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Comparison of MDRD, CKD-EPI, and Cockcroft-Gault equation in relation to measured glomerular filtration rate among a large cohort with diabetes

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Keywords: Diabetes type 1; Diabetes type 2; glomerular filtration rate (GFR)

Abstract

Aims: To analyze the performance of Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft-Gault (CG), and CG calculated with ideal bodyweight (CG-IBW) equations to estimate glomerular filtration rate (eGFR) based on serum creatinine in a large diabetic population.

Methods: 24,516 adults with type-1-diabetes or type-2-diabetes from the multicenter diabetes prospective follow-up registry DPV were analyzed. We compared eGFR and measured GFR (mGFR) based on 24-h urine collection by calculating mean bias (difference), precision (SD of this difference), accuracy (proportion of eGFR within $\pm 10\%$ of mGFR), Bland-Altman-plots.

Results: CG overestimates, whereas MDRD, CKD-EPI, and CG-IBW underestimate. Smallest mean bias and highest accuracy (75.3%) were observed for MDRD compared to the other equations ($p < 0.0001$). MDRD and CKD-EPI estimated most accurately in stages 1 (MDRD:57.7%, CKD-EPI:57.3%) and 2 (MDRD:80.2%, CKD-EPI:80.7%). In stages 3 to 5, highest accuracy was observed for the MDRD (stage3:82.3%, stage4:77.8%, stage5:71.0%). Among younger subjects, accuracy was higher using the CKD-EPI (18-<40 years:63.7%, 40-<60 years:72.8%). Above age 60 years, MDRD estimated most accurately (60-<70 years:77.3%, ≥ 70 years:78.8%). In males and females, MDRD estimated most accurately (males:75.3%, females:75.3%).

Conclusion: In this large diabetic cohort, smallest bias and highest accuracy were observed for the MDRD.

Words: 199

1. Introduction

Chronic kidney disease (CKD) is a worldwide public health problem with increasing prevalence (1). CKD describes heterogeneous disorders affecting the structure and function of the kidney (1). Impaired renal function is a risk factor for cardiovascular disease and all-cause mortality (2). Kidney disease is associated with diabetes, older age, hypertension, obesity as well as genetic factors (1,2). Overall, the leading cause of CKD is diabetes (3). Compared to the general population, the risk for impaired kidney function is higher in individuals with diabetes (2). The prevalence of nephropathy is 30% in subjects affected by type 1 diabetes (T1D) and 10 to 40% in individuals with type 2 diabetes (T2D) (4).

A degree of kidney failure is quantitated by the glomerular filtration rate (GFR) (5-7). The GFR is considered as the best overall indicator for renal function (6). However, depending on the method, measuring renal function is either expensive or time consuming and the reliability may depend on the accuracy of urine collection, particularly in older individuals (6). Therefore, several equations for estimating renal function based on serum creatinine have been developed. The commonly used formulas are Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Cockcroft-Gault (CG) (8-10). These equations have been discussed controversially. Currently, the MDRD is most frequently used by clinical laboratories (11). However, this formula might underestimate GFR in patients with normal to high creatinine levels (6). By analyzing subjects with a wide range of renal function, the CKD-EPI group suggested an equation applying different coefficients to the same parameters used in the MDRD formula (7,12). Due to the limited clinical information in the original study, the validity of the CKD-EPI could be limited for several subgroups (13,14). The CG overestimates renal function and estimates are less accurate (13). However, a previous study demonstrated that in a small geriatric cohort, the CG calculated with ideal body weight (IBW) performed better than the CG with actual bodyweight (15).

Routine monitoring of renal function is mandatory in diabetes care (13,16). Estimation of GFR is central to the diagnosis, evaluation, and management of kidney disease. In patients with diabetes the choice of medical treatment such as oral antidiabetics might be limited by renal function. The prevalence of impaired kidney function increases with age (17), highlighting the need for regular controls in older individuals. Hence, an accurate estimation is important, and improved accuracy has important implications for clinical practice and public health.

The performance of these equations has been rarely examined in large populations with diabetes. Thus, the aim of this study was to assess the agreement between measured and estimated renal function using the MDRD, CKD-EPI, CG, and CG-IBW equations among a large number of adult

patients with diabetes from the German/Austrian DPV registry. Moreover, we analyzed the performance within stages of CKD, among age groups, as well as in males and females.

