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A systematic review and meta-analysis comparing the bias and accuracy of the Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration equations in community based populations.

Running head: Bias and accuracy of MDRD and CKD-EPI

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Key words: Chronic Kidney Disease, glomerular filtration rate, MDRD, CKD-EPI

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Analyses from this literature review have previously been presented at South West Society for Academic Primary Care (SW SAPC) 6/7 March 2014, Bristol.

Abbreviations: Glomerular filtration rate (GFR), estimated glomercular filtration rate (eGFR), measured glomerular filtration rate (mGFR), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), confidence interval (CI), isotope dilution mass spectrometry (IDMS), Chronic kidney disease (CKD), quality assessment of diagnostic studies (QUADAS-2),

Abstract

Background: The majority of patients with chronic kidney disease are diagnosed and monitored in primary care. Glomerular filtration rate (GFR) is a key marker of renal function, but direct measurement is invasive; in routine practice, equations are used for estimated GFR (eGFR) from serum creatinine. We systematically assessed bias and accuracy of commonly used eGFR equations in populations relevant to primary care.

Content: MEDLINE, EMBASE and the Cochrane Library were searched for studies comparing measured GFR (mGFR) with eGFR in adult populations comparable to primary care and reporting both the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations based on standardised creatinine measurements. We pooled data on mean bias (difference between eGFR and mGFR) and on mean accuracy (proportion of eGFR within 30% of mGFR) using a random-effects inverse-variance weighted meta-analysis. We included 48 studies of 26,875 patients that reported data on bias and/or accuracy. Meta-analysis of within-study comparisons where both formulae were tested on the same patient cohorts using isotope dilution-mass spectrometry-traceable creatinine showed a lower mean bias in eGFR using CKD-EPI of 2.2 ml/min/1.73m^2 (95% CI 1.1 to 3.2; 30 studies; I^2=74.4%) and a higher mean accuracy of CKD-EPI of 2.7% (1.6 to 3.8; 47 studies; I^2=55.5%). Meta-regression showed that in both equations bias and accuracy favoured the CKD-EPI equation at higher mGFR values.

Summary: Both equations underestimated mGFR but CKD-EPI gave more accurate estimates of GFR.

INTRODUCTION

Chronic kidney disease (CKD) is associated with increased cardiovascular risk, progression to end stage renal failure and reduced survival (1, 2), and is increasing in prevalence globally (3). The majority of patients with CKD are managed in primary care in the UK (4), and, in the absence of interventions that can specifically reverse a decline in glomerular filtration rate (GFR) (5), management strategies address common risk factors for cardio-renal outcomes, such as hypertension and diabetes. Accurate identification of patients with CKD in primary care is therefore a key underpinning public health strategy to reduce the burden of disease associated with CKD.

While no easy method for directly measuring GFR exists, various indirect formulae, including the Modification of Diet in Renal Disease (MDRD) Study equation (6) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (7), provide estimated GFR (eGFR) based upon serum creatinine and other factors that influence creatinine production. These equations fulfil criteria important to a primary care setting: they both use a routinely available blood biomarker that can be sampled in primary care and require minimal additional patient level parameters. While alternative renal biomarkers such as cystatin C can be incorporated into eGFR equations (8) demonstrating improved correlation between eGFR and cardiovascular risk (9), the lack of availability of cystatin C in routine primary care limits the use of these equations in patients managed in the community.

The performance of creatinine-based eGFR equations in populations relevant to primary care appears to vary. MDRD has been commonly used since 2000, but is known to underestimate GFR, particularly in the early stages of CKD (10), which are typically seen in primary care populations (11), and crucially around the cut point

between stages 2 and 3a, which in the UK determines entry onto a CKD primary care register and recommendations for routine annual monitoring (12). By comparison, CKD-EPI has shown improved agreement between measured and estimated GFR, especially in the earlier stages of CKD (13), although this was validated in a pooled dataset comprising research study participants and specific clinical populations rather than patients representative of those seen in primary care. Nevertheless, national guidance on monitoring renal function in the UK (4) and the USA (5) has been updated to recommend estimating GFR using CKD-EPI instead of MDRD.

