Population-based reference values for kidney function and kidney function decline in 25- to 95-year-old Germans without and with diabetes

OPEN

Janina M. Herold[1], Simon Wiegrebe[1,2], Jana Nano[3], Bettina Jung[4,5,6], Mathias Gorski[1], Barbara Thorand[3,7,8], Wolfgang Koenig[9,10,11], Tanja Zeller[12,13], Martina E. Zimmermann[1], Ralph Burkhardt[14], Bernhard Banas[4], Helmut Küchenhoff[2], Klaus J. Stark[1], Annette Peters[3,7,8,15], Carsten A. Böger[4,5,6,15] and Iris M. Heid[1,15]

[1]Department of Genetic Epidemiology, University of Regensburg, Regensburg, Germany; [2]Statistical Consulting Unit StaBLab, Department of Statistics, LMU Munich, Munich, Germany; [3]Institute of Epidemiology, Helmholtz Zentrum München–German Research Center for Environmental Health (GmbH), Neuherberg, Germany; [4]Department of Nephrology, University of Regensburg, University Hospital Regensburg, Regensburg, Germany; [5]Department of Nephrology, Diabetology, and Rheumatology, Traunstein Hospital, Southeast Bavarian Clinics, Traunstein, Germany; [6]KfH Kidney Center Traunstein, Traunstein, Germany; [7]German Center for Diabetes Research (DZD), Partner München-Neuherberg, Neuherberg, Germany; [8]Institute for Medical Information Processing, Biometry and Epidemiology, Medical Faculty, Ludwig-Maximilians-Universität (LMU) Munich, Munich, Germany; [9]Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; [10]DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany; [11]Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany; [12]University Heart and Vascular Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [13]German Center for Cardiovascular Research (DZHK), Partner Site Hamburg, Hamburg, Germany; and [14]Institute of Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Regensburg, Germany

Understanding normal aging of kidney function is pivotal to help distinguish individuals at particular risk for chronic kidney disease. Glomerular filtration rate (GFR) is typically estimated via serum creatinine (eGFRcrea) or cystatin C (eGFRcys). Since population-based age-group-specific reference values for eGFR and eGFR-decline are scarce, we aimed to provide such reference values from population-based data of a wide age range. In four German population-based cohorts (KORA-3, KORA-4, AugUR, DIACORE), participants underwent medical exams, interview, and blood draw up to five times within up to 25 years. We analyzed eGFRcrea and eGFRcys cross-sectionally and longitudinally (12,000 individuals, age 25-95 years). Cross-sectionally, we found age-group-specific eGFRcrea to decrease approximately linearly across the full age range, for eGFRcys up to the age of 60 years. Within age-groups, there was little difference by sex or diabetes status. Longitudinally, linear mixed models estimated an annual eGFRcrea decline of -0.80 [95% confidence interval -0.82, -0.77], -0.79 [-0.83, -0.76], and -1.20 mL/min/1.73m^2 [-1.33, -1.08] for the general population, "healthy" individuals, or individuals with diabetes, respectively. Reference values for eGFR using cross-sectional data were shown as percentile curves for "healthy" individuals and for individuals with diabetes. Reference values for eGFR-decline using longitudinal data were presented as 95% prediction intervals for "healthy" individuals and for individuals with diabetes, obesity, and/or albuminuria. Thus, our results can help clinicians to judge eGFR values in individuals seen in clinical practice according to their age and to understand the expected range of annual eGFR-decline based on their risk profile.

Kidney International (2024) **106,** 699–711; https://doi.org/10.1016/j.kint.2024.06.024

KEYWORDS: chronic kidney disease; diabetes; general population; kidney function; kidney function decline; reference values

Lay Summary

Kidney function, assessed as estimated glomerular filtration rate (eGFR), declines by age. In clinical practice, it is important to understand whether a person has an eGFR value as expected given the person's age, or whether the value is lower than expected and potentially a reason for concern. Although chronic kidney disease is defined as eGFR <60 ml/min per 1.73 m^2, the question arises whether a value of, for example, 58 ml/min per 1.73 m^2 for an 80-year-old person is indicative of disease or age appropriate. We collected data from >12,000 individuals, aged 25 to 95 years, from population-based German studies. We provide age-specific reference values for eGFR usable in clinical practice to answer this question. Longitudinal information on eGFR decline was analyzed to also provide reference values for eGFR-decline by risk profile groups. Advanced regression models were applied for these analyses. Our results are interpretable and usable to help in clinical routine.

Correspondence: *Iris M. Heid, Department of Genetic Epidemiology, University of Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany. E-mail: iris.heid@ukr.de*

[15]AP, CAB, and IMH contributed jointly.

Received 26 January 2024; revised 4 June 2024; accepted 24 June 2024; published online 29 July 2024

Kidney function undergoes a natural decline by aging. The number of nephrons, the smallest units of the kidney and responsible for the filtration process, starts decreasing at the age of 30 years.[1] Glomerular filtration rate (GFR) is an established parameter to assess kidney function, typically estimated via serum creatinine ($eGFR_{crea}$), cystatin C ($eGFR_{cys}$), or both ($eGFR_{crea-cys}$). Values of eGFR <60 ml/min per 1.73 m^2 define chronic kidney disease (CKD).[2,3] Approximately 10% of the world's population[4] and 10% to 13% in Germany[5] are affected by CKD.

Elderly individuals often have eGFR <60 ml/min per 1.73 m^2 because of natural kidney aging,[6,7] causing a substantial debate on whether age-dependent CKD definitions are warranted.[8] Clinicians are typically faced with the question of whether an observed eGFR of, for example, 58 ml/min per 1.73 m^2 is within the normal range for a healthy 80-year-old individual. Another question is what annual eGFR decline can be expected for individuals with a certain risk profile (e.g., for individuals with obesity or with diabetes and microalbuminuria).

Reference values for eGFR using cross-sectional data from general populations, and particularly longitudinal data to derive reference values for eGFR decline, are limited. Some studies provide reference values for middle-aged adults,[9–11] and few include individuals aged >80 years,[12–15] including 2 German studies.[11,15] Furthermore, many studies provide only $eGFR_{crea}$ due to higher costs when measuring cystatin C, but $eGFR_{cys}$ or $eGFR_{crea-cys}$ are considered more suitable for individuals at old age.[16] There is thus a lack of reference values for eGFR or eGFR decline for individuals over a wide age range and limited data on cystatin-based eGFR. There is also no consensus on how to generate and present such reference values in an interpretable manner.

