Age- and sex-specific reference values of estimated glomerular filtration rate for European adults

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Kidney function, often assessed by estimated glomerular filtration rate (eGFR), declines naturally with age. However, there is a lack of eGFR reference values to describe normal and abnormal values for a specific age. The European Chronic Kidney Disease Burden Consortium is comprised of nine participating general population-based studies from seven European countries which provides European age- and sex-specific eGFR reference values in healthy adults using the European Kidney Function Consortium (EKFC) equation. Of 2,572,020 individuals, 1,535,253 (60%) were considered healthy, of which 45% were men. Ages ranged from 18 to 105 years old in men and 18 to 107 years old in women with a median age of 43 years in both sexes. At age 20 in men, the 5th, 50th and 95th eGFR percentiles were 78 ml/min per 1.73 m^2, 99 ml/min per 1.73 m^2, and 119 ml/min per 1.73 m^2. In 20-year-old women this was 81 ml/min per 1.73 m^2, 101 ml/min per 1.73 m^2, and 121 ml/min per 1.73 m^2. Consequently, in men aged 80 years old, the 5th, 50th and 95th eGFR percentiles were 49 ml/min per 1.73 m^2, 66 ml/min per 1.73 m^2, and 84 ml/min per 1.73 m^2. In 80 year old women this was 46 ml/min per 1.73 m^2, 63 ml/min per 1.73 m^2, and 81 ml/min per 1.73 m^2. Overall, our study shows that eGFR is not preserved with ageing in healthy individuals and these eGFR reference values can help determine abnormal and normal kidney function across the age range.

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An estimated 10% of the world has chronic kidney disease (CKD). The Kidney Disease: Improving Global Outcomes (KDIGO) definition is most commonly used to diagnose CKD stages.[1] Whatever the etiology, it classifies CKD into stages based on albuminuria and/or glomerular filtration rate values, from the less severe stage G1 to the more advanced stage G5, preluding dialysis or kidney transplantation. However, in the literature, a frequently used definition of CKD (actually corresponding to KDIGO stages 3–5) is an estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 present for a minimum of 3 consecutive months, independent of age and sex. This definition does not take into account kidney function decline that occurs with aging, even in healthy individuals, resulting in claims that CKD is being underdiagnosed in younger people and over-diagnosed in older people.[2] To account for age in the CKD definition, it has been suggested to use age-group–specific

Lay Summary

Kidney function, often assessed by estimated glomerular filtration rate (eGFR), naturally declines with age. Despite this, current criteria for diagnosing chronic kidney disease (CKD) do not account for this age-related decline. Overlooking age-related changes in kidney function may hinder the assessment, diagnosis, management, and treatment of kidney disease. Establishing age-specific eGFR reference values could be used to determine if an individual's eGFR is abnormal for his/her age and help refine the current standard to diagnose CKD. Using data collected on 1.5 million healthy individuals from Europe, we describe the distribution of eGFR values in adults aged 18 to 100 years. Our results show that the definition of abnormal kidney function varies by age and provide clinically relevant information that may contribute to improving practices and policies for the surveillance, identification, and appropriate management of abnormal kidney function and CKD.

eGFR thresholds or a continuous eGFR threshold based on the age- and sex-specific distribution of eGFR in healthy adults.[2]

A prerequisite for the development of a continuous threshold is the ability to distinguish between normal and abnormal kidney function, thus requiring the establishment of eGFR reference values.[3] Reference values are the range of values considered normal for a particular population and are used in other medical fields, such as for pediatric growth charts[4] and lung spirometry.[5] However, eGFR reference values have been difficult to define. Delanaye *et al.* outlined the most common obstacles that studies face, including small sample sizes, unrepresentative samples, poorly defined health criteria, and insufficient age ranges.[3]

To date, several studies described eGFR reference values in kidney donors.[6–11] These studies include highly selected groups of people and were mostly of small sample sizes. Other studies in healthy individuals sampled from European general populations have relatively small sample sizes, are single-country studies,[12,13] are likely unrepresentative of the larger European population, or use outdated eGFR equations.[14,15] A more recent study from Eriksen *et al.* provided reference values for measured glomerular filtration rate (mGFR) using samples from 3 European general population studies, but the age range was limited to individuals aged >50 years.[16] Regardless of the strengths of the aforementioned studies, fundamental differences between studies make it difficult to combine results and obtain eGFR reference values from a sufficiently large sample representative of the general population, and covering a full age range, for use in Europe.

Therefore, this study aims to establish European eGFR reference values by describing the distribution of eGFR values across a full age range by sex, in >1.5 million healthy individuals from a multinational, contemporary, adult European general population.

METHODS

Study selection

General population studies were identified by a literature database search, outreach, and from a previous study of the European CKD Burden Consortium.[17] Studies were included if they were designed to select a representative sample of the target population. Studies needed to have a minimum sample size of 2000 individuals and collected data after 1999 on adults aged ≥18 years with isotope dilution mass spectrometry traceable serum creatinine.

