Chronic Kidney Disease: call for an age-adapted definition

Pierre Delanaye[1*], Kitty J. Jager[2*], Arend Bökenkamp[3], Anders Christensson[4], Laurence Dubourg[5], Bjørn Odvar Eriksen[6], François Gaillard[7], Giovanni Gambaro[8], Markus van der Giet[9], Richard J. Glassock[10], Olafur S. Indridason[11], Marco van Londen[12], Christophe Mariat[13], Toralf Melsom[6], Olivier Moranne[14], Gunnar Nordin[15], Runolfur Palsson[11,16], Hans Pottel[17], Andrew D. Rule[18], Elke Schaeffner[19], Maarten W. Taal[20], Christine White[21], Anders Grubb[22$], Jan A.J.G. van den Brand[23$]

Authors are members of the European Kidney Function Consortium

***** These authors contributed equally to this work as first author

$ These authors contributed equally to this work as last senior author

[1] Department of Nephrology-Dialysis-Transplantation, University of Liège (ULg CHU), CHU Sart Tilman, Liège, Belgium

[2] Amsterdam UMC, University of Amsterdam, Department of Medical Informatics, Amsterdam Public Health research institute, Amsterdam, the Netherlands

[3] Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit, Amsterdam, Amsterdam, The Netherlands

[4] Department of Nephrology, Lund University, Skåne University Hospital, 20502 Malmö, Sweden

[5] Néphrologie, Dialyse, Hypertension et Exploration Fonctionnelle Rénale, Hôpital Edouard Herriot, Hospices Civils de Lyon and Université Lyon 1, Lyon, France

[6] Metabolic and Renal Research Group, University Hospital of North-Norway, and UIT, the Arctic University of Norway, Tromsø, Norway

[7] AP-HP, Necker hospital, Renal Transplantation department, Paris, France, Université Paris Sud, Orsay, France

[8] Division of Nephrology and Dialysis, Department of Medicine, University of Verona, Italy

[9] Charite – Universitätsmedizin Berlin, Department of Nephrology, Berlin, Germany

[10] Geffen School of Medicine at UCLA, Los Angeles, CA, USA

[11] Division of Nephrology, Landspitali-The National University Hospital of Iceland, Reykavik, Iceland

[12] Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, Groningen, The Netherlands.

[13] Nephrology, Dialysis and Renal Transplantation Department, Hôpital Nord, CHU de Saint-Etienne, Jean Monnet University, COMUE Université de Lyon, France

[14] Service Néphrologie-Dialyse-Aphérèse, CHU Caremeau Nimes, Université de Montpellier, France

[15] Equalis, Box 977, 751 09 Uppsala, Sweden

[16] Faculty of Medicine, School of Health Sciences, University of Iceland, Iceland

[17] Department of Public Health and Primary Care, KU Leuven Campus Kulak Kortrijk, Kortrijk, Belgium

[18] Mayo Clinic, Division of Nephrology and Hypertension, Rochester, Minnesota, USA

[19] Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt Universität zu Berlin, and Berlin Institute of Health, Institute of Public Health, Luisenstraße 57, 10625 Berlin, Germany

[20] Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, UK

[21] **Department of Medicine, Queen's University, Kingston, ON, Canada**
[22] **Department of Clinical Chemistry and Pharmacology, Laboratory Medicine, Lund University, Skåne University Hospital, SE-22185 Lund, Sweden**
[23] **Department of Nephrology, Radboud Institute for Health Sciences, Radboudumc, Nijmegen, The Netherlands**

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Corresponding author: Pierre Delanaye, Service de Dialyse, CHU Sart Tilman, 4000 Liège, Belgium, Phone: ++3243667111, Fax: ++3243667205, e-mail address: pierre_delanaye@yahoo.fr

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Abstract

Current criteria for the diagnosis of chronic kidney disease (CKD) in adults include persistent signs of kidney damage; for example, increased urine albumin-to-creatinine ratio or a glomerular filtration rate (GFR) below the threshold of 60 mL/min per 1.73m^2. The latter has important caveats. This threshold does not separate kidney disease from kidney aging, and therefore does not hold for all ages. In an extensive review of the literature, we found that GFR declines with healthy aging without any overt signs of compensation (such as elevated single nephron GFR) or kidney damage. Older living kidney donors, who are carefully selected based on good health, have a lower pre-donation GFR compared to younger donors. Furthermore, the results of the large meta-analyses conducted by the CKD Prognosis Consortium and of numerous other studies indicate that the GFR threshold above which the risk of mortality is increased, is not consistent across all ages. Among younger persons, mortality is increased at GFR lower than 75 mL/min per 1.73m^2, whereas in elderly people it is increased at levels lower than 45 mL/min per 1.73m^2. Therefore, we suggest the CKD definition to be amended to include age-specific thresholds for GFR. The implications of an updated definition are far reaching. Fewer elderly would be diagnosed with CKD, reducing inappropriate care and its associated adverse effects. Prevalence estimates for CKD globally would be substantially reduced. Furthermore, the onset of CKD may be identified sooner in younger persons, and at a point when progressive kidney damage may still be preventable.

Introduction

Perspectives on the definition of CKD

The current criteria used for the definition of chronic kidney disease (CKD) in adults are: 1) signs of kidney damage, most often determined by an elevated urine albumin (or protein)-to-creatinine ratio (ACR) or 2) glomerular filtration rate (GFR) less than 60 mL/min per 1.73m², as GFR is considered the best determinant of kidney function [1]. CKD is staged according to six GFR categories (G1, G2, G3a, G3b, G4 and G5) and three categories for urine ACR levels (A1, A2 and A3) (Table 1). There is a broad agreement that abnormal urine ACR should trigger a diagnosis of CKD, but controversy remains regarding the most appropriate diagnostic criteria regarding GFR. In this article, we will focus on the role of GFR in the definition of CKD. Laboratory thresholds for disease identification are commonly determined in two ways [2–4]. First, the distribution of the laboratory results in a representative population of healthy persons is obtained and thresholds for defining disease are calculated according to extreme values based on this distribution (typically 95th or 97.5th percentile for "too high" and 2.5th or 5th percentile for "too low"). Second, a threshold associated with an adverse outcome is identified through epidemiologic studies. These two strategies (reference distribution and prognosis) will be considered and discussed in the specific case of using GFR for CKD definition.

The current CKD definition and its caveats

The current and widely adopted definition of CKD in adults is based on the 2013 KDIGO guidelines [1]. Although not entirely undisputed, we do recognize the merit of these guidelines as they standardized the definition of CKD [5–11]. As pointed out, GFR is one of the two main criteria for diagnosis of CKD. More importantly, an isolated GFR below 60 mL/min per 1.73m² (confirmed with a second value after at least 90 days) suffices for the diagnosis of

CKD. In other words, anyone with a GFR below 60 mL/min per 1.73m² persisting for at least three months by definition has CKD, even if the urine ACR and structure or kidney morphology (imaging or biopsy) are normal (e.g. G3a/A1). This threshold of 60 mL/min per 1.73m² is irrespective of age. The considerations in favor of a fixed threshold at 60 mL/min per 1.73m² in the current CKD definition proposed by KDIGO are as follows [1]:

a) simplicity: only one number needs to be kept in mind. This argument is understandably relevant for non-nephrologists and patients, but carries the risk of oversimplification of the complexities of kidney pathophysiology.

b) biology: 60 mL/min per 1.73m² is believed to represent less than 50% of the kidney function measured in healthy, young adults [1]. The choice of 50% of normal function is however quite arbitrary. Moreover, whether GFR is actually ≈120 mL/min per 1.73m² in healthy young adults is debatable. This value was originally based on measured GFR (mGFR) values compiled and published in 1969 by Wesson [12]. More recent studies have shown that median GFR values in healthy young adults are lower than 120 mL/min per 1.73m² [13–15]. Indeed, one meta-analysis of mGFR data in living kidney donors (n=5,482), showed normal mean GFR values of 106.7 mL/min per 1.73m² at age 20-30 years [14]. Such values were also observed in a large cohort of 2,007 French living kidney donors below 40 years of age, with a mean mGFR of 107.2 mL/min per 1.73m² [15].

c) prognosis: the last argument for a threshold at 60 mL/min per 1.73m² was based on the association of lower GFR values with morbidity and mortality. The choice for the threshold at 60 mL/min per 1.73m² has seemingly been supported by many large epidemiological studies, especially from the CKD Prognosis Consortium. We will discuss this argument in depth below.