There has been no reported systematic review and meta-analysis of studies that assess equation performance in populations specifically relevant to primary care, i.e., those with a lower prevalence of renal disease (and therefore higher mean eGFR) than the sets of individuals used for derivation and validation of routinely used formulae (11). We therefore systematically reviewed published studies comparing measured GFR (mGFR) with eGFR, calculated from both MDRD and CKD-EPI equations in populations relevant to a primary care setting.

MATERIAL AND METHODS

Data sources, searches and study selection

MEDLINE, EMBASE and the Cochrane Library were searched from inception until 23rd June 2017 for studies comparing mGFR using a reference method (radionuclide or iodinated tracers) with a simultaneous eGFR using the four variable MDRD formula and the CKD-EPI formula calculated from a creatinine assay standardized to isotope dilution-mass spectrometry methods. We included studies that recruited patients over 18 y of age in different healthcare settings; those not

recruiting primary care patients were assessed for similar mean age and renal function distributions to primary care populations (11). Studies recruiting highly selected patient populations not generalisable to primary care were excluded (transplanted organs, critical illness, single disorder case series) but not those prevalent in primary care, such as hypertension or diabetes. Studies were required to report either mean bias (mean difference between calculated eGFR and measured GFR) or accuracy (percentage of eGFR values within 30% of mGFR (P_{30}) (4)). The search strategy is detailed in the online Supplemental Data file. A protocol for the systematic review was drafted for internal reference.

Data extraction and quality assessment

Two reviewers (JH, DL, JM, JV) independently selected abstracts for full text review and final inclusion, with any differences resolved by a third reviewer (CO'C, DL, EM). Two reviewers (JH, DL, JM, JV) extracted data in duplicate using a standardised data extraction form, with disagreement resolved by discussion and the third reviewer. Extracted items were mean bias, standard deviation (SD) or other measure of precision, accuracy, number of participants, recruitment setting, mean age, gender, co-morbid conditions and mean mGFR. Data on blood pressure, lipid concentrations, smoking status, body mass index and proteinuria were not extracted.

Risk of bias was assessed using the revised tool for quality assessment of diagnostic studies (QUADAS-2) to assess bias and applicability of four domains: patient selection, index test, reference test, flow and timing (14).

Data synthesis and analysis

We present analyses of within-study comparisons of *i*) difference in bias between MDRD and CKD-EPI, in studies that compared both equations with mGFR and *ii*)

difference in accuracy between MDRD and CKD-EPI, both stratified into subgroups of high and low mGFR. We also report meta-analyses of bias and accuracy separately for the MDRD equation and the CKD-EPI equation compared to mGFR.

Difference in bias was calculated by taking the differences in mean absolute bias between eGFR using CKD-EPI and MDRD equations. A negative difference in bias represented lower bias using the CKD-EPI equation compared with the MDRD equation. Data on difference in bias between equations and mean bias for each equation were pooled using random-effects inverse-variance weighted meta-analysis. If the SD could not be calculated from standard error or confidence intervals (CI), it was imputed by taking the mean SD from studies in which it could be calculated. We examined the impact of imputed SDs by conducting additional analyses which excluded studies where SDs could not be calculated.

Difference in mean accuracy was calculated by taking the differences in accuracy between eGFR by subtracting MDRD accuracy from CKD-EPI accuracy. A negative accuracy therefore represented higher accuracy using the MDRD equation compared with the CKD-EPI equation. Data on difference in mean accuracy between equations and mean accuracy for each equation were pooled using random-effects inverse-variance weighted meta-analysis. Standard errors of the accuracy were calculated as square root of [proportion x (1 - proportion) / n]. Studies were ordered in forest plots by mean mGFR in the included patients (low to high). Subgroup analyses were used to compare low and high mGFR (< 60 ml/min/1.73m^2, ≥ 60 ml/min/1.73m^2 respectively) for the difference in bias and difference in accuracy between MDRD and CKD-EPI.