Data collection

Studies provided an individual-level data set containing data on sex, age at moment of data collection, serum creatinine, and if the individual was considered healthy, based on the definition described further in the Methods. Missingness of data on comorbidities, medication use, and lifestyle-related risk factors used to define the healthy individual was also provided. Additional patient characteristics were collected as aggregated data. Date of data collection could be at any time between January 2000 and April 2024. Data collected were either self-reported or obtained through medical records using *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes. If *ICD-10* codes were used to identify comorbid conditions, we assumed that the absence of an *ICD-10* code indicated the absence of the considered comorbidity. Smoking was determined using self-reporting and not by *ICD-10* codes. We realize there is a difference between gender and sex, but we will use the term sex throughout this article as we expect differences observed between healthy men and women to be primarily a result of biological differences.

eGFR

eGFR was calculated using the European Kidney Function Consortium (EKFC) equation, which is listed as a validated equation by KDIGO.[18,19] Serum creatinine was determined by Jaffe or enzymatic assays and calibrated to isotope dilution mass spectrometry. The EKFC equation and Q values are described in detail in the Supplementary Methods.[18] We repeated the analysis using the Revised Lund-Malmö (RLM) equation,[20] the Chronic Kidney Disease Epidemiology Collaboration $(CKD\text{-}EPI)_{2009}$ equation,[21] and the $CKD\text{-}EPI_{2021}$ equation.[22] Race was considered as non-Black for all individuals in the calculation of eGFR using the $CKD\text{-}EPI_{2009}$ equation as most studies had a predominantly White study population, did not collect data on race, or were not allowed to collect data on race. Data on cystatin C were not collected, and only serum creatinine–based eGFR is reported.

Definition of healthy individuals

To minimize inclusion of individuals who may be at risk or have kidney damage, individuals were considered healthy if they met the following criteria at the time of data collection:

(i) no history of myocardial infarction, (ii) no history of angina pectoris, (iii) no history of heart failure, (iv) no history of coronary artery disease, (v) no history of hypertension, (vi) no history of stroke, (vii) no history of cancer, (viii) no history of diabetes, (ix) no history of kidney disease, (x) body mass index ≤30 kg/m^2, (xi) never smoked, (xii) no use of lipid-lowering medication or cardiac glycosides, (xiii) urine albumin-to-creatinine ratio ≤30 mg/g, and (xiv) no use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. These criteria to define healthy were based on, and slightly modified from, a healthy definition described by Eriksen *et al.*[16] Missingness in the variables used to define the healthy population is described in Supplementary Table S1 for each study. Collection methods among cohorts varied, with some variables missing at the cohort level. If the variable was not collected by a study, we considered the individuals to have no history or presence of that exclusion criteria rather than consider it missing. Individuals missing data were not included in the analysis.

Statistical analysis

Normally distributed continuous variables were presented as means with SD. Skewed continuous variables were presented as medians with interquartile range. Categorical variables were presented as frequencies with percentages.

The relationship between eGFR and age was explored using a generalized additive model for location, scale, and shape, which allows the distribution of eGFR to be modeled nonlinearly across age by sex with smoothing functions and random effects for study, which accounts for the clustering of observations within each study.[23] The generalized additive model for location, scale, and shape also allows the variance of eGFR to be modeled as a separate function of age. Model specifications are described in the Supplementary Methods. Analyses were performed using the gamlss package version 5.4-20 in R version 4.4.1.[24,25] Model comparisons were performed using Akaike information criterion to decide which smoothing functions should be used. Graphically, we present the median eGFR distribution with the 5th and 95th percentiles by sex for those aged 18 to 100 years.

Sensitivity analyses

To assess for the potential influence of cohorts with significantly larger sample sizes on our results, we repeated the main analysis on a subset of data by randomly selecting 1000 healthy individuals from each cohort where available, or all healthy individuals from cohorts with <1000 healthy individuals. eGFR calculated using the EKFC equation was compared with mGFR in a subset of individuals using bias, precision, and accuracy.