The prognostic argument for an age-adapted definition of CKD

Absolute risks of mortality are typically higher in older patients due to the limited human lifespan. Regarding relative risk, several studies from the CKD Prognosis Consortium have demonstrated that GFR lower than 60 mL/min per 1.73m² was independently associated with adverse outcomes, in particular cardiovascular events and all-cause mortality [16–28], thereby confirming the seminal study published by Go *et al.* in 2004 [29]. Of note, most of the Consortium analyses of GFR and risk of adverse events in both high-risk and general populations use as the reference group participants with only a single estimated GFR (eGFR) available (hence, no confirmation of chronicity) ≥ 95 mL/min per 1.73m² [16–28]. However, in their meta-analysis that included more than 2 million subjects from 46 different cohorts (33 cohorts from the general population and 13 CKD cohorts) that was dedicated to the effect of age, the reference group eGFR used was 80 mL/min per 1.73m² rather than 95 mL/min per 1.73m² [17]. The associations with mortality and end-stage renal disease (ESRD) remained significant when eGFR was lower than 60 mL/min per 1.73m² in all age categories, although hazard ratios (HR) were much lower in older people [17]. While the risk of ESRD was increased, the progression to ESRD in elderly patients with an eGFR of 45 to 59 mL/min per 1.73m² and no abnormal urine ACR is very rare (<1% risk in 5 years using the Kidney Failure Risk Equation)[30]. The choice of the reference group is of critical importance in such analyses and the data from the CKD Prognosis Consortium for mortality have therefore been re-analyzed by others using different reference groups based on age (Figure 1) [31–34]. In these analyses [31,34], the reference eGFR group in each age-category was defined as the one with the lowest mortality risk (in subsets with urine ACR <10 or 10-29 mg/g). The results revealed that in the 55 to 64 year age category (reference eGFR 90-104 mL/min per 1.73m²), the mortality risk began to increase when GFR fell below 60 mL/min per 1.73m². However, for subjects older than 65 years (reference eGFR 75-89 mL/min per 1.73m²), the risk was trivial

until the eGFR had fallen below 45 mL/min per 1.73m². In the youngest age category 18-54 years (reference eGFR above 105 mL/min per 1.73m²), the risk of mortality started to increase when eGFR was below 75 mL/min per 1.73m² [31–34]. Therefore, an age-specific analysis of the data used by the CKD Prognosis Consortium provides a strong argument for an age-adapted definition of CKD using prognostic strata appropriate for age.

Tables 2 and 3 summarize the studies on associations between eGFR and risk of adverse events outside of the CKD Prognosis Consortium. Only published full-length articles were considered in this analysis. Included are studies that used creatinine-based equations (Modification of Diet in Renal Disease equation (MDRD) Study or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations) and reported adjusted risks of cardiovascular or all-cause mortality [29,35–55]. We excluded studies that included only subjects with eGFR categories G3-G5 and those that excluded older subjects. Instead we focused on studies that were performed in elderly individuals or reported results in separate age categories. Our main hypothesis was that the increased risk of mortality associated with low eGFR differs across age categories and, notably, that in older age groups eGFR between 45 and 60 mL/min per 1.73m² is not associated with excess mortality. When looking at studies that presented a separate eGFR category between 45 and 60 mL/min per 1.73m² and used eGFR > 60 mL/min per 1.73m² as a reference category, only a few studies demonstrated an increased risk [43,45,49,56], whereas others reported no increase in risk [40,41,47,48]. The largest study to date included a separate analysis of individuals with eGFR between 50 and 60 mL/min per 1.73m² in the older age categories. The results showed that in this eGFR category the risk of death was not higher than in the category eGFR above 60 mL/min per 1.73m² [36]. In addition, the Renal Risk in Derby study deserves particular attention as it included follow-up data on eGFR [55]. A total of 1,741 subjects, most with confirmed CKD were prospectively followed for 5 years. The mean age of the cohort was 72.9±9 years, the mean eGFR using the CKD-

EPI equation was 54±12 mL/min per 1.73m² and most participants had normal urine ACR. After 5 years, 34.1% of the cohort was considered as being stable and 19.3% had even improved their GFR category. Nearly all the subjects who improved their CKD status had been classified as category G3a/A1 at baseline [55]. Interestingly, the age- and sex-standardized mortality rates of those with category G3a were similar to those in the general population, while those with category G3b or G4 at baseline had higher mortality rates [55,57].

Regarding the prognosis argument, we acknowledge that our proposal of an age-adapted definition for CKD is mainly based on mortality risk. We did not consider other outcomes, even though other publications have reported the risk of lower GFR with classic metabolic complications of CKD (anemia, hyperparathyroidism, acidosis, hyperphosphoremia) [58,59] and other clinical complications (frailty, impaired quality of life, fracture etc.) [60,61]. These studies unfortunately are of little utility in informing our proposal current of age-adapted threshold. While, if higher risk of these complications, is frequently observed when eGFR is below 45 mL/min per 1.73m² [58], results are very variable for higher eGFR, notably because the definitions of the complication or of the clinical status are not uniform (contrary to the death status).

In conclusion, most studies showed no or trivial additional mortality risk for older adult subjects with eGFR between 45 and 60 mL/min per 1.73m² and normal urine ACR. Prognostic arguments thus favor an age-adapted threshold for eGFR in the CKD definition.

Kidney senescence as an argument for an age-adapted definition of CKD

Structural differences between aging kidney and CKD

Another concern with an GFR threshold fixed at 60 mL/min per 1.73m² is that it fails to account for the distinct micro- and macro-structural differences between the aging kidney and kidneys affected by CKD. In healthy kidney donors, aging is reflected by a slow indolent

nephrosclerosis, characterized by arteriosclerosis, ischemic globally (but not segmentally) sclerotic glomeruli, and interstitial fibrosis and tubular atrophy (IFTA)[62]. Despite the IFTA with aging being fairly minimal [62], there is a substantial nephron loss and dropout (from about 1,000,000 nephrons per kidney in healthy 18-29 year olds to 500,000 per kidney in healthy 70-75 year olds) [63]. Despite this substantial nephron loss with age, there is no compensation by the remaining nephrons as glomerular volume, single-nephron GFR, and single-nephron glomerular filtration capacity remains stable [63–65]. CKD on the other hand is often characterized by disease-specific pathology that differs from age-induced nephrosclerosis. CKD can include unique micro-structural findings (e.g., specific immunofluorescent staining patterns) or macro-structural findings (e.g. polycystic kidney or renal artery stenosis) that are not seen with aging alone. Although risk factors for CKD, including obesity, diabetes and hypertension, are associated with nephrosclerosis, they are also associated with glomerular enlargement, segmental glomerulosclerosis and higher single-nephron GFR in intact non-sclerotic glomeruli [63,64]. Only when the degree of global glomerulosclerosis exceeds that expected for age or when there is increased metabolic demand (*e.g.*, obesity and hyperglycemia) is there an increase in single-nephron GFR. Therefore, application of age-adapted thresholds for glomerulosclerosis is also useful with kidney biopsies performed in clinical care, as only glomerulosclerosis exceeding that expected for age is a risk factor for CKD progression [66,67].