Heterogeneity is reported using the I^2 statistic (15). High heterogeneity was investigated using random-effects meta-regression of each outcome separately against three pre-specified key parameters that differed between renal clinic populations and primary care populations: mGFR, age and gender.

We assessed potential publication bias through sensitivity analyses excluding smaller studies (<100 participants).

Analyses were carried out using Stata (StataCorp. Stata Statistical Software: Release 14.1. College Station, TX) using the commands metan (16) and metareg (16).

RESULTS

Fig. 1 summarises the process of identification and selection of studies. In total, 9559 references were identified after duplicates were removed and 8030 were excluded after title and abstract review. Of the 1529 full-text articles that were reviewed, 182 studies reported eGFR but were excluded because they had no extractable data, did not use both MDRD and CKD-EPI equations, or did not use isotope dilution-mass spectrometry traceable assays. These and other reasons for exclusion are shown in Fig. 1 (1481 excluded studies). Forty-eight studies of 26,875 patients met all the inclusion criteria.

Characteristics of the included studies are summarised in Table 1. Of the 48 included studies, some studies separately reported data from multiple subgroups, resulting in 60 comparisons. Twenty-nine studies (31 comparisons) reported both mean bias and P_{30}, one study reported mean bias only and 18 studies (29

comparisons) reported P_{30} only. The mean age of participants across studies was 57 y, 52% were male, and mean±SD mGFR was 71.5±23.5 ml/min/1.73m^2.

The methodological quality was assessed in all included studies; only three studies were considered as unclear in five or more of the areas for consideration. For the domains of 'index test' and 'reference standard' no studies were assessed as high risk of bias, two studies were assessed as high risk of bias for 'flow and timing' and for all three domains the majority of studies (>85%) were assessed as low risk and therefore high quality. The domain of 'patient selection' was variable and in almost half of the papers it was not possible to determine the degree of bias due to inadequate descriptions of recruitment processes (online Supplemental Table 1).

Difference in bias between CKD-EPI and MDRD equations for eGFR

Across the 30 studies of 7453 patients that reported mean bias, the difference in bias was 2.2 ml/min/1.73m^2 (95% CI 1.1 to 3.2) lower in eGFR estimated using CKD-EPI than using MDRD (Fig. 2), but there was high heterogeneity between studies (I^2=74.4%, p<0.0001). Sub-group analysis of low and high mGFR showed CKD-EPI had significantly lower bias than MDRD only for those studies with mean mGFR ≥ 60 ml/min/1.73m^2 (Fig. 2). Considering bias in the MDRD equation, eGFR on average, across all studies, was 4.7 ml/min/1.73m^2 (95% CI 0.8 to 8.7) lower than mGFR, but varied between studies with high heterogeneity (I^2=99.2%, p<0.0001). Bias in the CKD-EPI equation was on average lower than mGFR by 2.8 ml/min/1.73m^2 (95% CI 0.5 to 6.0) with variation between studies (I^2=99.0, p<0.0001) (Fig. 3). Similar results were obtained in sensitivity analyses excluding one study (17) in which standard deviation was estimated or excluding studies with fewer than 100 participants (data not shown).

Difference in accuracy between CKD-EPI and MDRD equations for eGFR

Accuracy estimates for both formulae were reported in 47 studies of 26,358 patients. In a meta-analysis, mean accuracy of CKD-EPI was 2.7% higher than MDRD (95% CI 1.6 to 3.8) with moderate heterogeneity across studies (I^2=55.5%, p<0.0001) (Fig. 4). Sub group analysis of low and high mGFR showed CKD-EPI had significantly higher accuracy than MDRD only for those studies with mean mGFR ≥ 60 ml/min/1.73m^2. Mean accuracy of MDRD equation was 74% (95% CI 71 to 77) with high heterogeneity (I^2=97.8%, p<0.0001) whereas mean accuracy of the CKD-EPI equation was 77% (95% CI 74 to 80) again with high heterogeneity (I^2=98.6%, p<0.0001) (Fig. 5). Similar results were obtained in sensitivity analyses excluding studies with fewer than 100 participants (data not shown).

