**The global burden of chronic kidney disease: estimates, variability and pitfalls**

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**Abstract**

Chronic kidney disease (CKD) is currently defined by abnormalities of kidney structure or function as assessed using a matrix of variables including glomerular filtration rate (GFR), thresholds albuminuria and duration of injury, and is considered by many to be common disorder globally. However, estimates of its prevalence vary widely, both within and between countries. The reasons for these variations in epidemiological estimates of CKD prevalence are manifold, and include true regional differences in CKD prevalence, vagaries of using estimated GFR for identifying CKD, issues relating to the use of set GFR thresholds to define CKD in elderly populations, and concerns regarding “one-off” testing of eGFR or albuminuria to define prevalence of CKD in large-scale epidemiological studies. Although CKD is common, its prevalence might not be increasing in many countries, as has been suggested. Here we discuss possible origins of differences in estimates of CKD prevalence and present solutions for tackling the factors responsible for the reported variations in GFR measurements. The strategies we discuss include approaches to improve testing methodologies for more accurate assessment of GFR, improve awareness of factors that can alter GFR readouts and approaches to more accurately stage CKD for certain populations, including the elderly.

**[H1] Introduction**

Several epidemiological studies published over the past decade suggest that the prevalence of chronic kidney disease (CKD) in the general population is increasing. These findings, which are predominantly based serum and urinary biomarkers that are thought to reliably identify CKD, have led some researchers to describe CKD as a worldwide epidemic 1–8. The phenomenon is directly related to the epoch defining CKD classification and staging guidelines that were introduced in 2002 by the US-based National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI)9. The introduction of these guidelines catalysed the transformation of CKD from a plethora of ill-defined descriptions to a well‑organized uniform system for identifying and categorizing CKD. The KDOQI guidelines categorized CKD into one five stages on the basis of thresholds of estimated or measured glomerular filtration rate (GFR) that departed from normal young adult values, clinical features of kidney damage and duration of renal abnormalities.

These developments paved the way for a host of epidemiological studies designed to characterize the global burden of CKD in both the general population and in various subgroups believed to be at high risk of CKD, such as patients with diabetes mellitus. The cumulative effect of these epidemiological studies has been to propagate a common view that CKD is a common disorder that is often unrecognized by patients and providers alike. In this Review, we critically examine this view. We assess the impact of using estimated GFR (eGFR) to define CKD and critique the published analyses of the global frequency of CKD, as defined using KDOQI, KDIGO, or other schema. We suggest that the notion of a global epidemic of CKD be re-evaluated due to various issues, including the calibration of eGFR to gold-standard GFR measurements; the selection of eGFR formula; variations in serum creatinine —one of the most commonly used biomarkers to assess eGFR — due to diet and other environmental factors that are not related to kidney disease; and to misclassification introduced by ‘one-off’ testing of serum creatinine level to define eGFR and CKD prevalence.

Another point to note is that most epidemiological characterizations have used a ‘generic’ approach in which diverse aetiologies have been aggregated under the umbrella term, CKD. Attempts have been made to increase granularity by sub-classifying CKD into more specific forms10, such as diabetic nephropathy or immune-mediated glomerulonephritis; indeed, the KDIGO guidelines11 recommend identification of the specific underlying disease where possible. Although this issue of disease heterogeneity represents a major hurdle to the management of patients with CKD and affects definitions of disease prevalence, this topic is beyond the scope of this Review.

**[H1] Diagnosing chronic kidney disease**

***[H2]* Measuring GFR**

The reported prevalence of CKD in epidemiological studies varies depending on the clinical characteristics of the population analysed and the approach used to define and diagnose CKD1–7,12,13. The way in which GFR is assessed therefore has a considerable effect on our understanding of CKD epidemiology. Ideally, GFR should be measured. Measured GFR (mGFR) gives an accurate assessment of GFR, and avoids confounding by interactions with variables — such as age or weight — that are included in some eGFR equations, or non-GFR determinants impacting upon values derived from eGFR equations using creatinine or cystatin C as biomarkers — such as muscle wasting or increased muscle mass for creatinine or inflammation or obesity for cystatin C — known to influence the biomarkers on which the equations are based14–16.

The gold standard approach to measure GFR involves measurement of inulin urinary clearance17 (Box 1); however, this approach is too costly and cumbersome for use in large epidemiologic studies (in our estimation, such as those with >10,000 participants). Indeed, for inulin, only urinary clearances with intravenous continuous infusion (after a loading dose) are required. Two or three urine collections of 30 to 60 minutes are necessary after reaching a period of equilibrium around 60 minutes. The rate of plasma clearance of iodinated contrast agents, such as iohexol and iothalamate, has also been used to approach the measurement of GFR without urine collections in small to medium sized cohort studies and clinical trials, but this approach has its own unique drawbacks, such as a requirement for repetitive plasma samples over many hours and is also not well suited to very large epidemiological studies of CKD prevalence because of cost and inconvenience**.** However, use of iodinated contrast plasma clearance to asses GFR in some observational studies (with up to approximately 1,600 participants) might inform the interpretation of larger epidemiology studies that have relied on eGFR. For example, the Chronic Renal Insufficiency Cohort (CRIC; *n*= 1214), the Berlin Initiative Study (BIS; *n*= 570), the Age, Gene/Environment Susceptibility study (*n*= 805) and the Renal Iohexol Clearance Survey (RENIS;  *n*=1,632), are four observational cohorts that assessed plasma clearance of iothalamate (CRIC) or iohexol (BIS, the Age, Gene/Environment Susceptibility study, and RENIS) that could be used as reference studies for larger investigations18–22.