Decline of GFR with aging

As already stated, the definition of normality for laboratory results can also be obtained by the distribution of the results in healthy populations. Establishing reference interval values with a fixed threshold as per the KDIGO guidelines would mean that the GFR reference values are constant across all age categories [13,14,68–81]. However, more reliable studies using mGFR and realized in living kidney donors or healthy subjects selected from the general population

indicate a clear decrease in GFR with age [13–15,64,68–90], and the rate of mGFR decline becomes significant after the age of 40 years [2,12–15,73,76,80,85,88,91,92]. Importantly, such a decline in mGFR with aging has been established on different continents and in different ethnic groups [68,77,79–81,87,89]. From these data, it is obvious that a substantial proportion of healthy older people have a mGFR below 60 mL/min per 1.73m² despite the paucity of studies that have focused on the elderly and used mGFR. Regarding eGFR [93–95], available cross sectional studies from different parts of the world confirmed that many people older than 65 years of age have an eGFR value lower than 60 mL/min per 1.73m², suggesting a rather ubiquitous decline of eGFR with age [13,68,96–101]. Unfortunately, the few published longitudinal studies have shown discrepancies in the rate of kidney function decline or suffered from methodological limitations, such as use of eGFR or 24-h-creatinine clearance, inclusion of non-healthy subjects, limited follow-up duration, and study attrition, making it difficult to draw a definitive conclusion about the magnitude of the average rate of GFR decline with aging. Despite these limitations, all studies have shown a significant decline in GFR with aging in the majority of healthy subjects [48,96,102–114]. The only longitudinal study using mGFR in a healthy general population is the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6), which included a representative sample of 1,594 Caucasians aged 50 to 62 years from the general population without CKD, diabetes, or cardiovascular disease. Iohexol clearance measurement was repeated in 1,299 (81%) patients after a median time of 5.6 years. The authors showed a mean GFR decline rate of 0.84±2.00 mL/min per year (or 0.95±2.23 mL/min per 1.73m² per year). Although this may be the most valid study to date, it nevertheless had some limitations: it included only middle-aged Caucasians and had a relatively short follow-up with only two measurements in the majority of subjects [114].

Proposals for an age-adapted CKD definition

The concept of an age-adapted definition of CKD is not new and has been proposed by different authors [2,3,8,10,31,33,34,36,64,98,99,115–124]. Such age-adaptation could be achieved in different ways. We emphasize that the suggested change in CKD definition only pertains to people *without* other evidence of kidney damage (notably with normal urine ACR).

Age-related percentiles of GFR

First, one can use percentiles of GFR in the healthy population, which are available in the literature for mGFR and/or eGFR in different ethnic groups [13,68,96–99]. In practice, this would mean that a GFR result is interpreted in the light of age-specific GFR percentiles, and that CKD would be defined as a value below a given percentile in healthy persons (Figure 2). By relating measurements to percentiles using different mGFR or eGFR methods, this approach may overcome differences in mGFR measurement techniques [125,126] or eGFR equations [93,94,127]. Using percentiles for each year of age minimizes the "birthday paradox" (where healthy people can become diseased or diseased people can "recover", simply by becoming one year older), which is inherent to a single threshold approach or an age-based approach with only a few thresholds. By employing age-specific means and standard deviations, the individual patient levels can be transformed into a standard deviation score (SDS), a metric commonly used in pediatrics or even in adults for diagnosing other diseases like osteoporosis with bone mass density. An SDS value of minus 2 or less corresponds to an mGFR/eGFR at the 2.5th percentile or lower. Calculation of an SDS score requires well-characterized reference values across the whole age spectrum. Using these data, GFR-SDS can be reported directly by the laboratory analogous to the eGFR results. The SDS is age- and method-independent and therefore ideal for follow-up. Furthermore, reference values may be included in the laboratory report (Figure 2).

A limited set of age-specific thresholds

One can consider the CKD staging based on three different pivotal ages (Figure 3): <40 years, 40-65 years, and >65 years. For the youngest cohort, we suggest a cut-off of 75 mL/min per 1.73m², for individuals aged between 40 and 65 years, we suggest a GFR cut-off of 60 mL/min per 1.73m² and 45 mL/min per 1.73m² for those older than 65 years. In other words, in subjects aged above 65 years, the current CKD category G3a/A1 (GFR 45 to 60 mL/min per 1.73m²) would not be considered a disease. Moreover, if the GFR is below 75 mL/min per 1.73m² in young people, they would be considered to have CKD, as their kidney function is below what would be expected for their age. [31,34,97,120,123,128,129]. The choice of the different GFR thresholds can be justified by associations of these thresholds with prognosis (Figure 1).

The potential impact of an updated definition of CKD

A modification of the CKD definition would have a substantial impact on the estimation of CKD prevalence. The KDIGO guidelines used the data from the NHANES study (1999-2006) and estimated the CKD prevalence in the US adult general population at 11.5%. Subjects with GFR between 45 and 60 mL/min per 1.73m² and normal urine ACR represented 3.6% of the general population and 75% of all patients with CKD were classified as such solely by the GFR criterion. Subjects with category G3a/A1 represented more than 30% of all people with CKD [1]. Categories 3 or 3a are unequivocally the largest or second largest group in terms of CKD prevalence in other studies as well [47,48,55,56,97,123,130–139]. The epidemiological literature clearly shows that CKD prevalence increases with age when using the fixed-threshold CKD definition of 60 mL/min per 1.73m² [1,48,56,97,101,123,130–134,138–143]. Most older "patients" have a GFR of 45 to 60 mL/min per 1.73m², and normal urine ACR, whereas the younger patients more frequently have elevated urine ACR and GFR over 60 mL/min per 1.73m² [53,97,134,144]. Thus, among the 3.6% of the general population with normal urine ACR and GFR between 45 and 60 mL/min per 1.73m² in the NHANES (1999-2006) cohort, a large proportion is likely to

be subjects older than 65 years, without any other signs of kidney damage. These subjects would be considered *disease-free* with the age-adapted definition proposed above. Likewise, results from the MAREMAR ("Maladie Rénale Chronique au Maroc") study crucially illustrate the important impact of an age-adapted definition on the CKD prevalence. Among the 10,524 subjects screened, 2.7% had a confirmed eGFR below 60 mL/min per 1.73m². However, almost half of the subjects with eGFR below 60 mL/min per 1.73m² had an eGFR above the third percentile of the population. These people, all older than 55 years and with normal dipstick analysis, would not be considered to have CKD with the age-adapted definition (here percentiles) and the estimated CKD prevalence based on GFR would decrease from 2.7% to 1.8%, a 33% decrease [97].