We thus aimed to provide population-based reference values for eGFR and eGFR decline based on both creatinine and cystatin C in adult individuals of a wide age range (25–95 years), for *healthy* individuals, and for individuals with diabetes. Furthermore, we aimed to derive estimates of the association of sex, obesity, diabetes, and albuminuria with eGFR levels and annual eGFR decline and to use these to generate eGFR-decline reference values by risk groups. For this, we evaluated data from 4 comparably designed population-based cohorts from Germany enabling the analysis of >12,000 individuals cross-sectionally and >26,000 $eGFR_{crea}$ and $eGFR_{cys}$ assessments over up to 25 years longitudinally.

METHODS

Study populations

We analyzed 4 population-based cohorts from South Germany: (i–ii) 2 studies for the middle-aged adult population (Cooperative Health Research in the Region of Augsburg: KORA-3, KORA-4), (iii) 1 study for the old-aged population (Altersbezogene Untersuchungen zur Gesundheit der Universität Regensburg: AugUR), and (iv) 1 study on individuals with diabetes (DIAbetes COhoRtE: DIACORE). In the following, we used the term *KORA-3* for individuals in KORA-S3 with follow-up (F3, Fit) and *KORA-4* for individuals in S4 (F4, FF4, Fit). Studies were comparable in terms of recruitment, study conduct, and standard operating procedures. Detailed study descriptions were published previously[17–19] (Supplementary Note S1.1).

Processing of biomaterial and biomarker measurements

Processing of biomaterial for was equivalent across the 4 studies, as described previously[20–22] (Supplementary Note S1.2). Biomarkers were measured by certified laboratories with different arrays, where comparability of methods was assessed following Clinical and Laboratory Standards Institute guidelines. Serum creatinine concentrations were measured by enzymatic assays or modified Jaffé (if applicable, corrected by factor 0.95[23]) and standardized to information display measurements standard. Because KORA-S3 creatinine measurements lacked assay manufacturer's documentation and differed from the other KORA surveys (Supplementary Figure S1), we excluded these values from analyses and considered KORA-F3 *baseline* for analyses using creatinine. Cystatin C was measured via nephelometric methods or immunoassays and standardized according to the International Federation of Clinical Chemistry. Glycated hemoglobin was measured from ethylenediamine tetraacetic acid anticoagulated whole blood via ion-exchange high-performance liquid chromatographic assay (KORA, AugUR) or immunoassay (DIACORE). Urine albumin and creatinine were measured in each study and at each time point, except KORA-S4, KORA-Fit3, and KORA-Fit4. A detailed overview of blood processing and biomarker measurements is provided in Supplementary Table S1.

Variable assessment

The outcome of interest was GFR, and various formulas estimate GFR from creatinine and/or cystatin to fit eGFR as closely as possible to measured GFR. For our primary analyses, we derived $eGFR_{crea}$, $eGFR_{cys}$, and $eGFR_{crea-cys}$ using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation,[24] the CKD-EPI 2012 equation,[25] or the combined equation from 2021,[24] respectively. CKD-EPI 2021 includes sex-specific coefficients and an age term (e.g., 0.9938^{age}) and avoids the race term from CKD-EPI 2009.[26] CKD-EPI 2021 was used by the recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[27] However, most European laboratories still derive $eGFR_{crea}$ by CKD-EPI 2009,[26] and European societies recommended to stall the update to CKD-EPI 2021 because of limited advantages for European populations.[28] As potential update, alternative equations for $eGFR_{crea}$[29] and $eGFR_{cys}$[30] are suggested by the European Kidney Function Consortium (EKFC; sex-specific coefficients, no age term until 40 years; e.g., 0.990^{age-40} for age >40 years). We thus applied also CKD-EPI 2009 and EKFC for sensitivity analyses.

From each study center visit, time-dependent covariables were obtained in a similar manner across studies.

Albuminuria was derived from urinary albumin-to-creatinine ratio (UACR) as microalbuminuria (UACR ≥30 and <300 mg/g) or macroalbuminuria (UACR ≥300 mg/g).[31] Diabetes was defined via self-report, intake of antidiabetic medication (using Anatomical Therapeutic Chemical classification[32]), or glycated hemoglobin ≥6.5%. DIACORE was restricted to individuals with diabetes assessed via health insurance provider. History of cardiovascular disease was defined as self-report of any prior myocardial infarction or stroke (or interventional revascularization in AugUR and DIACORE). Body mass index was computed using measured weight (from each visit) divided by squared height (kg/m^2; from baseline visit). Body mass index ≥25 and <30 kg/m^2 was defined as *overweight*, and body mass index ≥30 kg/m^2 as *obese*. Blood pressure was measured 3 times at each study center visit, and the mean of second and third measurements was used for analyses. Sex was defined from self-report and validated by genetic data.

Inclusion and exclusion criteria

For our analyses, we included participants aged ≥25 years (minimum age in KORA studies), with neither kidney replacement therapy (dialysis or kidney transplantation) nor history of severe kidney disease (kidney failure, acute kidney injury, or disease requiring nephrectomy reported at baseline). For cross-sectional analyses, we excluded individuals without available eGFR assessment at baseline (Supplementary Figure S2A). For longitudinal analyses, we excluded eGFR values after an eGFR <15 ml/min per 1.73 m^2 or after onset of kidney replacement therapy or severe kidney disease; we excluded individuals without any available measurement of $eGFR_{crea}$ at any time point (Supplementary Figure S2B).

We analyzed the data focused on general population individuals (i.e., KORA-3, KORA-4, and AugUR), their *healthy* subgroup, or individuals with diabetes (adding DIACORE). For the *healthy* subgroup, eGFR values were excluded when the individual had diabetes, history of cardiovascular disease, systolic/diastolic blood pressure ≥140/90 mm Hg, or UACR ≥30 mg/g at baseline (cross-sectional analyses) or at the respective time point (longitudinal analyses); the *healthy*-defining variables were nonmissing in >99% individuals at baseline or any time point where eGFR was available (except for UACR in KORA). For the diabetes subgroup, we analyzed eGFR values when individuals had ascertained diabetes at baseline (cross-sectionally) or at 1 time point (longitudinally; excluding eGFR values before diabetes was observed).

Statistical analyses in cross-sectional and longitudinal data

We analyzed $eGFR_{crea}$, $eGFR_{cys}$, and $eGFR_{crea\text{-}cys}$ (CKD-EPI 2021 and 2012) as outcome on the original scale (winsorized at 15 and 200 ml/min per 1.73 m^2). Although studies were comparable in design and conduct, creatinine and cystatin were measured by different laboratories and assays. Therefore, we performed study-specific analyses and then evaluated whether fixed-effect meta-analyses or joint data analyses were applicable. All statistical analyses were performed using R, version 4.3.1. For all regression models, age was centered at 50 years.

In cross-sectional data (using baseline), we derived mean values of $eGFR_{crea}$ and $eGFR_{cys}$ and 95% confidence intervals (CIs) per sex and age group.