Relationship of bias and accuracy to renal function in each study

In meta-regression analyses, difference in bias between equations increased with increasing mGFR. Thus for each 10 ml/min/1.73m^2 increase in mGFR the difference in bias increased by 0.8 ml/min/1.73m^2 (0.3 to 1.3; p=0.002). Difference in accuracy between equations increased in favour of CKD-EPI with increasing mGFR. For each 10 ml/min/1.73m^2 increase in study mean mGFR, the difference in accuracy (P_{30}) increased by an additional 0.9% (0.4 to 1.5; p=0.001) (Supplemental Fig. 1).

No association was found between mean bias of the MDRD equation and increasing mean mGFR using meta-regression (p=0.325). MDRD mean accuracy increased with mean mGFR. For each 10 ml/min/1.73m^2 increase in study mean mGFR, the accuracy (P_{30}) of eGFR increased by an additional 2.5% (1.1 to 3.9; p=0.001) (Data not shown). Neither bias nor accuracy were associated with mean patient age (p=0.975, p=0.382 respectively) or the proportion of men (p=0.63, p=0.894

respectively), and we found no factor that reduced the I^2 statistics for heterogeneity by more than 5%.

No association was found between mean bias of the CKD-EPI equation and increasing mean mGFR using meta-regression (p=0.594). CKD-EPI mean accuracy increased with mean mGFR. For each 10 ml/min/1.73m^2 increase in study mean mGFR, the accuracy (P_{30}) of eGFR increased by an additional 3.6% (2.4 to 4.9; p<0.0001) (Data not shown). Neither bias nor accuracy were associated with patient age (p=0.476, p=0.291 respectively) or the proportion of men in the study (p=0.983, p=0.744 respectively), and no factor reduced the I^2 statistics for heterogeneity by more than 5%.

DISCUSSION

In populations relevant to primary care, we found that both the MDRD and CKD-EPI equations underestimated GFR, but that estimates from CKD-EPI were slightly more accurate than those from MDRD. Clinical and statistical heterogeneity between studies was high. In studies with lower mean levels of renal function (mGFR < 60 ml/min/1.73m^2) eGFR was no different whether using CKD-EPI or MDRD. However, at higher levels of renal function CKD-EPI performed better than MDRD both in terms of bias and accuracy. Therefore, given the distribution of renal function seen in primary care patients (11), this study supports the recent decision in national guidelines to estimate GFR using the CKD-EPI equation (4).

Our analysis shows that absolute bias is smaller in CKD-EPI than MDRD; however, it varies in both direction and magnitude between studies (high statistical heterogeneity for both mean absolute bias and mean bias).

Bias alone is not a straightforward indicator of accurate estimation of GFR, because high variability can cause poor accuracy even when bias is low. Therefore, our analyses of accuracy (P_{30}) are potentially more indicative of overall usefulness of the two equations. On this metric too, CKD-EPI performs better than MDRD, but the mean effect is small compared to the variation between studies.

Both the MDRD and CKD-EPI equations estimate GFR using the same variables (age, gender, ethnicity and serum creatinine), but there were large differences in the distribution of renal function in the populations from which they were derived. The MDRD study population had CKD and a mean GFR of 40 mL/min/1.73m^2,(6) while the CKD-EPI study population included subjects with and without CKD who had a mean GFR of 68 mL/min/1.73m^2 (7). Differences in non-renal determinants of serum creatinine, such as muscle mass and diet, are likely to contribute to the differences in equation performance seen across the range of renal function (18), as may the analytical techniques used to measure serum creatinine. Our results are consistent with a smaller systematic review (18). A further study reported that while CKD-EPI has slightly better performance, assessed using bias and accuracy, the differences were not clinically significant, other than bias at very low levels of renal function (19).

Further improvement in estimating renal function is, however, needed. Guidelines suggest that the proportion of eGFR measurements within 30% of mGFR should exceed 90% (20), yet accuracy within studies was rarely this high. Given that creatinine measurements have high levels of laboratory and biological variability (5, 21), alternative filtration markers, such as cystatin C, that are less dependent on muscle mass, may give better estimates of GFR, and have been included in UK guidelines for a more secure early stage diagnosis of CKD (4). While measured

GFR is sometimes used in clinical practice when a high degree of precision is required (22, 23), it is not a practical solution at population level in primary care.