Despite the associated costs and complexity of approaches to measure GFR, they provide a more accurate description of renal function than currently available equations to estimate GFR, and have potential to improve our understanding the epidemiology of CKD. The RENIS and the BIS studies are interesting examples of how the reported prevalence of CKD can differ according to the method used to assess GFR. The observational RENIS study used a single sample of iohexol clearance to assess GFR among individuals aged 50–62 years with a low risk of cardiovascular disease drawn from the general population in Tromsø, Norway20,23. The prevalence of CKD (defined as GFR <60 ml/min/1.73 m² according to iohexol clearance was extremely low (2.12%), but the ability of and two GFR estimation equations (MDRD and CKD-EPI; BOX 1) to detect an mGFR <60 ml/min/1.73 m² was extremely poor (100% specificity and only 18% sensitivity with an area under the receiving operating characteristic (ROC) curve of 0.76 for both equations)20. BIS also used iohexol clearance to assess GFR in a European cohort of elderly patients (mean age 79 years) 7,21. The prevalence of CKD (defined as GFR <60 ml/min/1.73 m²) was notably higher when assessed by plasma iohexol clearance than by creatinine-based eGFR equations, such as the MDRD or CKD-EPI equations. Indeed in the 570 subject with GFR measured by iohexol plasma clearance, prevalence of GFR below 60 ml/min/1.73 m² was 47.9, 27.7 and 30.2% with iohexol, MDRD and CKD-EPI, respectively 21 (TABLE 1; TABLE 2).

As described above, estimates of CKD prevalence are dependent on the approach used to assess GFR. It is our view that using measuring GFR through inulin, iohexol or iothalamate clearance will result in a more accurate understanding of the prevalence of CKD. At of the time of writing, however, the numbers of observational studies that utilize plasma disappearance or urinary clearance methods to assess GFR are still too few to be conclusive, but we expect the prevalence of CKD to differ according to whether GFR is measured or estimated using equations. Moreover, it must be noted that the difference between eGFR and mGFR could vary according to the age of the study population, depending on the GFR estimating equation employed and the biomarkers utilized.

***[H2] The limitations of biomarkers***

The two most commonly used biomarkers for assessing of GFR in clinical practice are serum creatinine and plasma cystatin C (BOX 2). These biomarkers present three potential issues that need to be considered in the context of epidemiological studies: the calibration of biomarker assays to ensure inter-laboratory consistency; interference by non-GFR determinants; and day to day biological variations in biomarker concentrations.

*[H3] Issues with assay calibration*

The calibration of biomarker assays is fundamental to the study of CKD prevalence in the general population. The reported level of serum creatinine in any given sample can vary depending on the assay used for analysis; for example, differences have been reported when analysing the same sample from a single patient by two different creatinine assays24,25. Although differences in measured serum creatinine levels from a single patient could be considered negligible, investigators must bear in mind that assay readouts are used in eGFR equations and that these equations apply an exponent to the serum creatinine value24.

An example of how variations in serum creatinine assay calibration can affect eGFR readouts is illustrated by a study25 in which investigators measured serum creatinine levels from non-diabetic patients from the National Health and Nutrition Examination Survey III (NHANES III) using two different **Jaffe assays** **[G]**. The reported serum creatinine concentrations from the two assays differed by 20.3 µmol/l (0.23 mg/dl). Variations of this size between readouts have a huge impact on eGFR calculations and staging of CKD using equations such as the MDRD equation. In this study, for example, the prevalence of eGFRs between 30 ml/min/1.73 m² and 59 ml/min/1.73 m² varied from 12.5% to 3.2% due solely to differences in the method used to measure serum creatinine level. Moreover, as the relationship between serum creatinine level and GFR is exponential, the impact of differences in serum creatinine levels on GFR estimates is even more pronounced in higher GFR ranges (>80ml/min/1.73m2). The reported prevalence of GFR above 80 ml/min/1.73 m² varied in the same study from 41.8% to 82.1%25. **[Au: REF. 25, OK?]OK for me PD**

According to these findings, intra-individual variations in eGFR calculations that result from shortfalls in assay calibrationcould be reduced if each eGFR equation was used solely with the specific assay it was developed alongside24,25; however, this approach can be problematic as newer assays are developed over time and replace older ones. For instance, the creatinine assay on which the Cockcroft–Gault (C–G) equation for estimated serum creatinine clearance was developed is no longer in use today26. Modern assays for serum creatinine concentration when applied to the C–G equation could lead to potential errors because the original formulation of the C–G equation was derived from obsolete creatinine-based methodology and the equation has never been validated using contemporary methods.

Over the past decade clinical chemists have made considerable advances in standardizing assays for serum creatinine27. Manufacturers of serum creatinine assays are recommended to calibrate their assays to an isotope dilution mass spectrometry (IDMS) reference method, making the assay **IDMS traceable** **[G]**28. A major advantage of using IDMS traceable assays is that an eGFR equation developed with one IDMS assay can be used with any other IDMS assays21,27,29–31.

The introduction of IDMS calibration for serum creatinine assays has gone some way to address the variability of serum creatinine readouts but issues remain with regard to using eGFR to assess CKD prevalence in epidemiological studies. A continuing complication is that the impact of assay calibration differs between eGFR equations. Variations in calibration have a greater impact on the MDRD equation, for example, than the CKD–EPI equation for eGFR. The reason for the different effect of variations in calibration between the two eGFR equations is due to the mathematical exponent that is applied to serum creatinine in high GFR ranges is lower in the CKD–EPI than the MDRD equation32,33. Although some studies have used IDMS traceable assays to measure serum creatinine, others have not directly calibrated serum creatinine to a mass spectrometry standard but rather have indirectly recalculated serum creatinine levels by comparing assays to other IDMS traceable assays34,35. Furthermore, not all Investigators agree that the accuracy of IDMS calibration is sufficient. Some have questioned the calibration of some assays, especially the Jaffe assays, even following manufacturer assurances that the assay was correctly calibrated36. We would argue, however, that most enzymatic assays for creatinine are well calibrated 28,36.

Cystatin C assays and associated equations can also be affected by calibration issues37,38. Difficulties in measuring cystatin C by mass spectrometry have hindered the development of a reliable mass spectroscopy reference standard39, but assay standardization has improved since 2010 when the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) made the international certified reference material ERM-DA471/IFCC for cystatin C assay calibration to all assay manufactures40. A 2016 publication reported major progress in the standardization of cystatin C assays41; however another study from 2015 reported significant method-specific differences in cystatin C measurements42.