In longitudinal data, we estimated $eGFR_{crea}$ decline over age without linearity assumption (generalized additive model [GAM], penalized splines to model age, f[age]) and with linearity assumption (linear mixed model [LMM]). The models included random intercepts (RIs), sex, interaction of sex with f(age) or age, study membership if applicable, and, in sensitivity analyses, random slopes (RI + RS; Supplementary Note S2.1). We analyzed $eGFR_{cys}$ decline analogously. Both GAM and LMM enabled the inclusion of all individuals with at least 1 eGFR value while accounting for intrasubject variation caused by repeated measurements.

Risk factor association in longitudinal data

In longitudinal data, we applied a further multivariable LMM to estimated risk factor association with $eGFR_{crea}$ levels (main effects) and $eGFR_{crea}$ decline (interaction with age): the LMM included RI, age, all risk factors (sex, diabetes, overweight, obesity, microalbuminuria, and macroalbuminuria), their interaction with age, and study membership if applicable (Supplementary Note S2.2); the model included time-constant (sex) and time-varying covariate effects (all other risk factors). We analyzed $eGFR_{cys}$ analogously.

Reference values for eGFR and eGFR decline

To generate reference values for $eGFR_{crea}$, we used cross-sectional data for the *healthy* subgroup and for individuals with diabetes. We derived 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97.5th percentile curves as age-appropriate reference values (using generalized additive mixed model for location, scale, and shape [GAMLSS]; Supplementary Note S2.3). The use of GAMLSS allowed us to model $eGFR_{crea}$ over age without linearity or normality assumption. We repeated this for $eGFR_{crea\text{-}cys}$, because this is judged by practitioners when cystatin is available.

To generate reference values for $eGFR_{crea}$ decline or $eGFR_{cys}$ decline, we used longitudinal data and risk factor association estimates from the LMM described above (here: RI + RS). By risk profile, we derived 95% prediction intervals that account for the variability in person-specific slopes (Supplementary Note S2.4).

Revisiting results using alternative equations for eGFR

We compared individuals' $eGFR_{crea}$ ($eGFR_{cys}$) values derived by CKD-EPI 2021[24] (CKD-EPI 2012[25]) with values derived by CKD-EPI 2009[26] or EKFC 2021[29] (EKFC 2023[30]). We also evaluated the impact of using these alternative eGFR equations on cross-sectional and longitudinal analyses results described above.

CKD proportions using tentative age-dependent cutoff values for eGFR

There is a substantial debate on the use of age-independent versus age-dependent eGFR cutoff values to define CKD.[8] We derived the proportion of CKD by age group based on $eGFR_{crea}$ <60 ml/min per 1.73 m^2, UACR ≥30 mg/g, or their combination. We contrasted these with CKD proportions that would be yielded if age-specific cutoff values for eGFR were based on our GALMSS-derived reference values (using midpoint age per age group and corresponding modeled 2.5th percentile).

Ethical approval

The AugUR study was approved by the Ethics Committee of the University of Regensburg, Germany (vote 12-101-0258). The study complies with the 1964 Declaration of Helsinki and its later amendments. The KORA-S3 study was approved by the local authorities and conducted in accordance with the data protection regulations as part of the World Health Organization MONICA (monitoring trends and determinants in cardiovascular disease) Project. All other KORA studies were approved by the Ethics Committee of the Bavarian Chamber of Physicians (KORA-F3 EC number 03097, KORA-S4 EC number 99186, KORA-F4/FF4 EC number 06068, KORA-Fit EC number 17040). The DIACORE study and its protocol have been approved by the participating universities' Ethics Committees and is in accordance with the Declaration of Helsinki. The study is registered at the German Registry of Clinical Trials (DRKS00010498) and at the International Clinical Trials Registry Platform of the World Health Organization. The study complies with the 1964 Declaration of Helsinki and its later amendments, and all participants provided written informed consent.

RESULTS

Cross-sectional data: participant characteristics and dependency of eGFR on age

Our cross-sectional analyses included 12,014 or 12,125 individuals with available $eGFR_{crea}$ or $eGFR_{cys}$ at baseline, respectively. Participants of the general population studies (KORA-3, KORA-4, and AugUR) covered a baseline age of 25 to 95 years, and 8%, 5%, or 24% had diabetes, respectively; individuals from the diabetes study (DIACORE) were aged 27 to 92 years (Table 1; by sex, Supplementary Table S2).

First, we evaluated the comparability between studies in the cross-sectional data. We observed comparable age-group–specific mean eGFR between studies, except slightly lower mean at older age for DIACORE in line with lower eGFR in diabetes (Supplementary Figure S3A and B). Second, we derived mean values by age group and sex in the joint cross-sectional data focused on general population (KORA-3, KORA-4, and AugUR; n = 5732), their *healthy* subgroup (n = 3042), or individuals with diabetes (including DIACORE: n = 3890;). We found (i) a predominant impact of age on $eGFR_{crea}$ and $eGFR_{cys}$, (ii) little difference by sex, (iii) an approximately linear decrease in eGFR by age, even for younger individuals aged 25 to 39 years compared with 40 to 49 years, and (iv) lower mean values for $eGFR_{cys}$ than for $eGFR_{crea}$ at older age (Figure 1; Supplementary Table S3). The pattern was similar for the general population, *healthy*, and diabetes, with slightly higher mean for *healthy* and lower mean for diabetes at older age.

Longitudinal data: participant characteristics and estimates of eGFR decline

Our longitudinal analyses included 12,076 or 12,638 individuals with up to 5 assessments of $eGFR_{crea}$ or $eGFR_{cys}$, respectively, covering an age range of 25 to 98 years (number of measurements $[m]_{eGFRcrea}$ = 26,179 or $m_{eGFRcys}$ = 24,507, respectively; Table 2). Study-specific analyses showed comparable course of eGFR (using GAM; Supplementary Figure S4) and annual decline estimates (using LMM; Supplementary Table S4) across KORA-3, KORA-4, and AugUR ($eGFR_{crea}$: –0.8 to –1.0 ml/min per 1.73 m^2 per year) and slightly steep decline in DIACORE (–1.5 ml/min per 1.73 m^2). We also found similar results in meta-analysis versus joint analyses or when adding random slopes (Supplementary Tables S4 and S5). We thus continued to analyze the longitudinal data jointly adjusting for study membership and without random slopes, if not indicated otherwise.