RESULTS

Participating cohorts' characteristics

Nine population-based cohorts from Iceland, Italy, Germany, the Netherlands, Norway, Sweden, and the United Kingdom participated (Table 1[26–35]). Most individuals came from the Stockholm CREAtinine Measurement (SCREAM) study (72%), the UK Biobank (14%), the Iceland CKD study (9%), and the Lifelines cohort (3%), whereas the remaining studies contributed <1% of the analytic cohort. Most studies recruited participants from general practitioner lists or population registers (Table 1 and Supplementary Table S2). Response rates ranged from 54% to 69%, with the exception of the UK Biobank (5.5%) and The Berlin Initiative Study (BIS; 8.1%), which still demonstrated a high agreement with regard to the distribution and frequency of chronic diseases when compared with its source population.[28] The smallest cohort had 2068 individuals (<1%; the BIS study, Germany) and the largest >1.6 million individuals (72%; SCREAM, Sweden). Six cohorts covered a relatively wide age spectrum, whereas the 3 remaining cohorts did not include individuals aged <40 years. The collection of the 14 variables used to define healthy ranged from as low as 10 variables to all 14 (Supplementary Table S1). Figure 1 describes the exclusion of individuals based on missing data and health status. Missingness in the variables used to define the healthy population was generally low (<3%), with some exceptions (Supplementary Table S1). Of 2,572,020 individuals, 2,504,048 (97%) had data to decide health status. Of these, 1,535,253 (60%) were classed as healthy, of which 45% were men. A similar proportion of women (63%) were categorized as healthy as men (60%). Density plots reflecting the distribution of healthy and not healthy individuals by sex, age, and study are presented in Supplementary Figure S1.

Population characteristics of healthy individuals by sex

Population characteristics for healthy individuals in each study are presented in Table 2, and by sex in Supplementary Table S3. Median age was 43 (interquartile range, 23) years in men and 42 (interquartile range, 24) years in women. Median eGFR using the EKFC equation was 95 ml/min per 1.73 m^2 in men and 96 ml/min per 1.73 m^2 in women.

eGFR distribution over age in healthy individuals by sex

The median eGFR distribution with 5th and 95th percentiles for men and women using the creatinine-based EKFC equation (EKFC$_{crea}$) is presented in Figure 2. eGFR distributions by 5-year age intervals by sex are presented in Table 3. eGFR was relatively stable until the age of 40 years, after which point eGFR decreased with age, reflecting the structure of the EKFC equation, which accounts for age-related changes in kidney function. Women had eGFR comparable to men before the age of 60 years, but a lower eGFR thereafter. There was a significant sex-age interaction ($P < 0.001$). The 5th and 95th percentiles of eGFR were on average 22 ml/min per 1.73 m^2 lower and 19 ml/min per 1.73 m^2 higher, respectively, than median eGFR in men and women. eGFR curves by study and sex are presented in Supplementary Figure S2. Results using the RLM, CKD-EPI$_{2009}$, and CKD-EPI$_{2021}$ equations are presented in Supplementary Tables S4–S6 and in Supplementary Figures S3–S5. Compared with the main

Table 1 | Description of participating studies and sampling characteristics

Country	Region(s) or cities	Study	Ages sampled, yr[a]	Sampling frame	Sample selection	Response, %
Iceland	All	Iceland CKD study[26]	≥18	National health service	Inhabitants of Iceland with ≥1 SCr measurements available	66
Italy	Northeast	INCIPE[27]	≥23	General practitioner lists	Random selection of participants from 62 randomly selected practices	62
Germany	Berlin	BIS[28]	≥70	Individuals insured with the AOK-Nordost statutory health insurance company	Random selection of participants insured by the AOK Nordost	8.1
	Northeast	SHIP[29]	20–80	Population registers	Stratification based on number of residents per municipality. Age and sex stratified random sample selection per community	69
The Netherlands	Northern	Lifelines[30]	≥18	General practitioner lists	General practitioners invited patients to participate, and patients invited family members to participate	58–84[b]
Norway	Central	The HUNT Study[31,32]	20–80	Census data	All residents in region	54
	Tromsø municipality	The Tromsø Study[33]	≥40	Population registries	Random selection of individuals from birth cohorts and population registries were invited to participate	65
Sweden	Region of Stockholm	SCREAM[34]	≥18	Complete health system	All Stockholm residents with a valid personal identifying number undertaking at least 1 measurement of creatinine in connection with a health care encounter	69[c]
United Kingdom	England, Wales, and Scotland	UK Biobank[35]	40–70	General practitioner lists	All individuals on NHS patient registers living within a reasonable traveling distance of an assessment center	5.5

AOK, Allgemeine Ortskrankenkasse; BIS, The Berlin Initiative Study; CKD, chronic kidney disease; The HUNT Study, The Trøndelag Health Study; INCIPE, Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints; NHS, National Health Service; SCr, serum creatinine; SCREAM, Stockholm CREAtinine Measurement; SHIP, Study of Health in Pomerania.
[a]Studies that collected data on all ages were asked to provide only data on those aged ≥18 years.
[b]Dependent on questionnaire.
[c]This is the proportion of the sampling population that underwent creatinine testing during the study period.