The current fixed GFR threshold of 60 mL/min per 1.73m² not only results in over-diagnosis of CKD in the older adults, it may also lead to missed diagnoses of CKD in younger subjects without overt signs of kidney damage, who have a GFR below the lowest percentile for age, although above the fixed threshold of 60 mL/min per 1.73m². This group may include young people with low-nephron endowment, e.g. individuals born with a single kidney [145], those born pre-term [146], low-birth weight subjects, patients with Down syndrome [147] or young people with a past history of treatment with nephrotoxic drugs [148]. Such people are at risk for developing progressive CKD over their remaining lifetime, and may suffer associated comorbidities and adverse events, including an increase in mortality [33,97,123,129]. Notably, as there are limited curative therapies available yet, the treatment of CKD rests on the prevention of progressive kidney damage. The sooner young people with CKD are identified, the greater the chance that poor health outcomes may be prevented. In the MAREMAR study, the young people with a low for-age GFR represented 1.3% of the population [97]. These persons remain unrecognized in most epidemiological studies that use a fixed GFR threshold of 60 mL/min per 1.73m² [97,123]. Using SDS scores, percentiles or age-adapted staging in the definition of

CKD, these patients would be classified as having a disease. Further work seems necessary with a focus on long-term follow-up data to elucidate if this category of patients should be considered at risk for adverse renal or other disease-related outcomes.

Conclusions

Moving from a CKD definition with a fixed GFR threshold to a definition based on GFR adapted to age has several advantages:

1. it takes into account the physiological age-related decline in GFR
2. it fits with reference distributions of mGFR and eGFR in healthy subjects
3. it is consistent with the observed associations between low GFR and prognosis
4. it reconciles the two ways to define a disease: the distribution of lab results and the prognostic approach
5. it facilitates the identification, evaluation and treatment of younger patients with GFR too low for their age
6. it avoids over-diagnosis of CKD in the elderly

An age-adapted definition of CKD will also lead to a much lower global CKD prevalence (perhaps by as much as 50%), particularly in the elderly. However, if we consider that: a) older subjects without increased urine ACR or other signs of kidney damage, usually have slightly decreased GFR; b) their GFR decrease is physiological; c) their GFR will on average remain stable (or could even improve) during follow-up; d) they have a mortality risk similar to those with higher GFR- then there are no reasons to consider such older subjects as suffering from disease and requiring investigations, referrals, and even therapeutic interventions with potential side effects [149]. At an individual level, the application of a CKD status in older people ("D" meaning "disease") can be source of unjustified stress. In some

countries, this diagnosis can also lead to adverse consequences in terms of insurance. The age-adapted CKD definition should eventually result in more appropriate attention and resources being directed to those who are at higher risk of adverse outcomes associated with CKD.

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Legend

Table 1: Current CKD staging according to glomerular filtration rate (GFR) and urine albumin-to-creatinine ratio (ACR).

Table2: Characteristics of studies that investigated outcomes in relation to GFR in general populations

Table3: Findings of studies that investigated outcomes in relation to GFR in general populations

Figure 1: Hazard ratio for mortality when the reference group is the one with the lowest risk. eGFR ranges are within the brackets (low risk) and are not significantly different from the reference group (from [34])

Figure 2: Examples of interpretation of GFR (here GFR estimated using the FAS equation but the same can be applied to measured GFR or eGFR using other estimating equations) according to age and normal percentiles. The red circle corresponds to FAS = 48mL/min per 1.73m² (Serum creatinine (SCr) = 1.3 mg/dL corresponds to (SCr/Q = 1.3/0.9 = 1.44 > 1.33) and the green circle corresponds to FAS = 58 mL/min per 1.73m² (SCr = 1.1 mg/dL corresponds to SCr/Q = 1.22 < 1.33). These results are abnormally low and normal predicted eGFR-FAS results with the age-adapted staging, respectively.
'Dark' green shaded area corresponds to reference intervals for mGFR ± SD and symmetrical limits for FAS based on SCr/Q = 1 (middle line) and SCr/Q = 1.33 (lower limit) [14, 18].
'Light' green area corresponds to the upper limit for FAS, based on SCr/Q = 0.67. The interval [0.67 – 1.33] is considered the reference interval for SCr/Q.

Figure 3: GFR cut-off values and percentiles according to age (here percentiles of estimated GFR calculated using the FAS equation). The black bold line represents an age adapted threshold for CKD: 75 mL/min per 1.73m² for age below 40 years, 60 mL/min per 1.73m² for age between 40 and 65 years, and 45 mL/min per 1.73m² for age above 65 years. The dashed bold line represents the median (50^{th}, percentile 50) and the black thin solid lines represent the 97.5^{th} and 2.5^{th} percentiles. The grey zone is considered as below the normal reference intervals for GFR (<2.5^{th} percentile).

Table 1

GFR category	GFR (mL/min per 1.73m²)
G1	≥90
G2	60-89
G3a	45-59
G3b	30-44
G4	15-29
G5	<15
ACR category	**Urine ACR (mg/g)**
A1	<30
A2	30-300
A3	>300

ACR: Albumin-to-Creatinine Ratio, GFR: Glomerular Filtration Rate

Table 2

Author [ref]	Study name	Country	Time period of data collection	Number of subjects, *N*	Age (in years; mean±SD /median (range) and other potentailly relevant characteristics	Follow-up time (years)	Clinical cohort/ General population
Manjunath et al. [35]	Cardiovascular Health Study	USA	1989-1990	4,893	73.4 (mean)	5.05	GP
Go et al.[29]	Kaiser Permanente Renal Registry	USA	1996-2000	1,120,295	52.2± 16.3 (mean±SD)	2.84 (median) 1.65-4.01 (IQR)	GP (health insurer)
O'Hare et al. [36]	Dept. of Veterans Affairs	USA	2001-2002	2,583,911	63.6±14(mean±SD) 95% men	3.17 ± 0.62 (mean±SD)	GP (health care provider)
Maaravi et al. [37]	Jerusalem Seventy Year Olds Longitudinal Study	Israel	1990-1991	441	70 (all)	12 (maximum)	GP
Hallan et al. [38]	HUNT II	Norway	1995-1997	9,709	All with DM or treated HT plus 5% random sample. DM/HT age 65.9± 11.9 (mean±SD); Random non-DM/HT age 49.6±16.0 (mean±SD).	8.3 (median)	GP (health survey) Population based, but in fact a **'high-risk' study population.**
Raymond et al.[56]	NA	United Kingdom	2000-2003	106,366	57.7± 19.1 (mean±SD)	3 (maximum)	GP
Brantsma et al. [39]	PREVEND	Netherlands	1997-1998	8,495	49.2±12.7 (mean±SD)	7.5 (median) 6.9-7.8 (IQR)	GP Oversampling of individuals with elevated ACR levels.
Hwang et al. [40]	Elderly Health Examination Program	Taiwan	2002-2004	35,529	75.7± 5.3 (mean±SD)	From 2.6±0.3 (mean±SD) for eGFR ≥ 60 mL/min to 2.3±0.7 (mean±SD) for stage 5	GP
Roderick et al. [41]	MRC GP research framework	UK	1994-1999	13,177	80.2 (median) (IQR 6.9)	7.3 (median) (IQR 5)	GP (primary care)
Van der Velde et al. [42]	PREVEND	Netherlands	1997-1998	8,047	49±13(mean±SD)	7.0±1.6 (mean±SD)	GP Oversampling of individuals with elevated ACR levels.