We analyzed the longitudinal data for general population, *healthy* individuals, or individuals with diabetes ($n_{eGFRcrea}$ = 9082, 4545, or 4323, $n_{eGFRcys}$ = 9644, 6126, or 4304, respectively). When estimating eGFR decline over age without linearity assumption (GAM; sex, age, and their interaction as covariables), we found (Figure 2): (i) a fairly linear decline with little difference by sex, (ii) a more pronounced decline in $eGFR_{cys}$ than in $eGFR_{crea}$, and (iii) a similar pattern between general population and *healthy* individuals, but slightly steeper decline in individuals with diabetes. When estimating eGFR decline over age with linearity assumption (LMM; sex, age, and their interaction as covariables), we found an annual $eGFR_{crea}$ decline of –0.80 (95% CI, –0.82 to –0.77), –0.79 (95% CI, –0.83 to –0.76), or –1.20 (95% CI, –1.33 to –1.08) ml/min per 1.73 m^2 per year for general population, *healthy* individuals, or individuals with diabetes, respectively. For $eGFR_{cys}$, the annual decline was more pronounced. We found little difference in annual eGFR decline by sex (Table 3) or by adding an age^2 term (not shown).

Risk factor association with eGFR levels and eGFR decline in longitudinal data

We quantified the association of risk factors with eGFR levels and eGFR decline in our longitudinal joint data (multivariable RI-only LMM, including sex, diabetes, overweight, obesity, microalbuminuria, and macroalbuminuria, and their interactions with age as covariables; $n_{eGFRcrea}$ = 10,815, $n_{eGFRcys}$ = 9725). Annual $eGFR_{crea}$ decline for the reference group (50-year-old normal-weight women without diabetes or albuminuria) was –0.73 (95% CI, –0.77 to –0.69) ml/min per 1.73 m^2 (Table 4, *age effect*), similar to the above stated estimate in *healthy* individuals. Most 95% CIs excluded 0,

Table 1 | Characteristics of cross-sectionally analyzed individuals by study

Variable	KORA 3 (n = 2906)	KORA 4 (n = 3732)	AugUR (n = 2385)	DIACORE (n = 2991)
Demographic characteristics				
Age, mean (SD), yr	57 (13)	50 (14)	78 (5)	65 (9)
Men, % (n)	48 (1422)	48 (1823)	48 (1151)	60 (1795)
Never smoked, % (n)	44 (1282)	41 (1539)	55 (1311)	42 (1260)
Ever smoked, % (n)	37 (1075)	33 (1240)	38 (921)	45 (1342)
BMI, mean (SD), kg/m^2	27.7 (4.6)	27.2 (4.7)	27.7 (4.5)	31.4 (5.7)
Clinical characteristics				
Obesity, % (n)	27 (772)	23 (858)	26 (624)	55 (1623)
Overweight, % (n)	44 (1255)	43 (1609)	46 (1091)	35 (1032)
Diabetes, % (n)	8 (241)	5 (197)	24 (534)	100 (2991)
Time since diabetes, mean (SD), yr	10 (10)	10 (8)	NA	10 (8)
Systolic BP, mean (SD), mm Hg	130 (20)	128 (19)	132 (18)	139 (18)
Diastolic BP, mean (SD), mm Hg	82 (11)	80 (10)	76 (11)	77 (11)
Hypertension, % (n)	34 (979)	29 (1068)	31 (739)	45 (1329)
CVD, % (n)	5 (137)	0.2 (7)	22 (516)	26 (773)
Medication intake, % (n)				
Glucose-lowering	6 (182)	3 (122)	16 (385)	88 (2616)
Blood pressure lowering	32 (916)	18 (674)	68 (1609)	78 (2324)
Lipid lowering	11 (318)	6 (224)	35 (828)	50 (1477)
Laboratory measurements, mean (SD)				
HbA1c, %	5.4 (0.5)	5.6 (0.6)	5.8 (0.7)	6.9 (1.1)
LDL cholesterol, mg/dl	128.1 (32.8)	137.3 (41.4)	141.2 (34.9)	118.1 (37.0)
HDL cholesterol, mg/dl	58.6 (17.1)	57. 9 (17.0)	61.3 (15.5)	52.9 (15.3)
Hemoglobin, g/dl	14.2 (1.2)	14.3 (1.3)	13.8 (1.3)	14.2 (1.3)
UACR, mg/g[a]	17.5 (137.1)	25.5 (199.3)	42.9 (127.8)	75.8 (342.4)
Creatinine, mg/dl	0.88 (0.28)	0.85 (0.24)	0.97 (0.31)	0.96 (0.36)
Cystatin C, mg/L[b]	0.93 (0.24)	0.86 (0.23)	1.20 (0.31)	1.10 (0.39)
Kidney function				
$eGFR_{crea}$, mean (SD), ml/min per 1.73 m^2	90.6 (17.2)	96.6 (16.0)	72.6 (16.7)	82.5 (20.6)
$eGFR_{cys}$, mean (SD), ml/min per 1.73 m^2[b]	90.0 (19.9)	97.2 (19.5)	61.1 (16.9)	74.6 (22.5)
$eGFR_{crea\text{-}cys}$, mean (SD), ml/min per 1.73 m^2	77.4 (21.3)	100.4 (16.8)	69.4 (17.2)	81.5 (22.3)
Microalbuminuria, % (n)	7 (189)	8 (241)	21 (476)	21 (617)
Macroalbuminuria, % (n)	0.8 (21)	1.1 (32)	2.9 (66)	4.3 (130)

AugUR, Altersbezogene Untersuchungen zur Gesundheit der Universität Regensburg; BMI, body mass index; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; DIACORE, DIAbetes COhoRtE; eGFR, estimated glomerular filtration rate; $eGFR_{crea}$, estimated glomerular filtration rate based on creatinine; $eGFR_{crea\text{-}cys}$, estimated glomerular filtration rate based on creatinine and cystatin C; $eGFR_{cys}$, estimated glomerular filtration rate based on cystatin C; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; KORA, Cooperative Health Research in the Region of Augsburg; LDL, low-density lipoprotein; NA, not available; UACR, urinary albumin-to-creatinine-ratio.

[a]UACR and albuminuria are shown for KORA-F4.

[b]Cystatin C and $eGFR_{cys}$ are shown for KORA-S3.