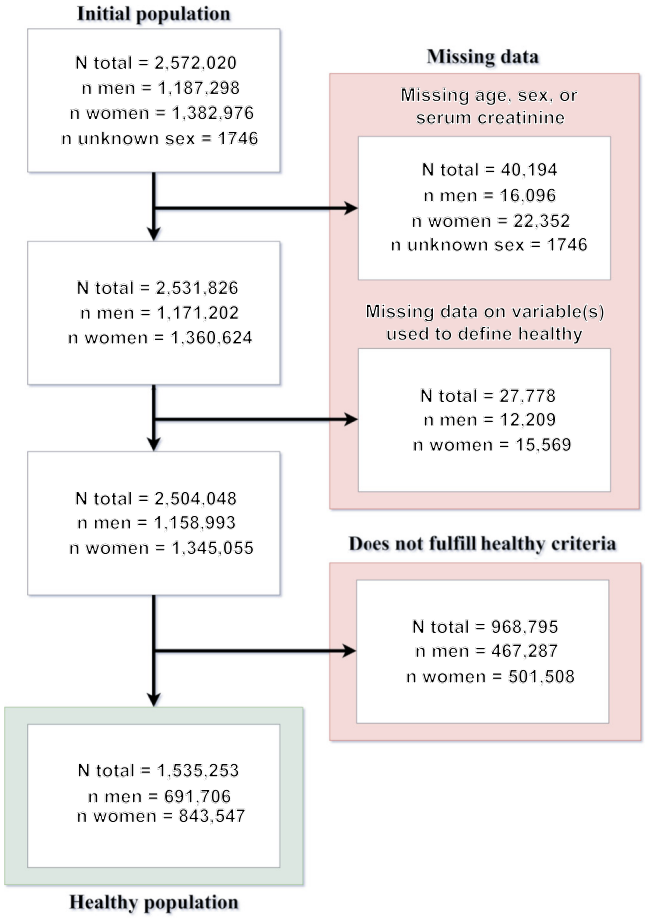

Figure 1 | Flowchart illustrating the process to select healthy individuals from the total amount of individuals combined from all 9 participating studies. Red boxes indicate excluded individuals, and the green box represents the individuals used in the analysis.

results, the RLM equation showed eGFR decreasing at a similar age but provided lower eGFR values. Both the CKD-EPI$_{2009}$ and CKD-EPI$_{2021}$ displayed slightly higher overall eGFR values and showed a linear decrease in eGFR from the age of 20 years.

Sensitivity analyses

Results remained similar in a randomly selected subset of data reflecting a more equal contribution from each cohort (Supplementary Table S7 and Supplementary Figure S6). The median difference in the 50th percentile of eGFR values between this sensitivity analysis and the main analysis was between 2% and 3%. A larger than 5% difference was seen after the age of 87 years in men and after the age of 86 years in women. However, only 5 men and 5 women in the sensitivity analysis were aged ≥90 years. In Supplementary Table S8, we present the bias, precision, and accuracy of eGFR calculated with the EKFC equation from 1324 individuals aged 55 to 70 years who had measurements of glomerular filtration rate (GFR) available in the Renal Iohexol Clearance Survey–Follow-up, a substudy of the Tromsø Study, Norway.[36]

DISCUSSION

Summary of findings

Our study describes sex-specific EKFC$_{crea}$-based eGFR reference values across the entire life span, in a large multicohort sample of healthy Europeans, and demonstrates that kidney function is not preserved with aging in healthy individuals. eGFR decreased after the age 40 years, reflecting the structure of the EKFC equation, with a slightly stronger eGFR-age association observed in women compared with men.

Measured GFR across age by sex in healthy individuals

Kidney function inevitably declines with aging, with loss of kidney function at the structural level paralleling the decline in mGFR associated with aging.[37,38] In studies of healthy individuals or kidney donors using mGFR, kidney function decreases linearly with age,[8,11,16,39] and in studies using nonlinear models, an initiation in decline occurs between the ages of 30 and 50 years.[7,10,40] The Renal Iohexol Clearance Survey in Tromsø, Norway, the only longitudinal study in the general population using repeated measurements of GFR, found healthy men had a steeper GFR decline compared with women from the ages of 50 to 75 years.[36] Consequently, women had a lower GFR than men at the age of 50 to 65 years, whereas men had a lower GFR after. In contrast, cross-sectional studies show a stronger association between age and lowering mGFR in women compared with men,[6,9,11,41] also reported by a meta-analysis consisting of 12 cross-sectional studies in healthy potential living kidney donors.[42] Consequently, women had lower or similar mGFR compared with men.[8–11,42,43] Cross-sectional studies describe the distribution of GFR at a specific time point (and thus specific year of age) independent of previous kidney function, whereas longitudinal studies describe GFR over a period of time, detailing age-related kidney function trajectories.