*[H3] Non-GFR determinants*

The second issue with every biomarker used to estimate GFR is the modifying effects of non-GFR determinants, or non-GFR related factors, on biomarker levels. The classic example is muscle mass, which influences serum creatinine level. Thus, creatinine based equations (such as the MDRD and CKD–EPI equations) can be inaccurate estimates of true mGFR when marked variation of muscle mass (too much or too little) is present21,43.

Cystatin C is not influenced by muscle mass but can be influenced by other non-GFR determinants. Many of these factors, such as obesity, chronic inflammation, diabetes mellitus smoking, abnormalities of thyroid function (hypo- or hyperthyroidism), are also cardiovascular risk factors, and contribute to the association between cystatin C levels and cardiovascular risk8,14,16,44–46. The choice of an appropriate eGFR equation is therefore imperative when assessing the influence of potential risk factors on CKD prevalence. Assessment of the influence of obesity on the risk of CKD, for example, would be poorly served by an eGFR equation that is based on a biomarker, such as cystatin C, which is influenced by non-GFR determinants related to obesity. Non-GFR determinants therefore have an undeniable and varying effect on estimates of CKD prevalence and assessment of CKD risk in populations with diverse characteristics.

**[H3] Biological variations in biomarker concentrations**

Serum creatinine concentrations can also fluctuate regularly under the influence of factors such as dietary intake of cooked red meat or other precursors of creatinine and diurnal rhythms. Non-GFR determinants that vary naturally throughout each day, such as food (especially meat) intake, or consumption of drugs (cimetidine, trimethoprim) that affect creatinine secretion by tubules, can affect serum creatinine levels. These factors can also be an important source of eGFR miscalculation, particularly if only a single serum creatinine is used to define the presence or absence of CKD.Just as with GFR, circadian variation has been described for cystatin C but, even if data are relatively limited, cystatin C concentration does not seem to be influenced by food intake47. **[Au:OK?]** The importance of multiple serum creatinine measurements is discussed in further detail below.

***[H2] Choosing an appropriate equation***

Before the introduction of the MDRD study equation in 199948 the Cockcroft–Gault equation was the most frequently used method to estimate creatinine clearance but was not developed as a method to estimate GFR26. The C–G equation is flawed, however, when used to assess CKD prevalence in epidemiological studies as the assay used to measure serum creatinine was not calibrated and the inclusion of patient weight in the equation led to overestimations of estimated creatinine clearance in obese populations49.

The MDRD and CKD–EPI equations, which can be used with IDMS-standardized creatinine values have improved on the C–G equation by removing weight from the calculation29,48. However, although the MDRD and CKD–EPI equations are designed to estimate GFR rather than endogenous creatinine clearance, their performance remains sub-optimal for estimating GFR in obese populations50,51. Moreover, the MDRD study equation has been criticized for underestimating GFR in patients with normal or near normal (e.g. 60-100ml/min/1.73m2) GFR levels24,52. The systematic underestimation of GFR with the MDRD equation would be expected to lead to an overestimation of CKD prevalence in epidemiological studies, and is the reason why the CKD–EPI equation has been advocated since its development in 200929. **[Au: REF. OK? OK for me PD]**

The main difference between the MDRD and CKD–EPI equations is in how exponents of serum creatinine are applied. Unlike the MDRD equation, the CKD–EPI equation applies a lower exponent to the serum creatinine value for low recorded creatinine concentrations (<61.9 µmol/l (<0.7 mg/dl) for males and <79.6 µmol/l (<0.9 mg/dl) for females), than for higher serum creatinine values. When compared to mGFR, however, the precision and accuracy of the CKD–EPI equation only marginally outperforms the MDRD equation, making the added value of this equation at the individual patient level doubtful. However, the systematic bias of the CKD–EPI equation is notably lower than that of other equations, which makes it more suitable than most other equations for estimating CKD prevalence in epidemiological studies. In the external validation dataset of the seminal study that directly compared the MDRD and CKD–EPI equations, the median bias (defined as the median difference between mGFR and eGFR), was 55% lower using the CKD–EPI equation than the MDRD equation (2.5 ml/min/1.73 m2 versus 5.5 ml/min/1.73 m2). By contrast, the precision of the equations (defined as the interquartile range of the differences) were comparable and suboptimal (16.6 ml/min/1.73 m2 versus 18.3 ml/min/1.73 m2 for CKD–EPI and MDRD, respectively; a difference of 9%), and their accuracy (defined as the percentage of eGFR values within 30% of mGFR values) was similar (84.1% versus 80.6% for CKD–EPI and MDRD, respectively; a difference of 4%). The added value of the CKD–EPI equation over the MDRD equation was especially relevant for estimation of GFRs >60 ml/min/1.73 m², with a 7 ml/min/1.73 m2 difference (67% improvement) in the median bias of the CKD–EPI equation compared with that of the MDRD equation in this subgroup29.

As expected use of the CKD–EPI equation gives a lower prevalence of CKD (or decreased GFR) in the general or specific population cohorts than do other equations29,53–61. Some more recently developed equations that also use IDMS-standardized creatinine measurements have been shown to be superior to the CKD–EPI equation for estimating GFR in the both the general and CKD population. For example, the full age spectrum (FAS) and the Lund–Malmö equations are reportedly superior to the CKD–EPI equation for estimating GFR in general population30,31, and the BIS equation is superior to the CKD–EPI equation for estimating GFR in the elderly21. However, the impact of the FAS, Lund–Malmö and BIS equations on the estimates of the prevalence of CKD in epidemiological studies remains to be defined in the general population60,61.