2. Subjects, Materials and Methods

2.1. Data source and subjects

The patients included in the current study were identified from the Diabetes-Patienten-Verlaufsdokumentation (DPV), a multicenter diabetes follow-up registry. For 20 years, more than 400 specialized health care facilities from Germany, Austria, and Luxembourg use the prospective, standardized documentation system of diabetes care and outcome. Anonymized data are collected locally and transmitted semiannually to Ulm, Germany. In case of implausibility or inconsistency, data are reported back to the centers for correction/verification. Data are aggregated into a cumulative database for clinical research and quality assurance. The Ethics Committee of the University of Ulm has authorized the DPV initiative as well as analyses of anonymized data related to quality of care. The local review board of each participating center has approved the collection of anonymized data (18).

Until September 2016, 453,380 patients were registered in DPV. Adult subjects (≥ 18 years of age) with T1D or T2D were included. Patients without documentation of measured GFR (mGFR) based on 24-h urine creatinine excretion or parameters required to calculate the estimated GFR (eGFR) were excluded. A further exclusion criterion was renal dialysis. The final study population comprised 24,516 patients with diabetes from 138 centers (Figure 1). For each patient, the last year of treatment was analyzed.

2.2. Outcomes

Demographic data (sex, age, duration of diabetes) and clinical data (hemoglobin A1c (HbA1c), body mass index (BMI), body surface area (BSA), hypertension (systolic blood pressure ≥ 140 mmHg/diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive drugs), microalbuminuria (urinary albumin excretion >30 mg/g creatinine), treatment with ACE inhibitors, smoking) were analyzed. HbA1c was mathematically standardized to the Diabetes Control and Complications Trial (DCCT) reference range (20.7-42.6 mmol/mol) by applying the multiple-of-the-mean transformation method (19). BMI was calculated as kg/m². BSA were estimated using the formula of DeBois and DeBois (20).

Stages for chronic kidney disease (CKD) were defined according to the National Kidney Foundation Disease Outcomes Quality Initiative (NKF KDOQI) guidelines: ≥ 90 , 60- <90 , 30- <60 ,

15- <30 , and <15 ml/min/1.73m² (21). 24-hour urine collection was used to determine creatinine clearance (ml/min/1.73m²). Serum creatinine was expressed as both μ mol/l and mg/dl. The MDRD (ml/min/1.73m²) (9), CKD-EPI (ml/min/1.73m²) (10), CG (ml/min) (8), and CG calculated with IBW (ml/min) (15) equations were used to determine eGFR. Definition of estimation methods are shown in Table 1.

Both the MDRD and CKD-EPI include a term for the African American race. Since the proportion of black population is less than 2% in Germany (22) and no data on race was available, the term was excluded. In many studies, the CG equation was adjusted to estimated BSA. However, a recent article reported that formulas used to estimate BSA should be used carefully, particularly in patients with overweight (23). Due to the high BMI observed in the current cohort, the estimates of BSA might be conflicting. Therefore, the CG equation was not adjusted for BSA.

2.3. Statistical analysis

Results of descriptive statistics are presented as median with quartiles for continuous variables and as proportion for binary variables. To examine the correlation between measured and estimated GFR, spearman correlation coefficient was used.

Performance of each eGFR equation was assessed in terms of bias, precision, and accuracy. Bias was defined as the mean difference between measured and estimated GFR, and the standard deviation (SD) of this difference was defined as precision. Accuracy was expressed as the proportion of eGFR results within $\pm 10\%$ of mGFR values. Bias, precision, and accuracy were also evaluated separately for stages of CKD, age groups (18- <40 , 40- <60 , 60- <70 , and ≥ 70 years), and gender. Additionally, BMI groups (normal weight BMI <25 , overweight $25 \leq \text{BMI} < 30$, obese BMI ≥ 30) were examined. Comparing the differences in bias and accuracy between the formulas, paired t-test and McNemar test were used. To investigate the agreement between the measured and estimated GFR, Bland-Altman-plots were performed (24). The difference between mGFR and eGFR is plotted against the mean of mGFR and eGFR. Bias and the 95% limits of agreement which were calculated as the mean difference ± 1.96 times the precision were examined. Agreement between mGFR and eGFR in their classification into CKD stages was analyzed by Cohen's κ .

Statistical Analysis Software 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. Due to the large number of subjects, a two-sided p-value < 0.01 was considered significant.

3. Results

In the current study, 22,294 subjects with T2D and 2,222 individuals with T1D were analyzed. Demographics of the entire study cohort as well as stratified by type of diabetes are described in Table 2.

