained from published studies. No new primary data were collected for this study. Extracted data used in the analysis will be made available to anyone upon request.

AUTHOR CONTRIBUTIONS

RG and KB conceived the study idea and design. Data collection was performed by RG and ASi. Data analysis was conducted by RG, ASi, ASa, and KD. The first draft of the manuscript was written by RG and ASi, with subsequent revisions by RG, PD, and KB. All the authors reviewed and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

Search Strategy.

Assessment of Bias.

Figure S1. Describes the equations used to calculate the weighted mean and weighted SD.

Figure S2. Forest plot illustrating the standardized mean difference of each eGFR equation stratified for each study.

Figure S3. Forest plot illustrating the mean difference of each eGFR equation stratified for each study.

Figure S4. Forest plot illustrating the standardized (logit-transformed) proportion of true 30% accuracy for each eGFR equation stratified for each study.

Figure S5. Subcohort excluding Gates method for mGFR. Forest plots illustrating the standardized mean difference for each study stratified by eGFR equation.

Figure S6. Subcohort excluding Gates method for mGFR. Forest Plot illustrating the standardized (logit transformed) proportion of true 30% accuracy for each study stratified by eGFR equation.

Figure S7. Subcohort excluding Gates method for mGFR and non–peer-reviewed publications. Forest plots illustrating the standardized mean difference for each study stratified by eGFR equation.

Figure S8. Subcohort excluding Gates method for mGFR and non–peer-reviewed publications. Forest plot illustrating the standardized (logit transformed) proportion of true 30% accuracy for each study stratified by eGFR equation.

Figure S9. Funnel plot for meta-analysis assessing the treatment effect for the bias outcome, for each eGFR equation with standardized mean difference (x-axis) against standard error (y-axis).

Table S1. Population characteristics, demographics, measured GFR and estimated GFR for reported in each study, with the weighted meta-analysis of the whole cohort included, where applicable.

Table S2. Frequency of equation use and the total number of participants that were assessed with each equation.

Table S3. Outcomes of a series of univariable meta-regression analyses assessing impact of standardized mean difference of eGFR equations compared to mGFR. Moderators included are mean age, mean BMI, ethnicity, sample size, article type (e.g., peer-reviewed publication vs. abstract), creatinine method, cohort type (e.g., CKD vs. prospective kidney donors / healthy controls) and mGFR methods. Analyses were performed on study level meta-analyses and report estimate with standard error, heterogeneity (I^2) and proportion of accounted variability (R^2).

Table S4. Population characteristics for studies, excluding those using the Gates method for mGFR calculation.

PRISMA Checklist.

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