A 2016 report from the BIS cohort illustrates how the choice of equation for estimating GFR can affect the reported prevalence of CKD in an elderly population (*n =*2069, mean age 80.4 ± 6.7 years). The results from the study are based on only one determination of eGFR or GFR by IDMS-calibrated values for of creatinine and cystatin C. The prevalence of CKD, defined as eGFR <60 ml/min/1.73 m², varied according to the creatinine-based equation used, with a prevalence of 37.9% using the CKD–EPI equation, 37.1% using the MDRD equation, 55.9% using the Cockcroft–Gault equation, 55.3% using the Lund–Malmö equation, and 61.7% using the BIS equation7. Such discrepancies question our understanding of CKD prevalence in the elderly, especially when GFR is only measured (or estimated) at the inception of a study — a scenario that raises questions about false positives due to the lack of confirmation, as discussed in further detail below*.* Using plasma clearance of iohexol to assess GFR, the BIS investigators also noted a high prevalence of stage 3–5 CKD (mGFR of <60ml/min/1.73m2 according to the KDIGO definitions) in individuals >70 years of age. 48.8% of individuals aged >70 years were identified as having CKD by iohexol clearance, and the prevalence ranged from 33.2% among individuals aged 70– 74 years up to 91.4% among individuals aged >90 years7 (TABLE 2).

We find the scarcity of and discrepancies within epidemiological studies that have compared the prevalence of CKD using creatinine, cystatin C or combined creatinine–cystatin C-based equations surprising and worrying. Not only are such comparative studies scarce, the findings of those available are discrepant54,56,58,60–64. Furthermore, of the studies that have been conducted, most are methodologically flawed, especially with regard to a lack of cystatin C calibration56,58,63, although, calibration of cystatin C assays does not eliminate the discrepant results obtained using cystatin C-based equations. For example, in a non-representative cohort of 4,189 Belgian citizens aged >50 years, we demonstrated that the prevalence of GFR <60 ml/min/1.73 m² differed depending on the eGFR equation used, with a prevalence of 13% with the MDRD equation, 9.8% with the serum creatinine-based CKD–EPI (CKD–EPIcr) equation, 4.7% with the cystatin C-based CKD–EPI (CKD–EPIcys) equation, and 5% with the combined serum creatinine–cystatin C-based CKD–EPI (CKD–EPIcr-cys) equation54.By contrast, an analysis of the NHANES 1999–2002 cohort (*n*= 8,238) found the prevalence of GFR <60 ml/min/1.73 m2 to be higher using calibrated cystatin C-based equations than with creatinine-based equations (8.7% with CKD–EPIcys; 7.1% with CKD–EPIcr-cys; and 6.5% with CKD–EPIcr)62. Finally, a comparison of cystatin C-based and combined equations in the elderly BIS cohort gave a CKD prevalence of 53.1% for the combined creatinine–cystatin C-based BIS equation and 39.3% for the CKD–EPIcr-cys equation. By contrast, the prevalences of CKD as calculated using CKD–EPIcys and the Caucasian, Asian, pediatric, and adult equation (CAPA) were 42.1% and 37.4%, respectively7.

The wide variation in CKD prevalence observed when different eGFR formulas are applied to populations of varying ages is a very real conundrum for investigators conducting epidemiological studies (TABLE 1). The choice of method to assess GFR, either by urinary or plasma clearance, or with one of the available eGFR equations, will therefore undoubtedly affect the reported prevalence of CKD in any given population.

***[H2] Overcoming false positives***

Typically, epidemiological studies that attempt to evaluate the prevalence of CKD only test the GFR or each participant once at the study initiation for practical reasons, as taking repeated measurements is time consuming and costly. These ‘single-test’ studies, however, fail to adhere to the 3 month duration component of the KDIGO guidelines, which is required to confirm a CKD diagnosis11. ‘One-off’ testing results in a false positive rate for CKD diagnosis of about 30% for eGFR and is even higher for albuminuria65–67. Of note, repeated GFR testing —although preferable to ‘one off’ testing — can also lead to false positives as a result of **regression to the mean [G]**. False negative results are also an issue for epidemiological studies, especially when in younger populations when a fixed GFR threshold of <60ml/min/1.73 m2 is used to define CKD as this value is below the lower limit of normal for a young population66.

Seminal findings that describe the misclassification of patients in epidemiological studies that have relied on ‘one-off’ measurements for determination of GFR are of great importance for establishing the true global burden of CKD. Indeed, any epidemiological study of the prevalence of CKD that employs only asingleeGFR or albuminuria determination must be regarded as potentially misleading. Repeated measurements over a defined interval of time after an initial determination of eGFR are therefore necessary in order to confirm CKD, evaluate the pace of its progression and avoid false positive errors66.

False positives can also arise in other situations. For example, many epidemiological studies do not control for the impact of diet on renal function, especially protein intake. Chronically low protein intake, prevalent in areas of limited food supply but also common in elderly populations, can lead to a physiologically reduced GFR, on a functional not on a disease basis. Protein intake is a major determinant of true or mGFR in normal individuals. High intake of meat protein can not only increase mGFR but it can transiently raise serum creatinine levels and have opposite effects on eGFRcr levels.

***[H2] The ancestry coefficient in eGFR equation***

The ancestry coefficient is an important componentof the MDRD and CKD–EPI creatinine-based equations that aides in understanding the prevalence of CKD in ethnically diverse populations. Application of the African American coefficient to the MDRD equation (1.21) and CKD–EPI creatinine based equations equation (1.15)29,48 results in eGFRs that are 21% and 15% higher for the MDRD and CKD–EPI equations, respectively, than calculations without the coefficient. This coefficient has been criticized as being too high when applied to African Americans with normal renal function and to Africans outside the USA68–71. This point is important from an epidemiological point of view as inaccuracies in the ancestry coefficient could have led to inaccurate estimates of CKD prevalence among African Americans. CKD prevalence is lower in African Americans than in white Americans, whereas the prevalence end-stage renal disease (ESRD) is much higher. This epidemiological paradox between CKD and ESRD prevalence could be explained in part by the application of an inappropriate ancestry coefficient68.