3.1. Comparing the MDRD, CKD-EPI, CG, and CG-IBW equations

Strong correlation between mGFR and eGFR was observed for all formulas, with $r_{\text{MDRD}}=0.95$, $r_{\text{CKD-EPI}}=0.95$, $r_{\text{CG}}=0.85$, and $r_{\text{CG-IBW}}=0.90$.

Figure 2 depicts Bland-Altman plots of the measured and estimated renal function with bias and 95% limits of agreement for each equation. The CG overestimates, whereas the MDRD, CKD-EPI, and CG-IBW underestimate GFR. Smallest mean bias was observed for the MDRD compared to the CKD-EPI, CG, and CG-IBW equations ($p<0.0001$).

The MDRD estimated measured GFR (based on 24-h urine creatinine) most accurately (75.3% of patients with less than 10% difference between mGFR and eGFR, $p<0.0001$). Accuracy was 70.4% for the CKD-EPI, 27.2% for the CG, and 30.5% for the CG-IBW.

Analyzing individuals with T1D and T2D separately, similar findings were observed among subjects with T2D; however, in individuals with T1D, performance of the CKD-EPI was better compared to the other equations.

3.2. Stratification by stages of kidney disease

Figure 3A depicts mean bias and precision stratified by stages of CKD. Larger mean bias was associated with higher GFR for all equations. Comparing all estimation methods, smallest mean bias was observed for the MDRD in the normal kidney function group ($\text{GFR} \geq 90 \text{ ml/min/1.73m}^2$, $p<0.0001$). In CKD stage 2 ($\text{GFR } 60-<90 \text{ ml/min/1.73m}^2$) a less biased estimate was found for the CKD-EPI ($p<0.0001$). Among patients in CKD stage 3 ($\text{GFR } 30-<60 \text{ ml/min/1.73m}^2$), the MDRD equation estimated least biased ($p<0.0001$). In patients with severely reduced kidney function ($\text{GFR } 15-<30 \text{ ml/min/1.73m}^2$) or endstage kidney function ($\text{GFR } <15 \text{ ml/min/1.73m}^2$), smallest mean bias was observed for the CKD-EPI (both $p<0.0001$).

Table 3 shows accuracy stratified by stages of kidney function for each estimation method. In CKD stage 1 and 2, highest accuracy was observed for the MDRD and CKD-EPI compared to the CG and CG-IBW equations ($p<0.0001$), while in stages 3 to 5 MDRD estimates renal function most accurately (all $p<0.0001$).

Among patients with renal hyperfiltration ($\text{GFR} \geq 160 \text{ ml/min/1.73m}^2$), correlation between measured and estimated renal function was low, with $r_{\text{MDRD}}=0.29$, $r_{\text{CKD-EPI}}=0.35$, $r_{\text{CG}}=0.26$, and $r_{\text{CG-IBW}}=0.27$.

Classification of patients according to measured or estimated renal function into stages of CKD were investigated. The CKD-EPI and MDRD classified most patients correctly into stages of kidney disease ($\kappa_{\text{CKD-EPI}}=0.77$, $\kappa_{\text{MDRD}}=0.74$) compared to the CG and CG-IBW equations ($\kappa_{\text{CG}}=0.49$, $\kappa_{\text{CG-IBW}}=0.49$).

3.3. Stratification by age groups

Mean bias and precision for age groups are shown in Figure 3B. With increasing age, performance of estimates was better for all equations. Comparing all estimation methods, mean bias was smallest for the CKD-EPI in the youngest age group (18-<40 years, $p<0.0001$). Among patients aged 40-<60 years, the CG-IBW estimated renal function less biased ($p<0.0001$). In the 60-<70 year olds, MDRD and CKD-EPI provided less biased estimates (both $p<0.0001$). In the oldest age group (≥ 70 years), smallest mean bias was found for CG ($p<0.0001$).

Accuracy stratified by age group is depicted in Table 3 for all formulas. The CKD-EPI estimated renal function most accurately in the younger individuals (<60 years), whereas in subjects aged ≥ 60 years, estimates were most accurate using MDRD (both $p<0.0001$).

3.4. Stratification by gender

Figure 3C depicts mean bias and precision separately for males and females. Comparing all equations, smallest mean bias was observed using the MDRD in males ($p<0.0001$), whereas in females the CKD-EPI performed a less biased estimate ($p<0.0001$).