This is the most comprehensive systematic review and meta-analysis to examine the accuracy of MDRD and CKD-EPI, by comparing eGFR with mGFR, in populations where relevance to primary care has been assessed. While the majority of studies did not clearly recruit from community settings, we used mean study mGFR to construct meta-regressions that estimate bias and accuracy at the higher levels of renal function seen in primary care populations. We used broad inclusion criteria, including all studies that compared eGFRs derived from MDRD or CKD-EPI with mGFR. A smaller previous review only presented descriptive results and restricted inclusion to larger studies comparing eGFRs derived from two or more equations with mGFR (18), While this means we have included smaller studies, sensitivity analyses excluding those with fewer than 100 participants, to investigate publication bias, gave similar results. Furthermore, effects were tested at the study level rather than individual level.

The quality of patient selection in included studies was variable; in many studies the generalisability of individual studies was unclear due to recruitment methods. Different reference tests for mGFR were used and the effect of this on equation performance is not known. The high clinical and statistical heterogeneity requires caution in the interpretation of specific numerical results, such as the estimates of mean bias and mean accuracy for each equation. However, there is a direct link between meta-analysis size and detected heterogeneity (24) and the within-study analysis of difference in accuracy supports the interpretation that CKD-EPI can be more accurate than MDRD. Additionally, some large studies reported metrics that were not analysable, such as median bias or mean % difference, and could therefore

not be included in the meta-analysis. If these studies reported a smaller bias or accuracy, then our meta-analyses could be overestimating the effect sizes.

In summary, CKD-EPI gave more accurate estimates of mGFR particularly in populations with higher mGFR (better renal function), such as those seen in primary care. However, continued investigation of improved estimating equations, novel biomarkers, or both, are merited to optimise CKD detection and monitoring.

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498 **Table 1. Characteristics of studies using both MDRD and CKD-EPI and IDMS-**

499 **traceable assays**

Author	Year	N	Recruitment setting	Population	mGFR	Age, y	% Male	Reported
Altiparmak (25)	2013	229	Renal	mix	45.6	53.9	49	Mean bias P30
Arreola-Guerra (26)	2014	97	NR	healthy	102.7	35.8	58.8	Mean bias P30
Bevc (27)	2012A	255	Renal	mix	55.5	59.7	53.7	Mean bias P30
Bevc (28)	2012	113	Renal	mix	42.9	64	61.9	Mean bias P30
Bhuvanakrishna (29)	2015	508	Potential donor	healthy	91.7	44.1	48	P30
Bjork (30)	2011	850	Other	mix	55	60	55.8	P30
Bjork (31)	2012	996	Other	healthy	44	61	56.1	P30
Bouquegneau (32)	2013	366	Other	mix	56	55	49.5	Mean bias P30
Camargo (33)	2011	55	Other	healthy	98	58	49	Mean bias P30
Camargo (33)	2011	56	Other	diabetes	106	58	49	Mean bias P30
Chen (34)	2014	139	Hospital	mix	68.8	51	51	P30
Chung (35)	2013	207	Potential donor	healthy	116.3	40.4	42	Mean bias P30
Craig (36, 37)	2011	516	Other	mix	65	61	54	Mean bias
Cvan (38)	2015	43	Other	CHF	53.1	73	58	Mean bias P30
Du (39)	2011	142	Other	renal	41.77	65.2	59.9	Mean bias P30
Eriksen (40)	2010	1621	Primary Care	healthy	91.7	56.9	49.3	P30
Flamant (41)	2012	782	Other	renal	42.6	72.8	65.2	P30
Hu (42)	2013	17	Potential donor	healthy		47	75	Mean bias P30
Iliadis (43)	2011	448	Diabetes	diabetes	72	65	47	Mean bias P30
Jeong (44)	2013	607	Other	mix	NR	NR	NR	Mean bias P30
Jessani (45)	2014	581	Primary Care	mix	91	50.6	50.3	P30
Kilbride (46)	2013	394	Primary Care	mix	NR	80	48	P30
Kong (47)	2013	977	Renal	mix	68.3	48.3	49	Mean bias P30
Koppe (48)	2013	224	Renal	mix	41.3	75.3	57.1	P30
Krones (49)	2015	24	Potential donor	healthy	97.5	51	25	Mean bias P30
Lemoine (17)	2013	218	Other	mix	51.8		57.8	P30
Levey (7)	2009	3896	Renal	healthy	68	50	55	P30
Liu (50)	2013	332	Renal	renal	39.7	70	62	Mean bias P30
Lui (51)	2014A	209	Hospital	diabetes	47.9	61.6	57.4	Mean bias P30
Lui (52)	2014	351	Hospital	non-diabetes	60.7	58.3	59.5	P30
Lui (52)	2014	351	Hospital	diabetes	62.8	60.3	59.3	P30