The confusion over ancestry coefficients is exacerbated for individuals of Asian descent due to distinct correction factors being proposed by different researchers, which hinders accurate estimates of the true CKD prevalence among Asian populations72,73. One approach to diminish potential inaccuracies caused by ancestry coefficients would be to use eGFR equations based on Cystatin C is not seemingly affected by ethnicity and cystatin C-based equations do not require an ancestry correction coefficient74. Moreover, the impact of ethnicity on the FAS equation is also theoretically low75, suggesting that epidemiological studies investigating the prevalence of CKD with cystatin C-based equations or the FAS equation will be of interest going forward, particularly in defining CKD prevalence among different ethnic populations. Another important limitation of all of the current eGFR equations is that they include demographics terms, such as ancestry, gender, sex and age. Developments in the past few years, however, suggest that eGFR equations can be developed that do not contain such demographic terms30,76. If successful, then the prospects for developing better estimates of the prevalence of CKD based on consensus eGFR thresholds will be enhanced as interactions with demographic covariates and eGFR will be minimized77.

**[H1] Determining the global burden of CKD**

**[H2] Current estimates of CKD prevalence**

CKD represents a major public health issue that can consume substantial financial and social resources. In addition, CKD is a risk factor for hypertension and cardiovascular disease, which together constitute a substantial cause of morbidity and mortality in the general population of most societies13,78,79. With the view of better understanding the influence of CKD on society there is a keen interest in assessing the burden of the disease across different populations worldwide. Using the widely accepted definitions of CKD advocated by KDOQI9 and KDIGO11, systematic and narrative reviews have estimated the global prevalence of CKD (stage 1–5) to be 3–18% 1,2,4,5,7,12. with a higher prevalence in females than in males, at least among those aged >40 years at the time of CKD diagnosis, and with a substantial contribution from the elderly population5. A comprehensive analysis in 2010 found that the age standardized prevalence of CKD stages 1–5 among adults residing in 32 countries to be 10.4% among men and 11.8% among women (range 4.5–25.7% for men and 4.1–18.4% for women)5. The population of these 32 countries accounts for approximately 49% of the adult global population, translating into an estimated global burden of CKD of about 500,000,000 persons. About 236,000,000 (48%) of the these individuals fall into CKD categories 3–5 as defined solely by an eGFR <60 ml/min/1.73 m², and of these individuals, 50% are >60 years of age5.

Single country estimations of CKD prevalence, vary widely 1,5,12,80. For instance, a comprehensive survey of 47,204 adults in China found a crude overall prevalence of CKD of 10.8% but only 15% had CKD Stage 3–5 and 80% of individuals with CKD eGFR Stage 3A had no albuminuria80. The reported prevalence of CKD also varies widely between European populations. Investigators of one study reported CKD prevalences of 3.3% in Norway, 17.1% in north-eastern Germany1 and 5.8% in Poland12. Further, a systematic survey found an almost fivefold difference between the CKD prevalence rates of South Korean men (4.5%) and San Salvadoran men (26%)5. The heterogeneity in prevalence observed from to country to country, or even within countries, can only be partially explained by the prevalence of CKD risk factors, such as obesity or diabetes in the populations1,13. Demographic and socioeconomic factors, which include age and income, genetic susceptibility, rural versus urban residence, prevailing diet, climate, communicable diseases, pollution and environmental toxins might all contribute in varying degrees to the observed wide global variations in prevalence of CKD13,81.

**[H1] The influence of age**

As discussed in this Review, the prevalence of CKD, as defined by KDOQI and KDIGO criteria, rises substantially with age and estimates of CKD prevalence depend on the method used to measure or estimate GFR (TABLE 1, TABLE 2)2,7,78. Moreover, physiologic decreases in kidney function occur with age82.Epidemiologic studies, particularly those that use ‘one-off’ testing of a biomarker to define GFR tend to capture many elderly individuals with a normal age-related decline in eGFR and are therefore more prone to over-estimate the burden of CKD, especially in an aged population82,83. Whether the selection of a single, absolute threshold for both eGFR or mGFR for identification of CKD (e.g. <60 ml/min/1.73 m²), which has been applied even in the absence of markers of kidney damage, has led to over-estimation of CKD prevalence in elderly populations exhibiting a normal ‘physiologic’ decline in GFR with ageing (**renal senescence** **[G]**) remains highly controversial 78,82,84. This controversy raises philosophical issues as to what is ‘disease’ and what is ‘normal ageing that are not easily resolved.

Thus, using current guideline based approaches, the overall prevalence of CKD in any given community is notably influenced by the age distribution of the population and by the specific eGFR equation used. Values for CKD prevalence vary from 16% to over 90% among individuals >70 years of age; further work is required to resolve the discrepancies in estimates of CKD prevalence among the elderly based on measured plasma iohexol clearance and eGFR calculations. Age-sensitive alterations in the thresholds to define CKD according to eGFR values, such as reducing the threshold to <45ml/min for subjects over age 65 years, been suggested as a way to deal with these issues82,83; however, this approach have proven to be highly controversial84 and possibly difficult to implement.

By contrast, systematic underestimation of CKD can also occur in analyses of younger age groups, when a single eGFR threshold of <60 ml/min/1.73 m² is used as the sole criterion for CKD 66,85. Quantitatively, however, young populations are much less likely to have CKD than older populations, and thus misclassification of CKD in individuals <40 years of age is likely to contribute minimally to overall errors in determining CKD prevalence. According to population-based surveys the prevalence of CKD in the USA has increased ~2% per year in the periods between 1988–1994 and 2005–2010. This reported increase was only identified using certain eGFR equations and occurred predominantly among individuals >65 years of age, notably in the absence of any increase in the prevalence of albuminuria86. A 2016 study, however, showed that the population prevalence of CKD using eGFR values in the USA has remained fairly constant since 200487.Due to issues concerning the definitions of CKD in the elderly employing eGFR values, as discussed above, one should view reports showing an increase in CKD prevalence in populations experiencing rapid aging demographics with some degree of caution.