Muntner et al.[43]	REGARDS	USA	2003-2007	24,350	≥ 45	4.5 (median)	GP Oversampling of African Americans.
Stengel et al. [44]	Three-City	France	1999-2001	8,705	74.3±5.5 (mean±SD)	6 (maximum)	GP
Van Pottelbergh et al. [45]	BELFRAIL	Belgium	2008-2009	539	84.7±3.6 (mean±SD)	2.9±0.3	GP (primary care)
Oh et al. [46]	KloSHA	Korea	2005-2006	949	75.8±9.0 (mean±SD)	5.3±1.4 (mean±SD)	GP
Minutolo et al.[47]	Health Search/Cegedim Strategic Data Longitudinal Patient Database	Italy	2003-2005	30,326	71.0± 11.0 (mean±SD)	7.2 (median) 4.7-7.7 (IQR)	GP (primary care) Population without nephrology consultation at baseline.
Malmgren et al.[48]	NA	Sweden	unknown	1,011	75.2 ± 0.2(mean±SD) 100% women	10	GP
Chowdhury et al. [49]	ANBP2	Australia	NA	6,083	71.9±4.9 (mean±SD)	10.8 (median) 9.6-11.4 (IQR)	RCT participants Hypertensive population.
Nagai et al. [50]	Ibaraki prefecture	Japan	1993	89,547	Men 60.2 (mean) Women 57.8 (mean)	17.1 (mean)	GP Exclusion of those with history of CVD.
Corsonello et al. [51]	InChianti	Italy	1998-2000	828	74.4±6.9 (mean±SD)	9 (maximum)	GP
Wu et al [52]	Kailuan Study	China	2006-2007	95,391	52.0±12.6 (mean±SD)	8 (maximum)	GP

Abbreviations: CVD: cardiovascular disease, DM: diabetes mellitus, GP: general population, HT: hypertension, NA: not available, RCT: randomized controlled trial

Table 3

Author [ref]	Study name	eGFR/ACR (GFR equation)	Outcome studied All-cause (ACM) or Cardiovascular (CVM) mortality	Comparison made + reference category	Adjusted Hazard Ratios in exposure categories (in green results important for our purpose)	Comments
Manjunath et al. [35]	Cardiovascular Health Study	MDRD	ACM	Reference category: 90-130 mL/min/1.73m2	60-89 mL/min 1.05 (0.78-1.41) 15-59 mL/min 1.47 (1.05-2.06)	
Go et al. [29]	Kaiser Permanente Renal Registry	MDRD	ACM CV events	Reference category: ≥ 60 mL/min/1.73m2.	**ACM** 45-59 mL/min 1.2 (1.1-1.2) 30-44 mL/min 1.8 (1.7-1.9) 15-29 mL/min 3.2 (3.1-3.4) < 15 mL/min 5.9 (5.4-6.5) **CV events** 45-59 mL/min 1.4 (1.4-1.5) 30-44 mL/min 2.0 (1.9-2.1) 15-29 mL/min 2.8 (2.6-2.9) < 15 mL/min 3.4 (3.1-3.8)	In a subgroup where chronicity was confirmed (repeated serum creatinine measurements) (n=172,144), eGFR at 45-59 mL/min was not associated with ACM 1.0 (1.0-1.1)
O'Hare et al [36]	Dept. of Veterans Affairs	MDRD	ACM	Reference category: ≥ 60 mL/min/1.73m2	**18-44 years** 50-59 mL/min 1.56 (1.30-1.88) 40-49 mL/min 1.90 (1.35-2.67) 30-39 mL/min 3.58 (2.54-5.05) **45-54 years** 50-59 mL/min 1.27 (1.19-1.36) 40-49 mL/min 1.89 (1.74-2.06) 30-39 mL/min 2.89 (2.63-3.18) **55-64 years** 50-59 mL/min 1.18 (1.13-1.23) 40-49 mL/min 1.75 (1.65-1.85) 30-39 mL/min 2.43 (2.27-2.59) **65-74 years** 50-59 mL/min 1.02 (0.99-1.05) 40-49 mL/min 1.35 (1.32-1.39) 30-39 mL/min 1.81 (1.75-1.87) **75-84 years** 50-59 mL/min 1.02 (0.99-1.04) 40-49 mL/min 1.21 (1.18-1.23) 30-39 mL/min 1.55 (1.51-1.58) **85+ years**	In **younger** age categories adjusted HRs were higher and statistically significant already from 50-59 mL/min. In **younger people and elderly** with stable eGFR adjusted HRs • were lower in all eGFR categories. • 50-59 mL/min was not associated with ACM Findings suggest that mortality risk stratification in younger and elderly people should not be based on the same eGFR cut-off points.

					50-59 mL/min 1.02 (0.97-1.06) 40-49 mL/min 1.10 (1.05-1.15) 30-39 mL/min 1.36 (1.29-1.44)	
Maaravi et al. [37]	Jerusalem Seventy Year Olds Longitudinal Study	CG MDRD Mayo Clinic	ACM	Reference category: ≥ 60 mL/min/1.73m2. Results presented fo MDRD	< 60 mL/min 1.19 (0.83-1.71)	
Hallan et al. [38]	HUNT II	MDRD	CVM	Reference category: ≥ 75 mL/min/1.73m2 and optimal ACR (ACR below sex specific median (<5 and 7 mg/g in men and women))	**< 70 years** **Optimal ACR** 60-74 mL/min 1.17 (0.35-3.91) 45-59 mL/min 0.73 (0.26-2.02) < 45 mL/min 1.08 (0.19-6.10) **High normal ACR** 60-74 mL/min 1.53 (0.55-4.26) 45-59 mL/min 3.29 (1.02-10.6) < 45 mL/min 2.57 (0.88-7.51) **Micro-albuminuria** 60-74 mL/min 1.92 (0.71-5.16) 45-59 mL/min 2.22 (0.87-5.70) < 45 mL/min 5.94 (2.06-17.2) **≥ 70 years** **Optimal ACR** 60-74 mL/min 0.79 (0.30-2.10) 45-59 mL/min 2.48 (0.76-8.13) < 45 mL/min 1.49 (0.46-4.86) **High normal ACR** 60-74 mL/min 1.68 (0.61-4.69) 45-59 mL/min 1.93 (0.63-5.92) < 45 mL/min 4.70 (1.57-14.1) **Micro-albuminuria** 60-74 mL/min 3.80 (1.33-10.80) 45-59 mL/min 4.09 (1.52-10.90) < 45 mL/min 8.38 (2.83-24.9)	
Raymond et al. [56]	NA	MDRD	ACM	Reference category: ≥ 60 mL/min/1.73m2.	**20-44 years** Stage 3a 13.6 (6.2-29.8) Stage 3b 12.1 (4.0-36.5) Stage 4 17.4 (5.9-51.4) Stage 5 26.1 (9.1-74.8) **45-54 years** Stage 3a 7.5 (4.4-12.6) Stage 3b 13.6 (7.5-24.7) Stage 4 4.6 (1.2-17.4) Stage 5 28.6 (17.4-47.2)	