For both males and females, the MDRD estimated GFR values most accurately compared to CKD-EPI, CG, and CG-IBW equations (Table 3, both $p<0.0001$).

3.5. Stratification by BMI groups

In the normal weight ($\text{BMI} < 25$), overweight ($25 \leq \text{BMI} < 30$), and obese ($\text{BMI} \geq 30$) group, the MDRD and CKD-EPI provided smaller mean bias compared to the CG and CG-IBW equations ($p<0.0001$, see Supplement Figure 1). With increasing BMI, larger mean bias was observed for the CG equation. Highest accuracy was observed for the MDRD in the normal weight, overweight, and obese group compared to the other formulas (Table 3, $p<0.0001$).

3.6. Subanalysis

Stratification by hypertension

Among patients with hypertension, the MDRD provided smaller mean bias compared to the other formulas (all $p<0.0001$), whereas in individuals without hypertension smaller mean bias was observed for the CKD-EPI (all $p<0.0001$). Highest accuracy was found for the MDRD among

subject with and without hypertension compared to the CKD-EPI, CG, and CG-IBW (Table 3, all $p < 0.0001$).

Stratification by microalbuminuria

Mean bias was smallest for the MDRD equation among patients with microalbuminuria (all $p < 0.0001$), while in subjects without microalbuminuria both the MDRD and CKD-EPI estimated renal function less biased (all $p < 0.0001$). Among individuals with and without microalbuminuria, estimates were most accurate using the MDRD equation compared to CKD-EPI, CG, and CG-IBW (Table 3, all $p < 0.0001$).

4. Discussion

The present multicenter study aimed to analyze the performance of the MDRD, CKD-EPI, CG, and CG-IBW equations to estimate renal function among a large German/Austrian cohort of adults with diabetes by comparing estimates to measured GFR based on 24-h urine creatinine excretion. The MDRD provided a least biased estimate together with the highest accuracy in the entire cohort. Moreover, we examined performance within subgroups. In patients with normal and mildly reduced kidney function ($\text{GFR} \geq 60 \text{ ml/min/1.73m}^2$), high accuracy was observed for MDRD and CKD-EPI. In patients with impaired renal function ($\text{GFR} < 60 \text{ ml/min/1.73m}^2$), estimates were most accurate using MDRD. In younger individuals (< 60 years), the CKD-EPI estimated more accurately, while in subjects aged ≥ 60 years, highest accuracy was found for the MDRD. MDRD estimated renal function most accurately in males and females.

Differences in performance of the MDRD, CKD-EPI, CG, and CG-IBW equations in a large diabetic cohort have not been compared before. Both the CKD-EPI and MDRD underestimate GFR in the general population as well as in patients with diabetes (25), whereas the CG overestimates renal function (26). Rognant et al. (27) confirmed our finding of smallest bias as well as highest accuracy for the MDRD in a diabetic population. Even though many studies concluded that in the general population CKD-EPI is more accurate than MDRD, it is not known whether the CKD-EPI can be applied across various populations such as in elderly or individuals with impaired renal function (6,7). The performance depends on the cohort examined (26). In subjects with diabetes, results are contradictory. Whereas in some previous studies the CKD-EPI did not perform better than the MDRD (6,12,25,27), other studies reported that the CKD-EPI is slightly more precise in predicting kidney function (5,10,13). Further reports stated that the CKD-EPI might not work equally well in subjects with a high risk of cardiovascular disease (5) or diabetes (25). It is well established that the MDRD provides more accurate estimates for GFR below $60 \text{ ml/min/1.73m}^2$. Therefore, an

explanation for the higher accuracy using the MDRD in the current study cohort might be the high frequency of subjects (47%) with impaired renal function.

Studies concluded that the CG equation should not be used in individuals with diabetes (27,28). The formula provides poor estimates and overestimates kidney function (27,29). A reason might be that the CG calculates creatinine clearance proportional to bodyweight (30,31). Especially in patients with T2D, bodyweight might be an important cause for poor performance due to the high frequency of overweight and obesity (29). The use of IBW instead of actual bodyweight may correct this bias; however, using the CG-IBW, underestimation of renal function was observed (28). A recent Dutch study compared in a small geriatric cohort the commonly used equations with a gold standard (sinistrin clearance) (15). The authors indicated that the CG-IBW provides better estimates. Furthermore, a study reported previously that the CG might be a good alternative in elderly patients or in those with low bodyweight (32). Conflicting results might be explained by heterogeneous study populations, different sample size, adjustment for BSA, or diverse reference methods used to determine mGFR.