Interestingly, in the USA the incidence of newly-treated ESRD has tended to be stable or decline (on a year by year basis) since about 2002, especially in the >65-year-old age group88. This emerging stability in the incidence rate of treated ESRD has been seen for nearly all aetiologies of CKD (including diabetes, hypertension and glomerulonephritis), but not in ESRD resulting from autosomal dominant polycystic kidney disease88. The prevalence of treated ESRD increased by about 2% per year from 1990 to 2002 but remained relatively stable from 2002 to 201288. This slight increase in the prevalence of treated ESRD in a period of stable or declining incidence of newly treated ESRD is best explained by low mortality of patients on ESRD treatment. Once a nadir of mortality on ESRD treatment is reached in the face of unchanging incidence rates, the prevalence of treated ESRD might be expected to fall, as mortality on treatment exceeds the intake of newly treated patients. This conjecture seems likely unless the incidence rate of newly treated ESRD rises again, back to values observed in the 1980s and 1990s. Such an increase seems improbable, given the notable decrease in the incidence of newly diagnosed diabetes mellitus (a major cause of renal failure) in the USA since about 200989 and, as mentioned above, the prevalence rates for CKD seem to be stable, at least in the USA87. Of note, the prevalence of CKD in the USA is higher in females but males have a higher prevalence of newly treated ESRD5,8. The origins of this apparent gender paradox are uncertain, but are likely multi-factorial. It is possible that the over-diagnosis of CKD is more marked in elderly females than in males. Females on average have lower eGFR and mGFR (uncorrected for body surface area) and they tend to develop a GFR value of <60ml/min/1.73m2 at an earlier age than men. This physiological gender difference in GFR might contribute to greater overdiagnosis of CKD in women and men as they age, particularly in the absence of abnormal albuminuria.

**[H2] The Global Burden of Disease study [Au:OK?]**

A unique perspective on the global burden of CKD is provided by the Global Burden of Disease (GBD) collaboration, who have undertaken the monumental task of cataloguing the worldwide epidemiology and burden of communicable and non-communicable diseases since 199090. The researchers involved in the effort catalogued over 300 diseases, including CKD in 188 countries from 1990 to 2013. Whether the coding system used by the GBD investigators to identify CKD overlaps with the KDOQI or KDIGO systems is unclear but categorization of CKD did require a sustained diagnosis of CKD for >3 months, as specified by KDIGO. The degree to which estimates of CKD provided by the GBD collaboration parallel with estimates with more renal-focused studies is also unclear; nevertheless, this large-scale study provides some useful insights into the global prevalence of CKD. For their analysis, the GBD investigators divided cases of CKD into four categories: those associated with or caused by diabetes mellitus, those associated with or caused by hypertension, those caused by glomerulonephritis and those resulting from other causes (polycystic kidney disease or congenital abnormalities of the kidney and urinary tracts). Crude and age-standardized overall CKD prevalence rates, **disability-adjusted life years** **[G]** experienced (DALY), years lived with disability, years lost to premature mortality and health life expectancy for communicable and non-communicable diseases, including CKD, were examined for each country91.

During the 23 year study the prevalence of CKD increased by 48%, from 318,665,000 to 471,916,000 cases (about 2.1% per year), which is as expected given the population growth over this time (TABLE 3). However, the overall age-standardized prevalence rate (per 100,000 adults) for all-cause CKD declined by 3.6% between 1990 and 2013 from a prevalence of 7,237 cases per 100,000 people in 1990 to 6,973 cases per 100,000 people in 2013. The GBD investigators also noted a>10% decline in the prevalence of CKD associated with hypertension and glomerulonephritis, whereas CKD associated with diabetes mellitus increased by almost 12% and CKD resulting from other causes increased by 3%. While the incidence of newly diagnosed diabetes (Type 2) has been decreasing in many developed countries (including the USA) it has been increasing is less developed countries, largely under the influence of obesity. In 2013, CKD resulting from other causes accounted for almost 37% of cases of CKD, whereas CKD associated with diabetes mellitus hypertension and glomerulonephritis accounted for 19%, 21% and 23% of all CKD cases, respectively.

Assessments of DALY, a measure of overall disease burden expressed as the number of years lost due to disability or early death, showed a decrease in the burden associated with glomerulonephritis-induced CKD from 1990 to 2013 but an increase in DALY for CKD associated with diabetes mellitus, hypertension and other causes. CKD was ranked among the top ten diseases that severely impact DALY in 27 of the 188 countries examined. Further, 14 of these 27 countries (52%) were in South or Central America and three of the four countries in which CKD was in the top five tier of DALY were in Central America (Mexico, El Salvador and Nicaragua)91. Many studies have documented poor awareness of the presence of CKD among individuals92. **[Au: REF. CITE, PLEASE I added a very recent reference on this topic PD]** The GBD has updated data through 2015 for the global prevalence of CKD90. **[Au: REF. OK?]** These data suggest a continuing stable or declining prevalence of non-dialysis dependent CKD in many, but not all, countries of the world**.**

The aggregate epidemiologic data strongly suggest that all cause **generic CKD** **[G]** is a common disorder that is distributed non-uniformly among the global population and that hot-spots exist, both between and within regions of countries. Such a phenomenon deserves close scrutiny as it could aid in the identification of aetiological factors that are susceptible to preventative strategies. When examined as a whole, however, the epidemiological data show that we are not currently in the midst of a global CKD epidemic, as has been previously suggested. The continuing g rise in global prevalence of treated ESRD may be a phenomenon more closely linked to improved access to such care rather than to a secular change of CKD itself. The data do, however, provide possible explanations for the reported variations in CKD prevalence and the consequence of CKD on disability. Although immensely important, the GBD data is weakened its inability to consistently ‘stage’ CKD according to the KDIGO guidelines due to the sheer size of the study. The GBD data also cannot be used to reliably evaluate the accuracy of the specific eGFR formula used or assess albuminuria if CKD is identified. A more detailed country-specific and sub-region evaluation, which includes assessment of duration of CKD, ancestry, nephron endowment at births, the genetics of progressive CKD and prevailing diet, climate and nephrotoxin exposure is needed to further explore the nuances identified by the GBD study13.