					55-64 years Stage 3a 3.0 (2.2-4.1) Stage 3b 5.9 (3.9-8.9) Stage 4 9.3 (6.1-14.2) Stage 5 18.2 (13.9-23.9) **65-74 years** Stage 3a 1.8 (1.5-2.1) Stage 3b 3.2 (2.6-3.9) Stage 4 5.2 (4.1-6.5) Stage 5 7.6 (5.7-10.1) **75-84 years** Stage 3a 1.2 (1.0-1.3) Stage 3b 1.9 (1.7-2.1) Stage 4 3.3 (2.9-3.8) Stage 5 4.4 (3.7-5.3) **85+ years** Stage 3a 0.9 (0.8-1.0) Stage 3b 1.3 (1.2-1.5) Stage 4 1.8 (1.7-2.0) Stage 5 2.5 (2.3-2.8)	
Brantsma et al. [39]	PREVEND	MDRD ACR	CVM and CV hospitalization combined	Reference category: no CKD	Stage 1 2.2 (1.5-3.3) Stage 2 1.6 (1.3-2.0) Stage 3 1.3 (1.0-1.7) Stage 3 with UAE < 30 mg/24hr 1.0 (0.7-1.4) Stage 3 with UAE > 30 mg/24 hr 1.6 (1.1-2.3)	
Hwang et al. [40]	Elderly Health Examination Program	MDRD	ACM CVM	Reference category: ≥ 60 mL/min/1.73m2	**ACM** 45-59 mL/min 1.10 (1.0-1.2) 30-44 mL/min 1.52 (1.3-1.8) 15-29 mL/min 2.1 (1.7-2.6) < 15 mL/min 2.55 (1.8-3.6) **CVM** 45-59 mL/min 1.30 (1.0-1.7) 30-44 mL/min 2.42 (1.7-3.4) 15-29 mL/min 3.62 (2.3-5.8) < 15 mL/min 3.22 (1.3-8.3)	
Roderick et al. [41]	MRC GP research framework	MDRD Dipstick proteinuria	ACM CVM in those without CVD at baseline	Reference category: ≥ 60 mL/min/1.73m2 Proteinuria negative	**ACM after 0-2 years** **Men** 45-59 mL/min 1.13 (0.93-1.37) 30-44 mL/min 1.69 (1.26-2.28) < 30 mL/min 3.87 (2.78-5.38) **Women**	Short-term (0-2 yr) eGFR-related risk is higher than long term (> 2 yr) risk (not shown).

					45-59 mL/min 1.14 (0.93-1.40) 30-44 mL/min 1.33 (1.06-1.68) < 30 mL/min 2.44 (1.68-3.56) **CVM after 0-2 years** **Men** 45-59 mL/min 1.67 (1.15-2.43) 30-44 mL/min 1.60 (0.94-2.73) < 30 mL/min 2.89 (1.22-6.84) **Women** 45-59 mL/min 1.59 (1.01-2.50) 30-44 mL/min 1.45 (0.93-2.28) < 30 mL/min 3.80 (1.87-7.75) **ACM** **Men** Proteinuria positive > 60 mL/min 1.29 (1.07-1.56) 45-59 mL/min 1.25 (1.02-1.52) 30-44 mL/min 1.08 (0.82-1.42) < 30 mL/min 0.95 (0.56-1.59) **Women** Proteinuria positive > 60 mL/min 1.19 (0.96-1.47) 45-59 mL/min 0.94 (0.77-1.15) 30-44 mL/min 1.39 (1.10-1.77) < 30 mL/min 1.70 (1.15-2.52) **CVM** **Men** Proteinuria positive > 60 mL/min 1.05 (0.70-1.57) 45-59 mL/min 1.31 (0.91-1.89) 30-44 mL/min 0.83 (0.47-1.46) < 30 mL/min 0.97 (0.35-2.68) **Women** Proteinuria positive > 60 mL/min 1.18 (0.80-1.74) 45-59 mL/min 0.93 (0.65-1.32) 30-44 mL/min 1.34 (0.88-2.03) < 30 mL/min 2.79 (1.40-5.54)	
Van der Velde et al. [42]	PREVEND	MDRD CKD EPI CysC Combi	Fatal and non-fatal CV events	+ 10 mL/min/1.73M2 increase in eGFR. Results presented for CKD EPI.	**< 60 years** 0.70 (0.62-0.79) **≥ 60 years** 1.02 (0.92-1.13)	The association between eGFR and risk of CV events is weaker in elderly subjects than in younger subjects.

		Creatinine Clearance				
Muntner et al. [43]	REGARDS	CKD-EPI ACR	ACM	Reference category: ≥ 60 mL/min/1.73m2.	**45-59 years** 45-60 mL/min 2.5 (1.3-4.6) < 45 mL/min 3.5 (1.8-6.8) **60-69 years** 45-60 mL/min 1.7 (1.3-2.3) < 45 mL/min 2.2 (1.6-3.0) **70-79 years** 45-60 mL/min 1.1 (0.9-1.3) < 45 mL/min 1.9 (1.5-2.4) **≥ 80 years** 45-60 mL/min 1.3 (1.0-1.7) < 45 mL/min 1.5 (1.1-2.0)	If ACR is < 10mg/g, the results are similar: **45-59 years** 45-60 mL/min 4.5 (1.8-11.1) < 45 mL/min 4.7 (0.7-34.2) **60-69 years** 45-60 mL/min 1.9 (1.2-3.1) < 45 mL/min 2.5 (1.0-6.1) **70-79 years** 45-60 mL/min 1.1 (0.8-1.6) < 45 mL/min 2.1 (1.2-3.6) **≥ 80 years** 45-60 mL/min 1.4 (0.9-2.2) < 45 mL/min 1.6 (0.9-2.8)
Stengel et al.[44]	Three City	CKD-EPI MDRD	ACM CVM	Reference category: ≥ 75-89 mL/min/1.73m2 Results presented for CKD-EPI.	**ACM** 60-74 mL/min 0.9 (0.8-1.1) 45-59 mL/min 1.1 (0.9-1.3) 30-44 mL/min 2.0 (1.5-2.7) < 30 mL/min 3.3 (2.0-5.5) **CVM** 60-74 mL/min 0.9 (0.6-1.3) 45-59 mL/min 1.6 (1.1-2.3) 30-44 mL/min 3.1 (1.8-5.0) < 30 mL/min 4.3 (1.8-10.2)	
Van Pottelbergh et al. [45]	BELFRAIL	MDRD CKD-EPI Creat CKD-EPI Cyst CKD-EPI Creatcyst BIS	ACM and RRT combined	Reference category: 60-90 mL/min/1.73m2. Results presented for CKD-EPI SCr.	45-60 mL/min 1.65 (1.05-2.61) 30-45 mL/min 1.72 (1.03-2.88) <30 mL/min 5.04 (2.95-8.60)	
Oh et al. [46]	KLoSHA	CKD-EPI ACR	ACM	Reference category: ≥ 90 mL/min/1.73m2 Proteinuria negative	60-89 mL/min 1.37 (0.75-2.52) 45-59 mL/min 1.65 (0.84-3.25) < 45 mL/min 2.36 (1.17-4.75)	If proteinuria (strips) Trace 1.24 (0.78-1.96) ≥ 1+ 1.73 (1.13-2.63)
Minutolo et al. [47]	Health Search/Cegedim Strategic Data Longitudinal Patient Database	MDRD	ACM	Reference category: ≥ 60 mL/min/1.73m2.	**ACM** Stage 3a 1.11 (0.99-1.23) Stage 3b 1.66 (1.49-1.86) Stage 4 2.75 (2.41-3.13) Stage 5 2.54 (2.01-3.22)	