Lui (52)	2014	210	Hospital	diabetes				P30
Lopes (53)	2013	95	Other	healthy	55	85.3	30	Mean bias P30
Lujan (54)	2012	85	Potential donor	healthy	116	41	45.9	Mean bias P30
MacIsaac (55)	2015	199	Diabetes	diabetes	80	62.8	67	Mean bias P30
Maple-Brown (56)	2014	224	Other	diabetes	97	52	37	P30
Maple-Brown (56)	2014	340	Other	non-diabetes	108	40	39	P30
Michels (57)	2010	271	Primary Care	mix	72.6	44.3	44	Mean bias P30
Murata (58)	2011	583	Other	healthy	98.9	56.1	55	P30
Murata (58)	2011	2324	Other	renal	98.9	56.1	55	P30
Nyman (59)	2011	850	Other	healthy	55	60	56	P30
Nyman (60)	2014							P30
Obiols (61)	2013	100	Other	mix	90	53.6	55	Mean bias P30
Praditpornsilpa (62)	2011	350	Other	renal	55.86	59.5	44.9	Mean bias P30
Qiu (63)	2013	176	Other	renal	40.7	48.8	51.6	Mean bias P30
Sagou (64)	2016	120	Other	healthy	100	34	50	Mean bias P30
Schaeffner (65)	2012	570	Primary Care	mix	60.4	78.5	57.2	Mean bias P30
Silveiro (66)	2011	105	Diabetes	diabetes	103	57	50	Mean bias P30
Spithoven (67)	2013	336	Renal	healthy	97.7	53.1	48	Mean bias P30
Tent (68)	2010	253	Potential donor	healthy	103	49.5	43	P30
Teo (69)	2010	232	Renal	renal	51.7	58.4	52	P30
Valente (70)	2014	120	Hospital	CHF	74	59	80	Mean bias P30
Veronese (71)	2014	354	Other	mix	87	53	45	Mean bias P30

NR: Not reported

Figure1. Study flow chart.

Figure 2. Difference in mean bias from CKD-EPI and mean bias from MDRD, and pooled estimate (diamond) stratified into subgroups of high and low mGFR using random effects meta-analysis

Horizontal bars and diamond width denote 95% CIs, and box sizes indicate relative weight in the analysis

Figure 3. Mean bias between eGFR and mGFR calculated using MDRD (left) and CKD-EPI (right) equations, stratified into subgroups of high and low mGFR using random effects meta-analysis

Horizontal bars and diamond width denote 95% CIs, and box sizes indicate relative weight in the analysis

Figure 4. Difference in mean accuracy from CKD-EPI and mean accuracy from MDRD, and pooled estimate (diamond) stratified into subgroups of high and low mGFR using random effects meta-analysis. (P_{30} – proportion of eGFR results within 30% of mGFR result)

Horizontal bars and diamond width denote 95% CIs, and box sizes indicate relative weight in the analysis

Figure 5. Mean accuracy between eGFR and mGFR calculated using MDRD (left) and CKD-EPI (right) equations, stratified into subgroups of high and low mGFR using random effects meta-analysis

Horizontal bars and diamond width denote 95% CIs, and box sizes indicate relative weight in the analysis