Microalbuminuria: UACR ≥ 30 and < 300 mg/g; macroalbuminuria: UACR ≥ 300 mg/g. *Overweight*: BMI ≥ 25 and < 30 kg/m^2; *obese*: BMI ≥ 30 kg/m^2. Nonmissing data used to calculate percentages (KORA3, KORA4, AugUR, and DIACORE, respectively: smoking: 2898, 3728, 2373, and 2979; BMI: 2882, 3705, 2370, and 2976; diabetes: 2899, 3719, 2260, and 2991; BP: 2893, 3719, 2379, and 2989; CVD: 2899, 3724, 2363, and 2985; intake of glucose-/lipid-lowering medication: 2900, 3724, 2378, and 2970; intake blood pressure–lowering medication: 2900, 3724, 2378, and 2991; UACR: 2701, 2894, 2310, and 2908). The *healthy*-defining variables were nonmissing in >99% individuals at baseline or any time point (except for UACR in KORA). For cross-sectional analyses, the analyzed sample was restricted to individuals with available $eGFR_{crea}$ value at baseline. For a total of 12,014 analyzed individuals, we show demographic characteristics, information on diseases and medication intake, and laboratory measurements with focus on established risk factors previously reported for kidney function decline.[33] eGFR was derived from serum creatinine via the CKD-EPI 2021 equation,[24] serum cystatin, or both via CKD-EPI 2012 equation.[25]

indicative of a well-powered analysis, and overlapped for $eGFR_{crea}$ and $eGFR_{cys}$, suggesting similar associations for both biomarkers. Compared with the reference group, we found steeper $eGFR_{crea}$ and $eGFR_{cys}$ decline for diabetes, overweight, obesity, or microalbuminuria (Table 4, *interaction effects*; also for macroalbuminuria when omitting diabetes in the model, Supplementary Table S6). Risk factor associations were independent and additive (e.g., women with diabetes, obesity, and microalbuminuria had an annual decline of –1.39 ml/min per 1.73 m^2 per year [= –0.73–0.45–0.12–0.09]).

Reference values for eGFR from cross-sectional data

Clinical practitioners are interested in comparing a patient's eGFR value with age-appropriate percentiles of *healthy*

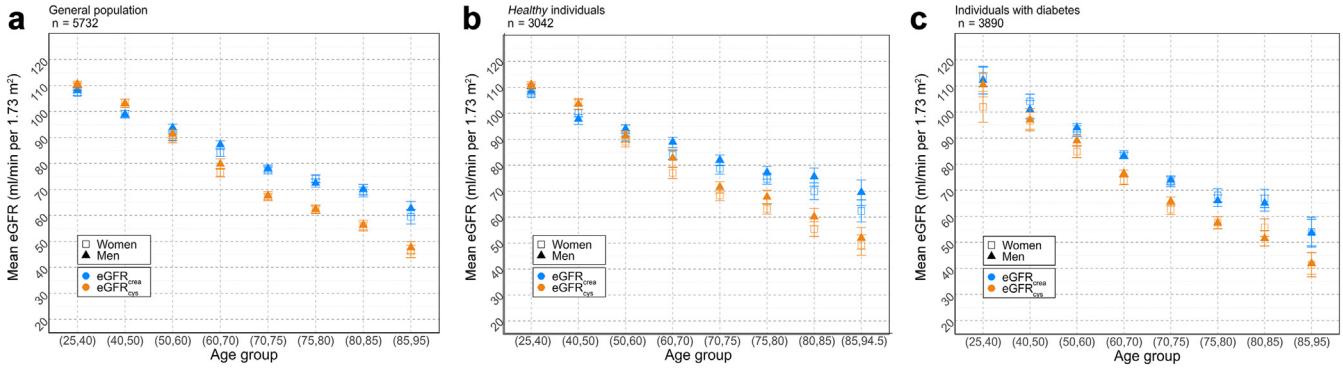

Figure 1 | Sex- and age-group–specific mean values of estimated glomerular filtration rate (eGFR) in cross-sectional data. The analyzed sample consisted of individuals with both eGFR based on creatinine ($eGFR_{crea}$) and cystatin C ($eGFR_{cys}$) values -available at baseline. Shown are mean values of $eGFR_{crea}$ (blue) and $eGFR_{cys}$ (orange) per age groups for (**a**) the general population, (**b**) *healthy* individuals, and (**c**) individuals with diabetes. Symbols indicate sex-specific mean values. Whiskers represent the 95% confidence intervals. Numbers are shown in Supplementary Table S3.

individuals. To provide age-specific reference values for eGFR, we estimated percentile curves for $eGFR_{crea}$ and $eGFR_{crea\text{-}cys}$ over age in the *healthy* subgroup of joint cross-sectional data (GAMLSS, $n_{eGFRcrea} = 4984$, $n_{eGFRcrea\text{-}cys} = 3042$). A person's $eGFR_{crea}$ value measured in clinical practice, or, if cystatin is also available, $eGFR_{crea\text{-}cys}$, can be judged against these reference value diagrams (Figure 3a and c; Supplementary Table S7): for example, $eGFR_{crea} = 62$ ml/min per 1.73 m^2 is way below the 5th percentile for a 60-year-old healthy individual, but near the 25th percentile if the person is 80 years old. Age-group–specific eGFR percentiles were highly comparable to previously reported measured GFR percentiles[34] (Supplementary Table S7).

Because many patients in the nephrologists' practice have diabetes, we also generated reference values for individuals with diabetes ($n_{eGFRcrea} = 3172$, $n_{eGFRcrea\text{-}cys} = 3890$): a person with diabetes and $eGFR_{crea} = 62$ ml/min per 1.73 m^2 will be above the 5th or 25th percentile when the patient is 60 or 80 years old, respectively (Figure 3b and d; Supplementary Table S7).

Reference values for annual eGFR decline for individuals without and with risk factors from longitudinal data

Clinical practitioners have also an interest in the expected annual decline of a person with certain risk factors compared with persons without risk factors. We derived 95% prediction intervals for individuals without and with overweight/obesity, diabetes, or microalbuminuria/macroalbuminuria (i.e., using risk factor association estimates from LMM RI + RS in longitudinal data; Supplementary Table S8). These intervals provide reference values for annual $eGFR_{crea}$ decline (Figure 4a): (i) When the clinician sees a 50-year-old woman without any risk factor, 95% of such individuals can be expected to have an annual $eGFR_{crea}$ decline between –0.02 and –1.44 ml/min per 1.73 m^2 per year. (ii) Because of the linearity assumption, this is the same when the woman is 70 years old. (iii) If the person is a man, this interval is similar (–0.05 to –1.47 ml/min per 1.73 m^2 per year). (iv) If the woman has diabetes or both diabetes and obesity, the interval is –0.49 to –1.90 or –0.61 to –2.03 ml/min per 1.73 m^2 per year, respectively (independent of age, similar for men). For

Table 2 | Descriptive statistics for longitudinal data

Variable	KORA3	KORA4	AugUR	DIACORE	Overall
Age, min–max, yr	34–85	25–88	70–98	27–93	25–98
FU time, 75th percentile (max), yr	11 (25)	9 (20)	3.3 (10)	9 (12)	5 (25)
Measurement intervals, median (max), yr	10 (11)	7 (9)	3.2 (5.5)	2.3 (5.2)	2.8 (11)
Individuals					
$n_{eGFRcrea}$	2933	3752	2397	2994	12,076
$n_{eGFRcys}$	3641	3614	2389	2994	12,638
$n_{eGFRcrea\text{-}cys}$	231	3614	2388	2994	9227
eGFR assessments					
$m_{eGFRcrea}$	3749	9644	3442	9344	26,179
$m_{eGFRcys}$	3866	8116	3206	9319	24,507
$m_{eGFRcrea\text{-}cys}$	231	8112	3196	9319	20,858

AugUR, Altersbezogene Untersuchungen zur Gesundheit der Universität Regensburg; DIACORE, DIAbetes COhoRtE; eGFR, estimated glomerular filtration rate; FU, follow-up; KORA, Cooperative Health Research in the Region of Augsburg; m, number of measurements; max, maximum; min, minimum; n, number of individuals included in analysis. For longitudinal data analyses, the analyzed sample consisted of individuals with at least 1 eGFR value available at any time point. Shown are age and follow-up time per study and overall. Numbers of individuals and respective number of measurements are given for each biomarker.