All equations display worse performance at normal renal function due to greater biologic and measurement variability at higher GFR (32,33). Further reasons for the wide variation among normal and high GFR values might be inter-laboratory variation which has larger effects at higher GFR values, differences of creatinine excretion among and within individuals, influence of drugs on creatinine clearance as well as muscle mass and dietary intake determining the generation of creatinine (34). Particularly in individuals with diabetes, CKD-EPI and MDRD significantly underestimate renal function at higher GFR (25,35). While in most studies the equations were compared between patients with and without CKD (27), only few studies have examined the performance stratified by stage of CKD (32,36). In a previous research the performance among stages of CKD was similar for the MDRD and CKD-EPI (32). However, Rognat et al. (27) revealed that the MDRD equation exhibited the highest accuracy in a diabetic population with and without CKD. In our study, highest accuracy was observed for the CKD-EPI and MDRD in subjects with normal and mildly reduced kidney function; however, in individuals with impaired renal function, highest accuracy was found for MDRD.

Due to similar creatinine levels, but higher GFR values in younger than in older individuals, all methods include a term for age (33). With increasing age, improved estimates of renal function were found (32,36). Previous studies demonstrated that the MDRD is less accurate in younger subjects with diabetes (2). A study conducted by Stevens et al. (37) corroborated our finding of better estimates using the CKD-EPI in younger individuals (<60 years) compared to the MDRD.

However, findings from other studies indicated that the MDRD predicted GFR more accurately in older subjects (17,38). This is in line with our finding of more precise estimates by the MDRD in older individuals (≥ 60 years). A reason for these findings might be higher GFR values in younger subjects and lower GFR in the elderly.

To account for higher GFR in males compared to females at the same serum creatinine level, a term for female sex is included in all equations (33). Irrespective of gender, accuracy was highest for the MDRD compared to the CKD-EPI, CG, and CG-IBW. White et al. (14) reported previously that the CKD-EPI equation provides a better estimate of CKD in females than in males. This confirms our finding that the CKD-EPI was less biased in females, whereas in males the MDRD provided smallest bias.

Whereas most studies examined a diabetic cohort (6) or either individuals with T1D or T2D (5,13), a recent study exhibited that the MDRD provided highest accuracy for both subjects with T1D and T2D (27). We observed similar findings in individuals with T2D; however, among subjects with T1D, performance of CKD-EPI was better compared to the other equations. Different findings might be due to age differences, diverse sample size or heterogeneous ranges of kidney function.

The relation between BMI and performance of estimation methods was investigated in a previous cross-sectional study (32). The authors demonstrated that using the CG equation the estimation of renal function depends on BMI contrary to the MDRD and CKD-EPI. With increasing BMI, larger bias was observed for the CG formula. Moreover, in our diabetic cohort, highest accuracy was found for the MDRD in the normal weight, overweight, and obese group.

Previous reports demonstrated limitations of generalizing an equation developed in one population to another population (33). The disappointing performance in subjects with diabetes can be partially attributed to the relationship between age, metabolic control, and renal function (25). Compared to the general population, hyperglycemia, glomerular hyperfiltration, higher BMI as well as higher creatinine levels despite similar GFR might be related to the algorithms in a diabetic population (25,35). Another reason might be the influence of medical treatment such as antidiabetic drugs on creatinine levels (12,39,40). New equations based on serum cystatin C have been developed. The ActiFE Study group investigated the prevalence of CKD estimated by the MDRD, CKD-EPI, and Cystatin C based equation. The authors demonstrated that the prevalence of CKD varied between 14.6% for the Cystatin C based equation to 33.0% and 34.3% for the CKD-EPI and MDRD (41). However, recently in a cross-sectional study, methods based on cystatin C

did not provide better estimates than creatinine based formulas (13). Therefore, further research is necessary to develop more precise tools to estimate GFR in individuals with diabetes.

We acknowledge some limitations of our study. Due to the multicenter structure of this study, renal function and serum creatinine were not measured centrally, and therefore differences cannot be excluded completely. The use of 24-hour urine collection to measure creatinine clearance has some limitations. Previous studies reported that this method is not considered precise enough to be used in assessment of renal function (42,43). Reliability of 24-hour urine collection may depend on completeness of urine sampling, especially in older age groups, and also on variation in creatinine excretion. We could not compare renal function determined by cystatin C methods or radionuclide clearance with results of eGFR, as cystatin C methods are expensive as well as radionuclide clearance is expensive and cumbersome, and therefore not suitable for daily practice. Since the current study cohort comprised German/Austrian subjects with diabetes, our results might not be generalizable to other populations, such as individuals without diabetes or other ethnic groups.