There is some evidence that longitudinal changes in kidney function may slightly differ when using eGFR or mGFR.[44–46] mGFR is likely best used in longitudinal studies on kidney function, and, because of its accuracy, in individuals with suspected kidney damage. Conversely, eGFR remains an important tool for describing trends at the population level because eGFR is commonly used as a first-line diagnostic tool for kidney function in primary care and clinical settings because of its accessibility and low cost.[47]

Differences in eGFR values between men and women

Although cross-sectional studies on eGFR over age have similar findings to those reported from studies in mGFR,[13,14,48] observed differences in mGFR and eGFR between men and women are likely caused by both gender (nonbiological) and sex (biological) differences. Gender-related differences can be attributed to one's cultural and societal environment, such that men and women have differences in prevalence of risk factors or comorbidities that may impact kidney function.[49] By selecting only healthy individuals, we sought to remove the impact of disease-related gender risk factors for kidney damage, which allows for a

Table 2| Study population characteristics for individuals who fulfill the healthy[a] criteria

Variable	Iceland CKD study (Iceland)	INCIPE (Italy)	BIS (Germany)	SHIP (Germany)	Lifelines (The Netherlands)	The HUNT Study (Norway)	The Tromsø Study (Norway)	SCREAM (Sweden)	UK Biobank (United Kingdom)	Total
Individuals who fulfill the healthy criteria, n (%)[b]	155,185 (71)	808 (22)	138 (7)	987 (24)	40,557 (31)	9491 (23)	4415 (23)	1,101,694 (68)	221,978 (47)	1,535,253 (60)
Healthy men, n (%) (of healthy individuals)	71,918 (46)	265 (33)	62 (45)	373 (38)	16,657 (41)	4208 (44)	2072 (47)	507,632 (46)	88,519 (40)	691,706 (45)
Age range, yr, minimum-maximum	18–105	24–93	69–97	20–80	18–90	19–96	40–91	18–107	37–70	18–107
Age, yr	41 (16)	56 (11)	78 (7)	43 (13)	39 (12)	44 (14)	52 (10)	41 (15)	54 (8)	43 (15)
eGFR by EKFC, ml/min per 1.73 m^2	92 (16)	87 (15)	66 (12)	92 (15)	95 (13)	98 (14)	89 (13)	96 (15)	89 (12)	94 (15)
eGFR by revised Lund-Malmö, ml/min per 1.73 m^2	86 (15)	82 (13)	64 (12)	86 (13)	88 (10)	92 (13)	83 (11)	89 (14)	84 (11)	88 (14)
eGFR by CKD-EPI_{2009}, ml/min per 1.73 m^2	98 (19)	90 (15)	73 (14)	96 (17)	100 (15)	103 (16)	91 (13)	102 (18)	93 (12)	100 (18)
eGFR by CKD-EPI_{2021}, ml/min per 1.73 m^2	101 (18)	94 (14)	78 (14)	99 (16)	103 (15)	106 (15)	95 (12)	104 (17)	96 (12)	103 (16)

BIS, The Berlin Initiative Study; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; EKFC, European Kidney Function Consortium; The HUNT Study, The Trøndelag Health Study; INCIPE, Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints; SCREAM, Stockholm CREAtinine Measurement; SHIP, Study of Health in Pomerania.

[a]Healthy refers to individuals with (i) no history of myocardial infarction, (ii) no history of angina pectoris, (iii) no history of heart failure, (iv) no history of coronary artery disease, (v) no history of hypertension, (vi) no history of stroke, (vii) no history of cancer, (viii) no history of diabetes, (ix) no history of kidney disease, (x) body mass index $\leq$30 kg/m^2, (xi) never smoked, (xii) no use of lipid-lowering medication or cardiac glycosides, (xiii) urine albumin-to-creatinine ratio $\leq$30 mg/g, and (xiv) no use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

[b]This proportion of individuals who fulfill the healthy criteria is calculated from eligible individuals with no missing data.

Data are mean (SD) unless otherwise noted.