The impact of greater awareness of CKD on patients by physicians (leading to more testing of eGFR or albuminuria) and increased coding of CKD and its stages in medical records must be considered when evaluating changes in reported global CKD prevalence. Furthermore, **Ascertainment bias** **[G]** can operate when populations are self-selected for inclusion in prevalence surveys. Subjects might volunteer for screening programs designed to identify CKD when they have concerns about kidney disease or have relatives with CKD. Such biases can influence reports of prevalence of CKD applicable to the general population. These biases can add to considerations of age and ancestry on CKD diagnosis and staging. Nephron endowment at birth, which is currently only estimated by birth weight, and its contribution to the rate of decline in GFR with normal ageing might also warrant consideration for its effects on CKD staging and future risk of 93,94; although, such parameters would be difficult to assess in large epidemiologic studies.

**[H1] Conclusions**

The present Review of issues relating to the interpretation of studies of CKD prevalence raises questions that challenge the existence of a global epidemic of CKD. The pitfalls that exist in translating available epidemiological data hinder accurate assessment of the global burden of CKD. These pitfalls include issues in the accuracy of formulas to estimate GFR including issues with biomarker calibration, the choice of biomarker and equation, and the influence of non-GFR determinants on biomarker levels; issues relating to the presence of false positives, particularly with single-test studies; issues relating to our understanding and application of ancestry coefficients to eGFR equations; lack of a disease duration component or assessment of albuminuria in population studies; and ascertainment bias in non-random selections of survey participants. Based on the arguments presented in this Review, one might take the view that we are currently unable to fully knowthe global prevalence of generic CKD to any meaningful degree of precision. Alternatively, one could posit that many studies have overestimated the burden of CKD and its rate of change in the general population*.* The cumulative impact of pitfalls in prevalence estimates could mean that the global prevalence of CKD has been over-estimated by > 50%82. A focus on the origins of the variation of CKD prevalence within regions and between countries could be a rewarding approach to determine the epidemiology of CKD on a global basis. We believe that advances in the testing methodology for identification and classification of CKD will improve our ability to better understand this all too common disorder. However, advances in testing methods can only do so much — nephrologists and epidemiologists need to ensure that data generated from future epidemiological studies investigating the burden of CKD in defined populations are reliable. Investigators can improve the reliability of data by controlling for some of the errors that are commonly encountered when defining CKD and avoid universally applying criteria for CKD diagnosis across all segments of a given population.

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**Author contributions**

All authors contributed to writing the article, to the discussion of the article’s content and to review/editing of the manuscript before submission.

**Competing interests**

The authors declare no competing interests.

Table 1 | Prevalence of CKD\* in the elderly by eGFR equation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Frequency of CKD (%) according to age** | | | | |
|  | **70–74 years** | **75–79 years** | **80–84 years** | **85–89 years of age** | **>90 years** |
| **CKD–EPIcr** | 20 | 29 | 43 | 46 | 66 |
| **CKD–EPIcys** | 19 | 32 | 50 | 61 | 79 |
| **CKD-E–PI-Cr + CyC** | 16 | 28 | 47 | 58 | 76 |
| **BIS-1cr** | 33 | 52 | 76 | 84 | 93 |
| **BIS-2cr-cys CyC** | 24 | 42 | 66 | 76 | 90 |
| **Range** | 16–33 | 28–52 | 43–76 | 46–84 | 66–93 |

**\*CKD** **stages 3–5. BIS, Berlin Initiative Study; CKD, chronic kidney disease; CKD–EPI, Chronic Kidney Disease Epidemiology collaboration; cr, creatinine; cys, cystatin C; GFR, estimated glomerular filtration rate.**

Table 2 | Mean GFR and prevalence of CKD\* in the elderly by iohexol clearance

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Frequency of CKD (%) according to age** | | | | | |
|  | **70–74 years** | **75–79 years** | **80–84 years** | **85–89 years** | **>90+ years** | **>70 years** |
| **Prevalence %** | 33.2 | 43.7 | 53.8 | 72.5 | 91.4 | 48.8 |
| **Mean mGFR ± 2SD** | 67±32 | 61±28 | 57±28 | 51±28 | 43±23 | 60±33 |

\*CKD stages 3–5**.** CKD, chronic kidney disease; mGFR, measured GFR; SD, standard deviations.

Table 3 | **Global burden of CKD: case counts and adjusted prevalence rates**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Cases: 1990/2013 (x1,000)** | **% Change** | **Prevalence per 100,000 adults: 1990/2013** | **% change** |
| **CKD-DM** | 43,339/88,711 | +82.5% | 1,230/1,355 | +11.85% |
| **CKD-HTN** | 79,945/101,253 | +26.8% | 1,634/1,453 | –10.7% |
| **CDK-GN** | 82,920/108,861 | +32.7% | 1,866/1,590 | –13.5% |
| **CKD-other** | 112,461/173,091 | +53.9% | 2,507/2,575 | +3.1% |
| **CKD-all** | 318,665/471,916 | +48.1% | 7,237/6,973 | –3.6% |

CKD, chronic kidney disease; CKD-all, all cases of CKD; CKD-DM, CKD associated with diabetes mellitus; CKD-HTN, CKD associated with hypertension; CKD-GN, CKD associated with glomerulonephritis; CKD-other, CKD resulting from other causes.