A strength of this study is the huge number of adult subjects with T1D or T2D, as we are able to compare the commonly used equations based on serum creatinine to estimate the kidney function in a large diabetic population. The DPV database provides detailed information on characteristics of the study population that allow to analyze the influence of CKD stages, age, and gender on the performance of estimation methods.

In conclusion, the MDRD equation provides a clinically useful estimate of renal function among adults with diabetes as well as in most subgroups. However, further estimation methods or the use of biomarkers instead of serum creatinine might lead to more accurate estimates of kidney function.

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Declaration of Interest

The authors declare that they have no conflicts of interest relevant to this article.

Author Contributions

Data analysis: AS and RWH. AS wrote/edited the manuscript. RWH is the principle investigator of the study, contributed to data analysis and interpretation, and reviewed/edited the manuscript. MD, PF, MP, CW, JW, and AZ researched data und reviewed/edited the manuscript. All co-authors approved the final version to be published.

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Figures

Figure 1

Figure depicts selection of the study cohort. Patients without documentation of measured GFR or parameters required to calculate the estimated GFR (eGFR) using the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Cockcroft-Gault (CG) equations were excluded. A further exclusion criterion was renal dialysis.

Figure 2

Bland-Altman plots of the estimated and measured renal function for each estimation method. Differences between mGFR and eGFR are plotted against mean GFR values. The dashed lines represent the mean difference, the solid lines depict the lines of agreement calculated as mean difference ± 1.96 times the SD of this difference.

Abbreviations: glomerular filtration rate (GFR), measured GFR (mGFR), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft-Gault (CG), CG calculated with ideal body weight (CG-IBW).

Figure 3

Comparison of mean bias and precisions across subgroups. Mean bias and precision between estimated and measured GFR was calculated separately for stages of CKD, age groups, and gender.

Abbreviations: chronic kidney disease (CKD), glomerular filtration rate (GFR), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft-Gault (CG), CG calculated with ideal body weight (CG-IBW).

Supplement Figure 1

Comparison of mean bias and precisions across BMI groups (normal weight BMI<25, overweight 25≤BMI<30, obese BMI≥30).

Abbreviations: chronic kidney disease (CKD), glomerular filtration rate (GFR), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft-Gault (CG), CG calculated with ideal body weight (CG-IBW), Body mass index (BMI).

Table 1 Definition of estimation methods

Estimation Method	Equation
<i>MDRD</i>	$175 \times \text{creatinine [mg/dl]}^{-1.154} \times \text{age [years]}^{-0.203} \times 0.742 \text{ [if female]}$
<i>CKD-EPI</i>	$141 \times \min\{\text{creatinine}/k, 1\}^{\alpha} \times \max\{\text{creatinine}/k, 1\}^{-1.209} \times 0.993^{\text{age [years]}} \times 1.018 \text{ [if female]}$ where k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males
<i>CG</i>	$((140 - \text{age [years]}) \times \text{body weight [kg]}) / \text{creatinine [\mu mol/l]} \times 0.85 \text{ [if female]}$
<i>CG-IBW</i>	$((140 - \text{age [years]}) \times \text{IBW}) / \text{creatinine [\mu mol/l]} \times 0.85 \text{ [if female]}$ where $\text{IBW} = 50 + 0.9 \times (\text{length [cm]} - 152)$ for males and $\text{IBW} = 45.5 + 0.9 \times (\text{length [cm]} - 152)$ for females

Equations for estimating renal function based on serum creatinine.

Abbreviations: glomerular filtration rate (GFR), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft-Gault (CG), ideal body weight (IBW), Cockcroft-Gault with IBW (CG-IBW).

Table 2 Demographics of the entire study cohort and separated by type of diabetes.