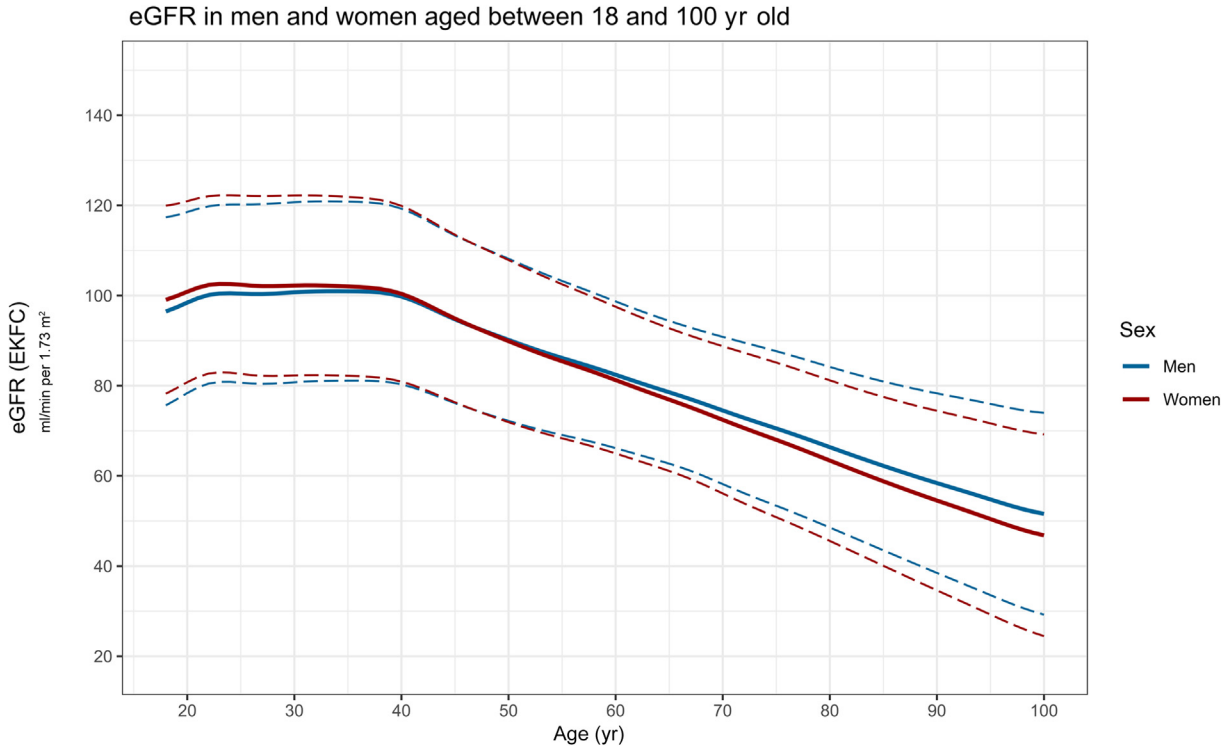

Figure 2 | Median estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2) using the creatinine-based European Kidney Function Consortium (EKFC) equation in healthy European adult populations aged 18 to 100 years by sex. The line colors indicate sex, with blue for men and red for women. The solid line indicates the 50th percentile. The dashed lines represent the 5th (lower) and 95th (upper) percentiles.

more accurate evaluation of the impact of biological sex on eGFR, although there likely still remains some residual gender bias. Sex-related hormonal differences have been hypothesized to contribute to the differences in GFR between men and women. Some have speculated that sex hormones, especially estrogen, may protect nonmenopaused women from GFR decline, potentially explaining a possible steeper decline in GFR around middle age in women compared with men.[7,8,50] However, studies in postmenopausal women have found conflicting results, with some studies reporting hormone use to be protective against kidney function loss,[51] whereas others have not found any association.[52–54] On the other hand, studies have shown low testosterone to be associated with reduced eGFR[55] and CKD,[56–58] but 2 studies reported low-dose testosterone supplements to delay CKD progression in hypogonadal men.[59,60] Therefore, a lack of consensus of the effects of sex hormones on kidney function remains, and further research on the relationship between hormones and kidney function in humans is warranted.

In addition to hormonal differences, differences in eGFR between men and women may be due to non–GFR-related confounding in the calculation of creatinine estimated GFR. eGFR equations traditionally use a standard body surface area of 1.73 m^2 for normalization of GFR regardless of sex. However, body surface area averages around 2.0 m^2 in men and 1.8 m^2 in women.[41,61] Considering this, Eriksen *et al.* found that in women, eGFR indexed to sex-specific average body surface area was 14% higher than eGFR indexed to 1.73 m^2 (99.8 vs. 86.5 ml/min).[61] In men however, the difference was <1% (105.7 vs. 105.0 ml/min),[61] suggesting that indexing to the same body surface area for both men and women—as is currently common practice—may induce or amplify sex differences in eGFR.[62,63] Muscle mass also impacts creatinine production, potentially contributing to sex differences in eGFR[64] and the trajectory of eGFR associated with aging in men and women.[36] To overcome this, eGFR calculated using cystatin C has been shown to estimate GFR more accurately than serum creatinine, both in individuals with low muscle mass and in the general population.[65–67] An assessment of eGFR reference values based on cystatin C may account for muscle mass–related sex differences.

eGFR equations

There are many equations to estimate GFR, but in this study, we chose the EKFC equation for the following reasons. Although the CKD-EPI_{2009} equation has been commonly used and was recommended by the 2012 KDIGO guidelines for diagnosis of CKD,[1] its use in European populations may not be ideal, as the equation was derived from an ethnically diverse American population with a small number of elderly persons, includes a race parameter, and assumes a linear decline in kidney function with age in adulthood. This linear decline assumption explains why eGFR values in younger individuals estimated with the CKD-EPI_{2009} are higher, and more biased, than with the EKFC equation.[68] The updated CKD-EPI_{2021} equation removed the race parameter, but