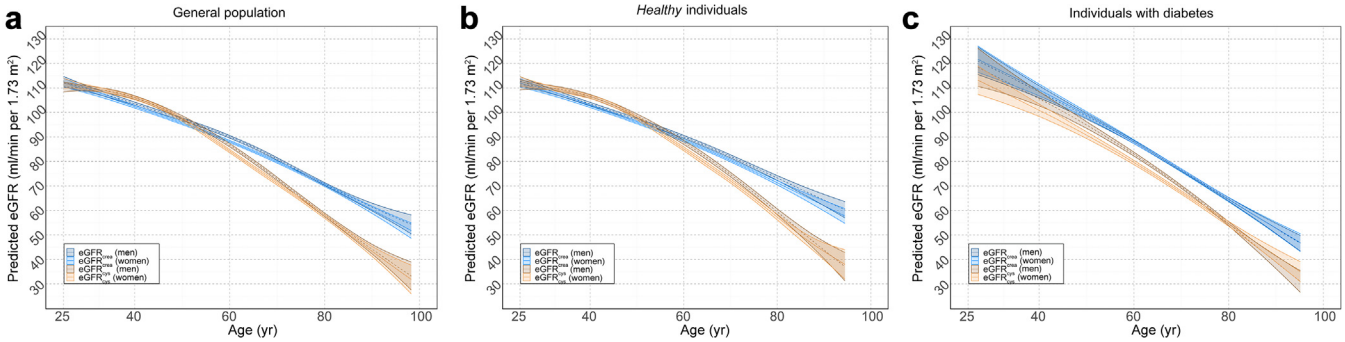

Figure 2 | Longitudinal analysis of decline of estimated glomerular filtration rate (eGFR) over age. The analyzed sample consisted of individuals with at least 1 eGFR value available at any time point. Shown are predicted values of eGFR based on creatinine ($eGFR_{crea}$) and cystatin C ($eGFR_{cys}$) over the full age range (25–98 years) for (**a**) the general population ($n_{eGFRcrea} = 9082$, $m_{eGFRcrea} = 16{,}835$, $n_{eGFRcys} = 9644$, $m_{eGFRcys} = 15{,}188$), (**b**) a subset of *healthy* individuals ($n_{eGFRcrea} = 4545$, $m_{eGFRcrea} = 5848$, $n_{eGFRcys} = 3896$, $m_{eGFRcys} = 5188$), and (**c**) individuals with diabetes from all studies ($n_{eGFRcrea} = 4323$, $m_{eGFRcrea} = 11{,}179$, $n_{eGFRcys} = 4304$, $m_{eGFRcys} = 11{,}091$). Data of all studies were analyzed jointly for the outcome $eGFR_{crea}$ and $eGFR_{cys}$ (generalized additive model, random intercept only; f[age], sex, their interaction, and study membership as covariables). Color code differentiates between $eGFR_{crea}$ (blue) and $eGFR_{cys}$ (orange) and line type between men (dashed) and women (solid). Bands represent the 95% confidence intervals.

$eGFR_{cys}$, these intervals were smaller because of a lower variability of $eGFR_{cys}$ random slopes (Figure 4b).

Revisiting results using alternative formulas to derive eGFR

In cross-sectional data of general population individuals (both creatinine and cystatin measurement available at baseline, n = 5732), we compared individuals' values of $eGFR_{crea}$ and $eGFR_{cys}$ across the formulas (CKD-EPI 2021,[24] CKD-EPI 2009,[26] EKFC 2021,[29] and CKD-EPI 2012,[25] EKFC 2023,[30] respectively; Supplementary Figure S5A and B): although CKD-EPI 2009 showed little differences to CKD-EPI 2021, EKFC 2021 yielded lower $eGFR_{crea}$ values than CKD-EPI 2021 for all age groups (similarly, CKD-EPI 2012 vs. EKFC 2023 for $eGFR_{cys}$; Supplementary Figure S5C).

We thus compared the impact of using EKFC rather than CKD-EPI on our cross-sectional and longitudinal results. The overall pattern was similar (Supplementary Figures S6 and S7), but 2 aspects differed: in cross-sectional data, mean levels differed between $eGFR_{cys}$ and $eGFR_{crea}$ in young individuals (Supplementary Figure S6A–C); in longitudinal data, no eGFR decline was observed in general population individuals until the age of 40 years (Supplementary Figure S6D).

Table 3 | Annual decline of eGFR in longitudinal analyses for the general population, the *healthy* individuals, and individuals with diabetes

	General population	*Healthy* individuals	Individuals with diabetes
$eGFR_{crea}$			
n	9082	4545	4323
m	16,835	5848	11,179
Intercept	95.1 [94.6 to 95.7]	95.9 [95.3 to 96.4]	100.4 [97.7 to 103.1]
Age	−0.80 [−0.82 to −0.77]	−0.79 [−0.83 to −0.76]	−1.20 [−1.33 to −1.08]
Sex	1.35 [0.70 to 2.01]	1.14 [0.29 to 1.99]	0.28 [−1.58 to 2.14]
Age × sex	0.00 [−0.03 to 0.03]	0.05 [−0.003 to 0.10]	−0.00 [−0.08 to 0.08]
$eGFR_{cys}$			
n	9644	6126	4304
m	15,188	9127	11,091
Intercept	95.7 [95.2 to 96.3]	92.9 [92.4 to 93.4]	94.2 [91.1 to 97.3]
Age	−1.1 [−1.10 to −1.04]	−1.09 [−1.13 to −1.06]	−1.29 [−1.44 to −1.14]
Sex	0.38 [−0.25 to 1.01]	0.92 [−0.05 to 1.90]	6.95 [5.00 to 8.89]
Age × sex	0.021 [−0.01 to 0.051]	0.07 [0.02 to 0.13]	−0.26 [−0.33 to 0.11]