	Study population	Type-1-diabetes	Type-2-diabetes
N	24,516	2,222	22,294
Demographics			
Male (%)	52.5	55.1	52.3
Age (years)	72.0 [61.0; 79.2]	48.2 [31.0; 62.0]	73.1 [63.5; 79.8]
Duration of diabetes (years)	9.9 [4.2; 16.0]	15.8 [7.6; 29.0]	9.7 [4.0; 15.4]
HbA1c (mmol/mol)	54.9 [45.8; 69.2]	60.1 [50.4; 77.1]	54.2 [45.4; 68.1]
BMI (kg/m ²)	29.2 [25.6; 33.6]	24.7 [22.3; 28.2]	29.6 [26.1; 34.0]
BSA (m ²)	2.0 [1.8; 2.1]	1.9 [1.7; 2.0]	2.0 [1.8; 2.1]
Comorbidities			
Hypertension, %	70.9	46.7	73.3
Microalbuminuria, %	39.6	31.4	40.5
Treatment with ACE inhibitors, %	15.6	8.1	15.2
Smoking, %	7.6	14.0	7.0
Kidney function			
Creatinine (mg/dl)	1.1 [0.8; 1.4]	0.9 [0.8; 1.1]	1.1 [0.9; 1.5]
Creatinine (μmol/l)	93.7 [73.4; 126.4]	79.6 [66.3; 97.2]	96.4 [75.0; 130.0]
Measured GFR (ml/min/1.73m ²)	63.0 [43.1; 88.0]	90.9 [64.0; 113.0]	60.8 [42.0; 85.0]
Estimated GFR	67.3±32.7	90.0±37.3	65.1±31.3

MDRD (ml/min/1.73m ²)	60.7 [42.2; 82.6] 63.9±29.7	84.0 [62.4; 102.0] 82.8±32.4	58.6 [41.0; 80.0] 62.0±28.7
CKD-EPI (ml/min/1.73m ²)	61.9 [41.5; 86.1] 63.6±27.9	92.0 [66.4; 108.9] 86.6±30.5	59.1 [40.3; 83.1] 61.3±26.5
CG (ml/min)	69.2 [45.4; 104.5] 79.4±45.8	100.5 [68.7; 131.1] 101.8±45.3	66.8 [44.3; 100.4] 77.2±45.2
CG-IBW (ml/min)	52.2 [34.7; 77.6] 59.0±32.4	89.0 [59.5; 116.7] 90.1±40.1	49.8 [33.7; 73.0] 55.9±29.7

Results are given as median with quartiles for continuous variables and as proportions for binary variables. Measured and estimated GFR are additionally presented as mean $\pm$ SD.

Abbreviations: hemoglobin A1c (HbA1c), body mass index (BMI), body surface area (BSA), glomerular filtration rate (GFR), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft-Gault (CG), CG calculated with ideal body weight (CG-IBW).

Table 3 Accuracy (%) for each estimation method.

	MDRD	CKD-EPI	CG	CG-IBW
Entire study cohort	75.3	70.4	27.2	30.5
Strata of GFR				
GFR ≥ 90 ml/min/1.73m ²	57.8	57.3	24.4	33.5
GFR 60-<90 ml/min/1.73m ²	80.2	80.7	28.6	29.2
GFR 30-<60 ml/min/1.73m ²	82.3	74.0	28.9	28.2
GFR 15-<30 ml/min/1.73m ²	77.8	60.1	25.4	35.4
GFR <15 ml/min/1.73m ²	71.0	49.8	14.4	35.6
Age groups				
18-<40 years	50.3	63.7	19.7	34.6
40-<60 years	68.7	72.8	16.3	44.2
60-<70 years	77.3	75.7	22.9	42.1
≥ 70 years	78.9	68.1	33.1	21.2
Gender				
Male	75.3	69.6	27.3	40.3
Female	75.3	71.2	27.1	19.5
BMI groups				
BMI <25	72.6	66.0	29.7	25.3
25 $\leq$ BMI <30	76.0	69.1	40.2	27.3
BMI ≥ 30	75.6	72.9	15.6	29.8
Hypertension				
Yes	74.8	68.9	27.4	28.6
No	76.4	73.8	26.6	34.7
Microalbuminuria				
Yes	70.8	62.6	26.0	26.0
No	74.8	71.4	28.3	30.5

Comparison of accuracy (proportion of eGFR within $\pm 10\%$ of mGFR values) across subgroups of stages of CKD, age groups, gender, and BMI groups. Values in bold depict highest accuracy compared to the other formulas (all $p < 0.01$).

Abbreviations: glomerular filtration rate (GFR), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft-Gault (CG), CG calculated with ideal body weight (CG-IBW), Body mass index (BMI).