Table 3 | eGFR percentiles by age and sex in 5-year intervals from 20 to 100 years using the $EKFC_{crea}$ equation in healthy individuals[a] and σ parameter[b] at each age interval

			eGFR, ml/min per 1.73 m^2, by percentiles									
Sex	Age, yr	N	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	σ[b]
Men	20	12,806	75	78	83	90	99	107	114	119	122	12
	25	12,714	77	81	85	92	101	109	116	120	124	12
	30	14,164	77	81	85	93	101	109	116	121	125	12
	35	13,947	77	81	86	93	101	109	116	121	125	12
	40	16,284	77	80	85	92	100	108	115	119	123	12
	45	17,304	73	76	80	87	95	102	109	113	117	11
	50	15,789	69	72	76	83	90	98	104	108	112	11
	55	12,563	66	69	73	79	86	93	100	103	107	10
	60	10,647	63	66	70	76	82	89	95	99	102	10
	65	7540	60	63	66	72	79	85	91	94	97	10
	70	3324	55	58	62	68	75	81	87	91	94	10
	75	1708	50	53	57	64	71	78	84	88	91	10
	80	820	45	49	53	59	66	74	80	84	88	11
	85	436	40	44	48	55	62	70	77	81	85	11
	90	178	35	39	43	50	58	67	74	78	82	12
	95	30	30	34	38	46	55	64	71	76	80	13
	100	5	25	29	34	42	52	61	69	74	78	14
Women	20	18,069	77	81	85	93	101	109	117	121	125	12
	25	16,895	79	83	87	94	102	111	118	122	126	12
	30	17,108	79	82	87	94	102	110	118	122	126	12
	35	15,807	78	82	87	94	102	110	118	122	126	12
	40	18,059	77	81	85	92	100	108	116	120	124	12
	45	19,482	73	76	80	87	95	103	109	114	117	11
	50	18,018	69	72	76	83	90	97	104	108	111	11
	55	14,614	65	68	72	78	85	92	99	103	106	10
	60	13,205	62	65	69	75	81	88	94	98	101	10
	65	9704	58	61	65	70	77	83	89	93	96	10
	70	4297	53	56	60	66	72	79	85	89	92	10
	75	2251	48	51	55	61	68	75	81	85	88	10
	80	1241	42	46	50	56	63	71	77	81	85	11
	85	736	37	40	44	51	59	67	73	78	81	11
	90	387	31	35	39	46	55	63	70	74	78	12
	95	131	25	29	34	42	50	59	67	72	76	13
	100	28	20	25	29	38	47	56	64	69	74	14

eGFR, estimated glomerular filtration rate; $EKFC_{crea}$, creatinine-based European Kidney Function Consortium equation.
[a]Healthy refers to individuals with (i) no history of myocardial infarction, (ii) no history of angina pectoris, (iii) no history of heart failure, (iv) no history of coronary artery disease, (v) no history of hypertension, (vi) no history of stroke, (vii) no history of cancer, (viii) no history of diabetes, (ix) no history of kidney disease, (x) body mass index ≤30 kg/m^2, (xi) never smoked, (xii) no use of lipid-lowering medication or cardiac glycosides, (xiii) urine albumin-to-creatinine ratio ≤30 mg/g, and (xiv) no use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.
[b]This proportion of individuals who fulfill the healthy criteria is calculated from eligible individuals with no missing data. The σ parameter is a coefficient of variation representing the SD of the normal distribution.

performs worse than the $CKD\text{-}EPI_{2009}$ in European populations.[69] More accurate estimates of GFR in European populations have been achieved with the EKFC[68,70–73] or RLM[74–77] equations, both derived from White European populations with a larger age range and incorporation of a nonlinear dependency on age. However, there is still no consensus on whether the EKFC equation or RLM equation has a better performance in European populations.[78,79]Studies in predominantly European populations show bias of the EKFC equation to range between –0.9 and 3.5 ml/min per 1.73 m^2,[18,68,70] precision (the interquartile range of the absolute bias) ranging between 14.5 and 16.8 ml/min per 1.73 m^2,[18,68] and accuracy (percentage of individuals with an eGFR within 30% of the value of mGFR) ranging between 88.0% and 90.6%.[18,70] One study in the SCREAM cohort, which constituted most of our analytical cohort, found the EKFC to have a bias of 2.7 ml/min per 1.73 m^2, a precision of 15.6 ml/min per 1.73 m^2, and an accuracy of 79.5%.[76]