**Glossary terms**

**Jaffe assays** **[G]**

**IDMS traceable [G]**

**Regression to the mean [G]**

**Disability- adjusted life years [G]**

**Renal senescence** **[G]** The normal physiologic decline of GFR with ageing

**Generic CKD** **[G]**

**IDMS traceable** **[G]**

**Ascertainment bias** **[G]**

**regression to the mean [G]**

**disability-adjusted life years** **[G]**

**Key points**

* Chronic kidney disease (CKD) is presently defined by a matrix of biomarkers, specifically, glomerular filtration rate (GFR) <60 ml/min/1.73 m2 and albuminuria in the context of manifestations of kidney damage and duration >3 months
* GFR can be measured or estimated but both of these approaches to assessment of kidney function has drawbacks when applied to epidemiologic studies of the CKD population prevalence
* Failure to apply ≥3 month duration requirement for CKD diagnosis can lead to an overestimation of CKD prevalence , especially when age, sex, ethnicity and diet are not taken into account
* Data from multiple sources indicate that CKD is a common disorder that contributes markedly to morbidity and mortality; however, the prevalence of CKD shows wide variations between and within specific geographic locations
* In many nations, including the USA, the prevalence of CKD and newly treated end-stage renal disease (ESRD) is stable; future trends in ESRD prevalence will likely depend on changes in access to treatment, population demographics and mortality

**Author Biographies**

Dr. Richard J. Glassock is an Emeritus Professor of Medicine at the Geffen School of Medicine at UCLA. He was previously the Chair of the Department of Medicine at the University of Kentucky College of Medicine and Chief of the Division of Nephrology and Chair of the Department of Medicine at Harbour-UCLA Medical Centre. His main interests are Clinical Nephrology, glomerular disease and CKD. He has published extensively in experimental and human glomerular disease and in the epidemiology of CKD, particularly the relationship of aging to CKD diagnosis.

Dr. David G. Warnock was the Director of Nephrology at the University of Alabama at Birmingham (UAB) from 1988 to 2008, served as the Marie K Ingalls Professor of Medicine and the Hilda B. Anderson Endowed Professor in Nephrology, and became an Emeritus Professor at UAB in October, 2015. His focus of research is on the genetic and environmental factors that contribute to hypertension and CKD, extending from basic studies of salt and water transport systems to population-based examination of the prevalence of CKD and the association with stroke and heart disease. Another focus is inherited disorders of renal function, with a current emphasis on the renal manifestations of Fabry disease. Additional research interests include acid-base physiology, sodium transport mechanisms, chronic kidney disease, diabetes and kidney disease, and inherited renal diseases.

Dr. Pierre Delanaye is currently Nephrologist at the University Hospital of Liège (CHU Sart Tilman), Belgium. His daily practice is the care of haemodialysis patients. His clinical research interest is the estimation and measurement of glomerular filtration rate, the epidemiology of CKD and Mineral Bone Disease in dialysis patients. In his research, he underlines the strong and necessary links between Nephrology and Clinical Chemistry. He has published extensively on the epidemiology of CKD and on the evaluation of eGFR formulas.

Box 1 | **Approaches to measuring GFR**

Measured GFR requires exogenous marker with specific physiological characteristics: free in plasma (not bound to proteins), freely and fully filtrated through the glomerulus, neither secreted nor absorbed by tubules, inert, safe, only excreted by kidneys and relatively easy to measure in plasma and/or urine. Since urinary clearance of inulin first described by pioneers in Nephrology in the thirties95,96, this method is still considered as the gold standard method. Because renal clearance of inulin is relatively cumbersome (see the text), some authors have proposed alternatives such as isotopic (51Cr-EDTA, 99Tc DTPA and 125I-Iothalamate) or non-isotopic methods (iohexol and iothalamate).Contrary to inulin that can be used only with urinary clearances, these markers can be used in plasma clearances protocols. Plasma clearances, even if less physiologic and inaccurate in cirrhotic or oedema patients, are easier to implement in daily practice or in specific populations such as pediatric or geriatric subjects. Different procedures of plasma clearances (number of samples and timing) have been described in the literature97. Each marker and each procedure has strengths and limitations. Even if lack of standardization in measured GFR procedures and markers has been objected, recent data suggest that urinary clearance of Cr-EDTA and iothalamate on one side and plasma clearance of Cr-EDTA and iohexol on the other side are acceptable alternative to urinary clearance if inulin98.

Box 2 | **eGFR equations**

The first widely used creatinine-based equation was the Cockcroft–Gault equation published in 1976. This easy-to-use equation was actually an estimation of creatinine clearance, not GFR. Compared to other, more recent equations, Cockcroft equation includes the variable “weight” and eventually gives a results not indexed for BSA26. Recent equations, as discussed in the text, have the advantage to be IDMS traceable and have globally a better performance than the prior Cockcroft equation to estimate GFR52,99. The first IDMS (see the text) traceable was the MDRD study equation100, then replaced by the CKD-EPI equation whose performance was slightly better in high GFR ranges29. Other equations have been proposed: the BIS equation21, specifically proposed for estimating GFR in elderly population, the Lund-Malmö equation31 and recently the FAS equation30. The FAS equation is particularly original in its development but, as the Lund-Malmö equation, must be still externally validated. Among cystatin C- and combined (i.e. including both creatinine and cystatin C) equations, different equations developed from a standardized cystatin C are currently available (CKD-EPI, Lund-Malmö, BIS and CAPA equations)21,31,74,101.

Box 3 | **Jaffe versus enzymatic methods for measuring biomarkers**

Serum creatinine remains the main variable in all proposed estimating GFR equations. However, measuring serum creatinine in serum is cheap but not so simple. The first, and still most used method nowadays, is called the Jaffe method. This colorimetric method is based on the reaction between creatinine and picric acid, giving a yellow-red colour to serum that can be so quantified. However, other components in plasma, known as pseudochromogens, can also react and/or interfere with picric acid (acetone, glucose, acetoacetate, proteins, ascorbate and glucose). This lack of specificity will lead to abnormal high values (this value being around 0.2 to 0.3 mg/dL according to the assay considered). Even if several improvements have been obtained in the Jaffe method, the precision of this method remains relatively limited, impacting the precision of the equations. Enzymatic methods are based on successive and different (assay-dependent) enzymatic reactions. This method is much more precise than Jaffe method, notably because it specificity regarding pseudochromogens but also other interferences is much higher. The errors or imprecision associated with Jaffe assays particularly impacts low creatinine concentrations. For this reason, enzymatic creatinine methods are particularly recommended in paediatrics 32,102,103.