AugUR, Altersbezogene Untersuchungen zur Gesundheit der Universität Regensburg; CI, confidence interval; CVD, cardiovascular disease; DIACORE, DIAbetes COhoRtE; eGFR, estimated glomerular filtration rate; $eGFR_{crea}$, estimated glomerular filtration rate based on creatinine; $eGFR_{cys}$, estimated glomerular filtration rate based on cystatin C; HbA1c, glycated hemoglobin; KORA, Cooperative Health Research in the Region of Augsburg; LMM, linear mixed model; m, number of measurements; n, number of individuals included in analysis; UACR, urinary albumin-to-creatinine ratio.
Longitudinal data of all studies were analyzed jointly in individuals with at least 1 available eGFR value at any time point. For each outcome $eGFR_{crea}$ and $eGFR_{cys}$, an LMM (random intercept only; age centered at 50 years, sex, their interaction, and study membership as covariables) was fitted to the general population individuals (KORA-3, KORA-4, and AugUR), their subgroup of *healthy* individuals (excluding individuals with diabetes, CVD, HbA1c ≥ 6.5%, UACR ≥ 30 mg/g, or blood pressure ≥ 140/90 mm Hg; from KORA-3, KORA-4, and AugUR), and individuals with diabetes (DIACORE; individuals with diabetes from KORA-3, KORA-4, and AugUR). The β estimates with respective 95% CIs are given. There was no evidence for interaction of age with sex (except for a small age × sex interaction for $eGFR_{cys}$ in healthy individuals).

Table 4 | Longitudinal analyses for risk factor association with eGFR levels and eGFR decline

Variable	$eGFR_{crea}$	$eGFR_{cys}$
n	10,815	9725
m	19,183	18,165
Main effects		
Intercept	97.09 [96.4 to 97.8]	95.1 [94.3 to 95.9]
Age	−0.73 [−0.77 to −0.69]	−1.03 [−1.07 to −0.99]
Men	1.46 [0.66 to 2.26]	2.15 [1.25 to 3.05]
Diabetes	5.64 [4.62 to 6.66]	5.33 [4.25 to 6.41]
Overweight	−1.77 [−2.59 to −0.95]	−0.76 [−1.64 to 0.12]
Obesity	−2.50 [−3.50 to −1.50]	−3.73 [−4.81 to −2.65]
Microalbuminuria	0.96 [−0.14 to 2.06]	0.16 [−0.96 to 1.28]
Macroalbuminuria	−3.65 [−6.20 to −1.10]	−3.92 [−6.55 to −1.29]
Interaction effects		
Age × men	−0.03 [−0.07 to 0.01]	−0.04 [−0.08 to −0.00]
Age × diabetes	−0.45 [−0.49 to −0.41]	−0.43 [−0.49 to −0.37]
Age × overweight	−0.03 [−0.07 to 0.01]	−0.05 [−0.09 to −0.01]
Age × obesity	−0.12 [−0.16 to −0.08]	−0.11 [−0.17 to −0.05]
Age × microalbuminuria	−0.09 [−0.13 to −0.05]	−0.09 [−0.15 to −0.03]
Age × macroalbuminuria	−0.08 [−0.20 to 0.04]	−0.10 [−0.22 to 0.02]

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; $eGFR_{crea}$, estimated glomerular filtration rate based on creatinine; $eGFR_{cys}$, estimated glomerular filtration rate based on cystatin C; LMM, linear mixed model; m, number of measurements; n, number of individuals included in analysis; UACR, urinary albumin-to-creatinine ratio.
Microalbuminuria was defined as UACR ≥ 30 and < 300 mg/g; and macroalbuminuria as UACR ≥ 300 mg/g. BMI ≥ 25 and < 30 kg/m^2 was defined as *overweight*; and BMI ≥ 30 kg/m^2 as *obese*. The analyzed sample consisted of individuals with at least 1 eGFR value available at any time point and with available information on diabetes, BMI, and UACR. For each outcome, $eGFR_{crea}$ or $eGFR_{cys}$, a multivariable linear regression model (LMM) was fitted (random intercept only; age centered at 50 years, sex, diabetes, overweight, obesity, microalbuminuria, and macroalbuminuria, their interactions with age, and study membership as covariables). The β estimates are shown in ml/min per 1.73 m^2 with 95% CIs. The intercept can be interpreted as mean eGFR level for the reference group and the age effect as the mean annual decline of the reference group (50-year-old women with normal weight, no diabetes, and no albuminuria). The main effect of a risk factor can be interpreted as the change of eGFR level when this risk factor is present (e.g., for *obesity*, 50-year-old women with obesity [no diabetes, no albuminuria] have on average −2.50 ml/min per 1.73 m^2 lower $eGFR_{crea}$ than women without obesity). The interaction effect of risk factor with age is the additional annual decline for individuals with this risk factor versus the reference group (e.g., 50-year-old women with obesity [no diabetes, no albuminuria] have on average −0.12 ml/min per 1.73 m^2 steeper annual $eGFR_{crea}$ decline [average decline of −0.73 + −0.12 = −0.85 ml/min per 1.73 m^2 per year] than women without obesity).

Reference values for $eGFR_{crea}$ based on 2.5th percentiles in *healthy* individuals were similar for EKFC compared with CKD-EPI for individuals aged <70 years (Supplementary Table S9).

CKD proportions with age-independent and age-dependent cutoff values for eGFR

When using the established CKD definition[2] based on $eGFR_{crea}$ CKD-EPI 2021 in our cross-sectional general population data (UACR ≥30 mg/g or eGFR <60 ml/min per 1.73 m^2), we yielded the following CKD proportions: 4%, 4%, 7%, 14%, 30%, or 48% for age groups 30 to 40, 40 to 50, 50 to 60, 60 to 70, 70 to 80, or ≥80 years, respectively (Figure 5a). Although almost no one in the young age group had CKD via the eGFR criterion, approximately one-third of the individuals aged ≥70 years had CKD only due to *eGFR <60*. For individuals with diabetes, CKD proportions were 20%, 24%, 26%, 29%, 44%, and 60%, respectively (Figure 5b).

While acknowledging that large longitudinal data on kidney failure and mortality are needed to develop age-dependent cutoff values, we were interested in the impact of age-dependent cutoffs for eGFR on these CKD proportions: when using GAMLSS-estimated 2.5th percentiles in *healthy* (rounded to next 5 or 10 units), yielded 75, 70, 60, 50, 40, and 30 ml/min per 1.73 m^2 for the age groups 30 to 40, 40 to 50, 50 to 60, 60 to 70, 70 to 80, and ≥80 years, respectively. This resulted, for the general population, 6%, 5%, 7%, 11%, 21%, and 30% CKD, respectively.