Application of eGFR reference values

Reference values are commonly used in medical fields to define abnormal biological values, making them important tools within clinical and public health settings.[80] eGFR reference values play an important role in the field of

nephrology and throughout the life course of a kidney. A study assessing potential kidney donors by age and eGFR suggested that age-calibrated eGFR assessments could improve the efficiency of living kidney donor selection.[81,82] Others have suggested that reference values could improve the detection of abnormal kidney function, and be especially relevant for screening and management of risk factors, and referral to specialist care. This is especially important in younger adults, as they are less likely to be referred when their eGFR is below the expected normal value compared with older age groups.[83] For instance, as the lower 5th percentile of eGFR in healthy people aged <50 years lies between 75 and 85 ml/min per 1.73 m^2, clinicians may opt to test for other signs of kidney damage, such as albuminuria, before eGFR reaches the KDIGO threshold of 60 ml/min per 1.73 m^2. This situation was explored in a randomized vignette study, which found that providing general practitioners (GPs) with age-specific eGFR reference values significantly increased the proportion of GPs identifying a clinical problem in younger adults with reduced kidney function from 47% to 84% of GPs, even when eGFR was >60 ml/min per 1.73 m^2.[84] A follow-up study found that 89% of GPs had positive views of the incorporation of eGFR reference values in clinical settings (the remaining GPs had neutral views) and described it as "easy to use" and a "valuable tool" to assess kidney function by age.[85(p.3)]

The observation of declining eGFR with age has also prompted some people to suggest the use of an age-adapted CKD definition to account for "kidney aging."[2,86–88] Using the reference values established in this study, it is possible to develop a continuous age-adapted CKD definition using the age- and sex-specific lower 5th percentile of the eGFR reference value distribution.[2] Furthermore, there is a large proportion of elderly individuals needing kidney replacement therapy who do not have an identified cause of CKD. An insufficient diagnostic workup may contribute to this observation, or there may be no specific cause and these individuals represent one extreme of kidney aging that may be labeled "accelerated kidney aging" because of the interaction of genetic predisposition,[89] nephron number at birth,[90–92] and environment.[93] The 5th percentile of the eGFR reference value distribution in otherwise healthy individuals may help to develop the conceptual framework to define accelerated kidney aging.

Strengths and limitations

Although eGFR may provide a biased estimate of GFR at the individual level compared with mGFR, the bias between eGFR and mGFR at a population level within a healthy, homogeneous adult population should be minimal.[94] Our cross-sectional study design allows us to describe normal and abnormal eGFR distribution across an age spectrum, but kidney function trajectories cannot be extrapolated from our results. We sampled from general population studies across multiple European countries, but the generalizability of these results in Europe should be considered with caution, especially as no cohorts from Eastern Europe were able to participate. Also, the contribution of each participating study (sample size) was not equal, but our sensitivity analysis showed cohort sample sizes had little impact on the results. Our healthy definition, which included 14 criteria, should identify individuals without comorbid conditions or certain CKD risk factors. Although these variables had varying collection methods among the cohorts, with some missing variables at the cohort level, we believe that most individuals who would not fulfill the healthy criteria were captured by at least 1 of the other exclusion criteria. For instance, individuals with elevated albumin-to-creatinine ratio, a variable missing for most of the cohort, may be captured by the variable kidney disease, available in all cohorts. Similarly, missing data on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use may be captured by variables on cardiovascular disease or kidney disease. Nonetheless, the consequence of missing these critical variables to assess kidney health is that individuals with subclinical or unrecognized kidney disease may still be present in our healthy population. Residual bias may also remain as other relevant comorbidities and lifestyle factors impacting kidney health, such as diet and genetic factors, were not included in our healthy criteria. Results from our study may be impacted by survivor bias, as only the healthiest individuals are likely to survive to old age, so our estimates of GFR in especially older healthy individuals may be slightly inflated. Additionally, by defining normal and abnormal values from a healthy population based purely on statistical distributions, we assume that 5% of otherwise healthy individuals had an abnormal eGFR.

Conclusion

Our results from >1.5 million healthy individuals from a multinational, contemporary, adult European general population suggest that kidney function is not preserved with aging in healthy individuals. Creatinine-based eGFR is lower at higher ages with a slightly steeper eGFR-age decrease in women than men, leading to a lower eGFR in women compared with men after the age of ∼60 years. The eGFR reference values described here provide important information relevant to understanding kidney health in relation to aging by sex and can contribute to the debate on how CKD should be defined and handled throughout the life course.

DISCLOSURE

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DATA STATEMENT

The data used in this study are not available because of data protection laws and regulations.

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AUTHOR CONTRIBUTIONS

KJJ, VSS, AO, SH, GG, NCC, and MEA conceived and designed the analysis; SH, GG, J-JC, NE, BOE, A-LF, PMF, OSI, TI, AJJ, KARL, TM, ES, and SS collected or contributed data; MEA and NCC performed the analysis; and MEA, KJJ, VSS, AO, SH, GG, NCC, J-JC, NE, BOE, A-LF, PMF, OSI, TI, AJJ, KARL, TM, ES, and SS performed writing and reviewing.

Supplementary material is available online at www.kidney-international.org.

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