Malmgren et al.[48]	NA	CKD-EPI MDRD Revised Lund-Malmö BIS-1 Cockroft-Gault	ACM	Reference category: ≥ 60 mL/min/1.73m2. Results presented for CKD-EPI.	**75-80 years** 45-60 mL/min 1.1 (0.6-2.0) 0-45 mL/min 4.5 (2.2-9.2) **75-85 years** 45-60 mL/min 1.4 (1.0-1.9) 0-45 mL/min 3.5 (2.1-5.8) **80-85 years** 45-60 mL/min 1.7 (1.1-2.6) 0-45 mL/min 2.6 (1.4-5.0)	
Chowdhury et al. [49]	ANBP2	MDRD CKD-EPI	ACM CVM	Reference category: ≥ 60 mL/min/1.73m2. Results presented for CKD-EPI.	**ACM** 45-59 mL/min 1.13 (1.01-1.27) 30-44 mL/min 1.65 (1.37-1.99) < 30 mL/min 5.16 (3.17-8.42) **CVM** 45-59 mL/min 1.05 (0.89-1.23) 30-44 mL/min 1.64 (1.27-2.13) < 30 mL/min 5.60 (2.32-13.51)	
Nagai et al. [50]	Ibaraki prefecture	MDRD	ACM CVM	Reference category: ≥ 60 mL/min/1.73m2.	**ACM** **Men** **40-69 years** 45-49 mL/min 1.33 (1.06-1.67) 30-44 mL/min 1.53 (1.20-1.96) **70-80 years** 45-49 mL/min 1.02 (0.82-1.25) 30-44 mL/min 1.63 (1.33-2.00) **Women** **40-69 years** 45-49 mL/min 1.50 (1.27-1.78) 30-44 mL/min 2.21 (1.81-2.71) **70-80 years** 45-49 mL/min 1.19 (1.02-1.38) 30-44 mL/min 1.53 (1.31-1.79) **CVM** **Men** **40-69 years** 45-49 mL/min 1.82 (1.23-2.69) 30-44 mL/min 1.65 (1.04-2.62) **70-80 years** 45-49 mL/min 1.03 (0.72-1.48) 30-44 mL/min 1.37 (0.93-2.02) **Women** **40-69 years** 45-49 mL/min 1.34 (0.98-1.82)	

					30-44 mL/min 2.24 (1.58-3.17) **70-80 years** 45-49 mL/min 1.43 (1.14-1.79) 30-44 mL/min 1.57 (1.23-2.00)	
Corsonello et al. [51]	InChianti	CKD-EPI SCr BIS1 SCr FAS CKD EPI SCr-CysC Bis2 SCr-CysC	ACM	Reference category: ≥ 90 mL/min/1.73m2 Results presented for CKD-EPI SCr	60-89.9 mL/min 1.63 (0.84-3.17) 45-59.9 mL/min 2.50 (1.21-5.15) 30-44.9 mL/min 5.44 (1.10-27.7) <30 mL/min 7.42 (1.79-30.6)	
Wu et al. [52]	Kailuan Study	CKD-EPI ACR	ACM	Reference category: ≥ 90 mL/min/1.73m2	**All** 60-89 mL/min 1.01 (0.93-1.09) 45-59 mL/min 1.11 (0.99-1.24) <45 mL/min 1.51 (1.30-1.74) **Men** 60-89 mL/min 1.01 (0.94-1.10) 45-59 mL/min 1.11 (0.99-1.23) <45 mL/min 1.35 (1.17-1.57) **Women** 60-89 mL/min 1.65 (1.16-2.34) 45-59 mL/min 1.92 (1.25-2.96) <45 mL/min 4.11 (2.50-6.76)	

Abbreviations: ACR: albumin-to-creatinine ratio, BIS: Berlin Intitiative Study, CKD EPI: Chronic Kidney Disease Epidemiology Collaboration equation, SCr: serum creatinine, CV: cardiovascular, CVD: cardiovascular disease, CysC; cystatin C, eGFR: estimated Glomerular Filtration Rate, FAS: Full Age Spectrum, GP: general population, MDRD: Modified Diet in Renal Disease Study equation, NA: not available

Figure 1.

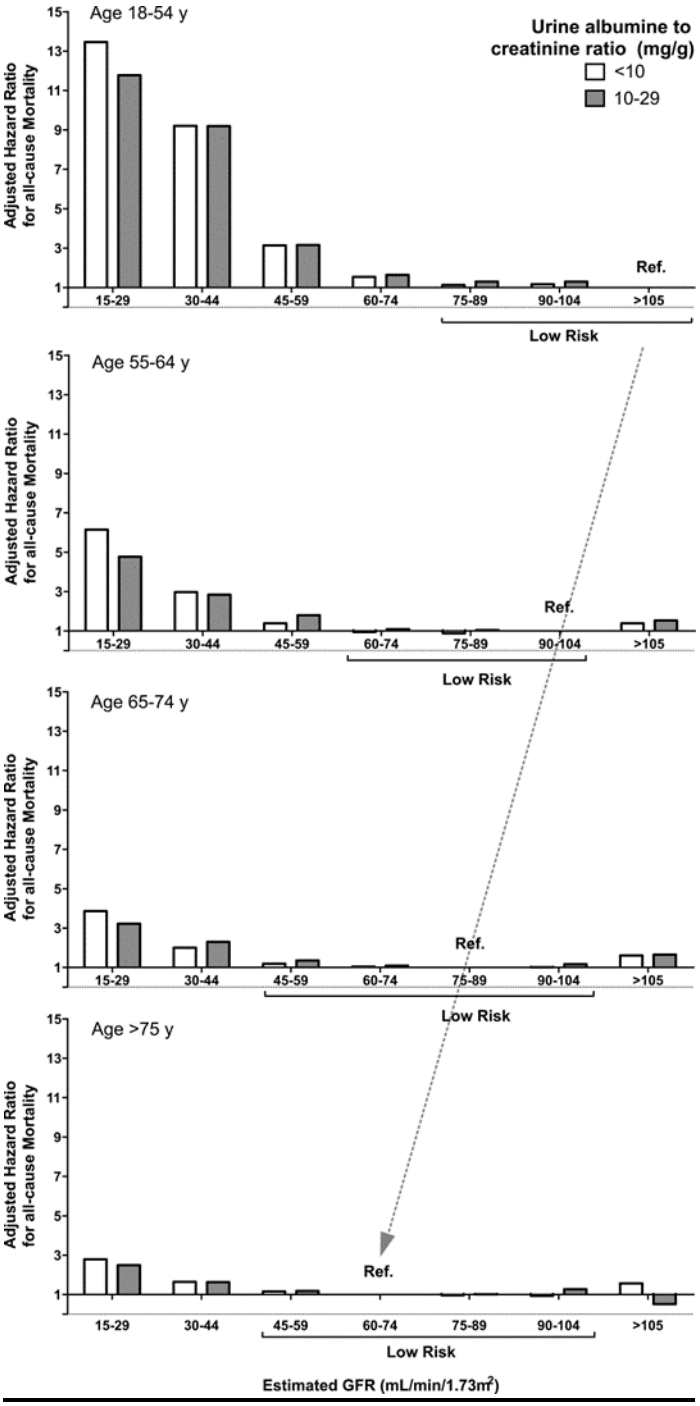

Age 18-54 y
Urine albumine to creatinine ratio (mg/g)
<10
10-29
Adjusted Hazard Ratio for all-cause Mortality
Ref.
15-29
30-44
45-59
60-74
75-89
90-104
>105
Low Risk
Age 55-64 y
Age 65-74 y
Age >75 y
Estimated GFR (mL/min/1.73m²)

Figure 2.

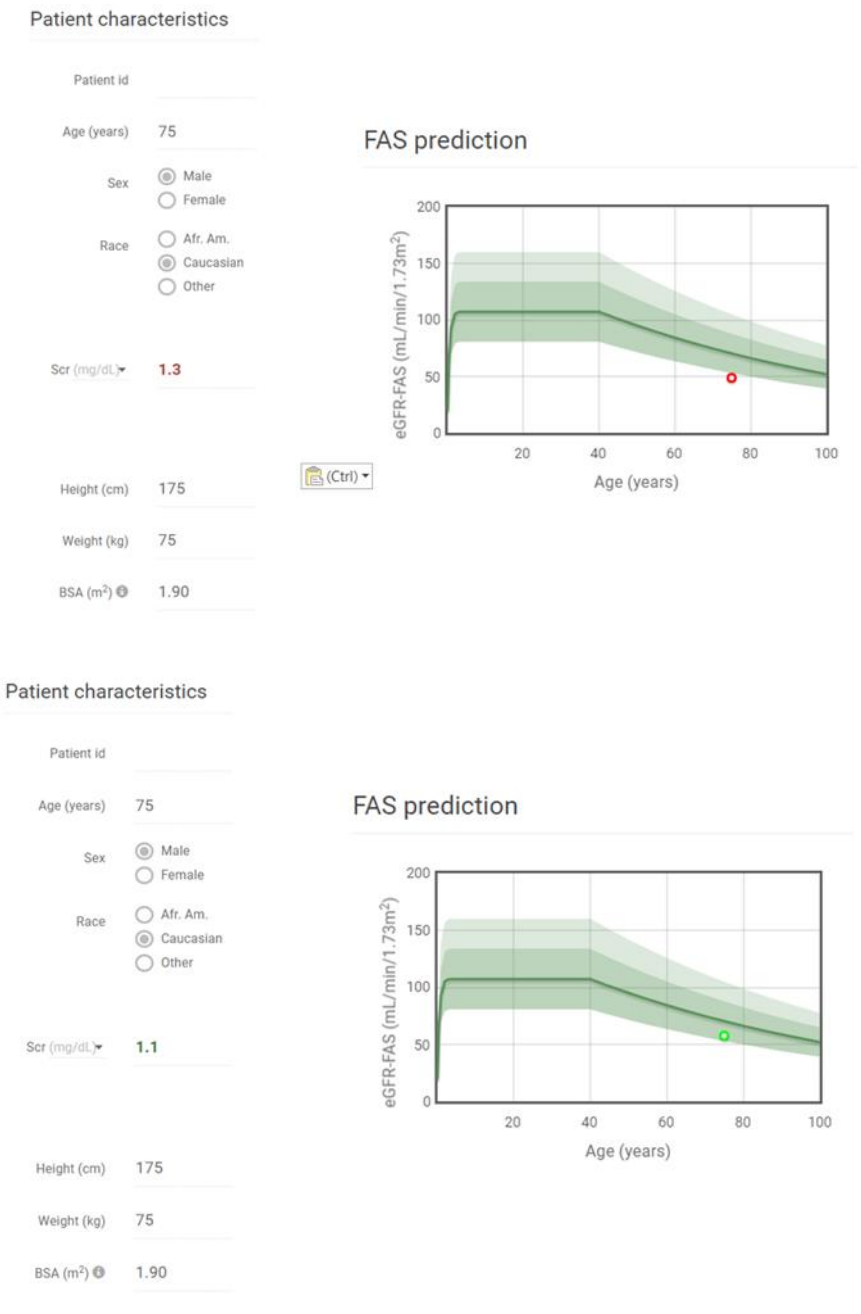
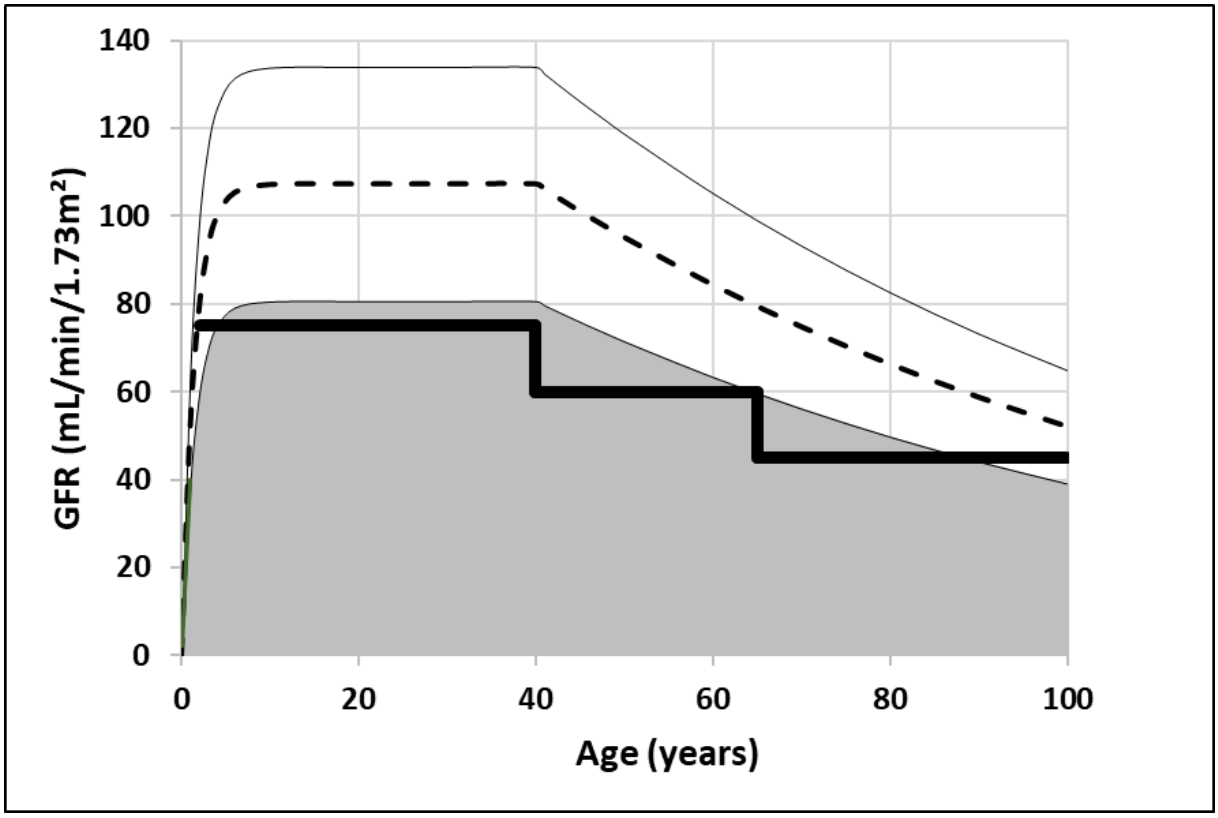

Patient characteristics
Patient id
Age (years) 75
Sex Male Female
Race Afr. Am. Caucasian Other
Scr (mg/dL) 1.3
Height (cm) 175
Weight (kg) 75
BSA (m²) 1.90
FAS prediction
eGFR-FAS (mL/min/1.73m²)
200
150
100
50
0
20
40
60
80
100
Age (years)
(Ctrl)
Patient characteristics
Patient id
Age (years) 75
Sex Male Female
Race Afr. Am. Caucasian Other
Scr (mg/dL) 1.1
Height (cm) 175
Weight (kg) 75
BSA (m²) 1.90
FAS prediction
eGFR-FAS (mL/min/1.73m²)
200
150
100
50
0
20
40
60
80
100
Age (years)

Figure 3.


140
120
100
80
60
40
20
0
GFR (mL/min/1.73m²)
0
20
40
60
80
100
Age (years)