DISCUSSION

We provided reference values for eGFR and eGFR decline for adult individuals of a wide age range from Germany. Our cross-sectional and longitudinal data on >26,000 assessments of eGFR based on creatinine and cystatin C yielded 3 main results: (i) annual $eGFR_{crea}$ decline estimates of −0.80 in the general population, −0.79 in *healthy* individuals, and −1.20 ml/min per 1.73 m^2 per year for individuals with diabetes were in line with literature.[17,35] (ii) Our age-specific percentile curves for eGFR via GAMLSS in cross-sectional data provide interpretable reference values without assuming linear eGFR decrease by age. (iii) A unique aspect of our work are the reference values for eGFR decline from longitudinal data provided as 95% prediction intervals. These intervals account for intraperson variability, are readily interpretable, and fill an important gap of epidemiologic data on eGFR in current literature. The use of GAMLSS and LMM-based prediction intervals is established in the statistical community,[36] but—to our knowledge—novel in the literature of nephrology.

Our results cover numerous further aspects enabled by sex-specific analyses and the use of alternative biomarkers,

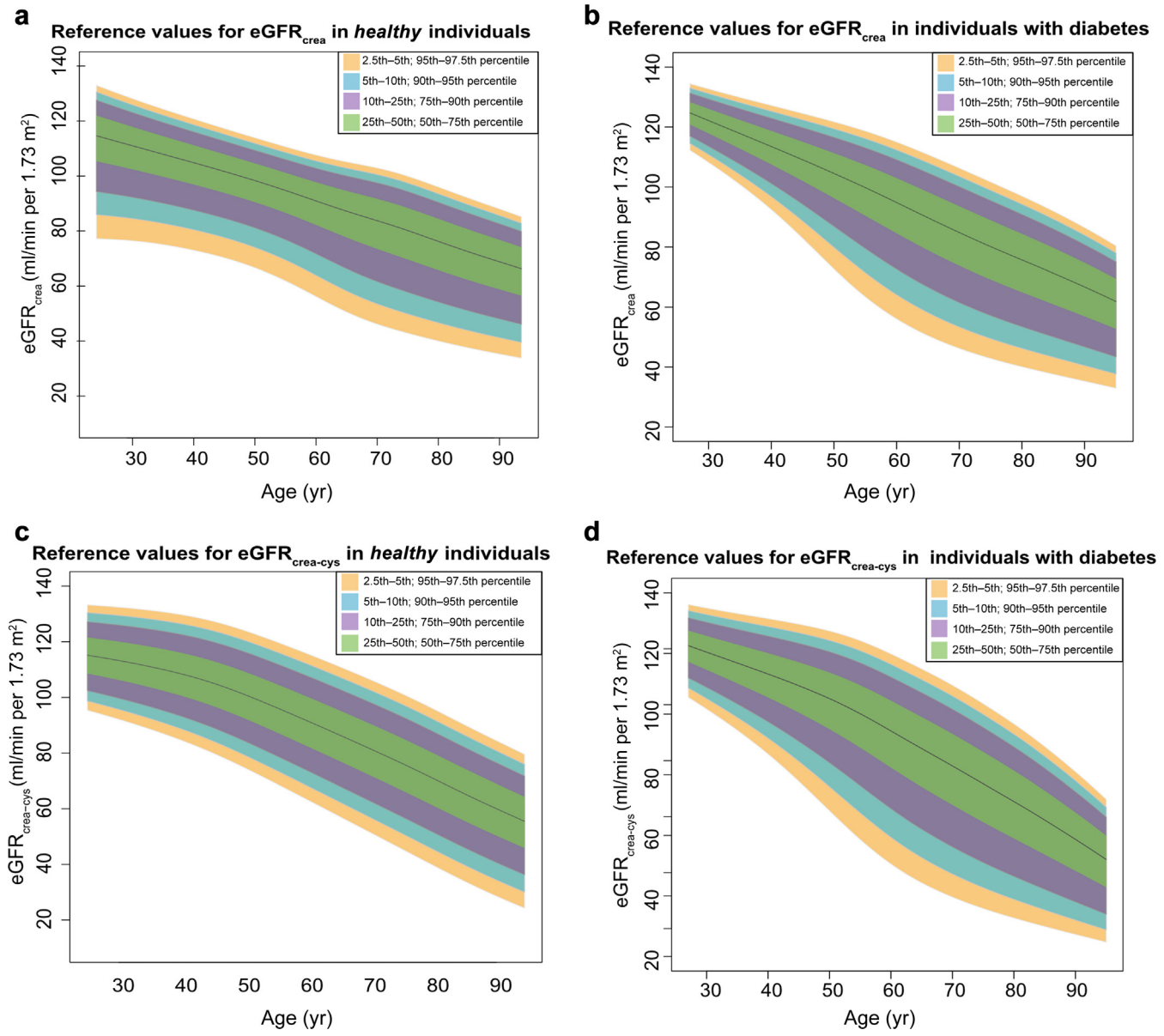

Figure 3 | Reference values for estimated glomerular filtration rate based on creatinine (eGFR$_{crea}$) and creatinine and cystatin C (eGFR$_{crea-cys}$) based on cross-sectional data. The analyzed sample was restricted to individuals with eGFR values available at baseline. Shown are percentiles curves of eGFR$_{crea}$ and eGFR$_{crea-cys}$ based on data from (**a,c**) *healthy* individuals ($n_{eGFRcrea}$ = 4984, $n_{eGFRcrea-cys}$ = 3042) and (**b,d**) individuals with diabetes ($n_{eGFRcrea}$ = 3172, $neGFR_{crea-cys}$ = 3890). The color code was used to differentiate areas between selected percentiles (yellow: 2.5th–5th and 95th–97.5th; blue: 5th–10th and 90th–95th percentile; purple: 10th–25th and 75th–90th percentile; green: 25th–50th and 50th–75th percentile). Age-group–specific percentiles are shown in Supplementary Table S7.

and alternative eGFR equations. Our cross-sectional and longitudinal analyses of eGFR underscored the predominant impact of age, which was substantially larger than any differences by sex, the use of cystatin rather than creatinine, or alternative equations to estimate GFR. Although there have been reported differences in measured GFR between men and women,[13] our data showed little sex differences in eGFR accounting for age. Lower levels of eGFR$_{cys}$ compared with eGFR$_{crea}$ levels in elderly individuals, shown in cross-sectional data, were also in line with longitudinal data results that eGFR$_{cys}$ decline was steeper than eGFR$_{crea}$ decline. Both are an indication of overestimated GFR by eGFR$_{crea}$ and underestimated eGFR decline in the older age range because of muscle mass loss, described previously.[37] Although individuals' eGFR values differed when using alternative eGFR equations from EKFC rather than CKD-EPI, the 2.5th or 5th percentiles in healthy individuals were relatively stable when using alternative eGFR equations to estimate GFR and in line with published data on measured GFR.[34]

Our reference values from population-based cross-sectional data are unique for Germany because of their wide age range and smooth percentile curves. European reference

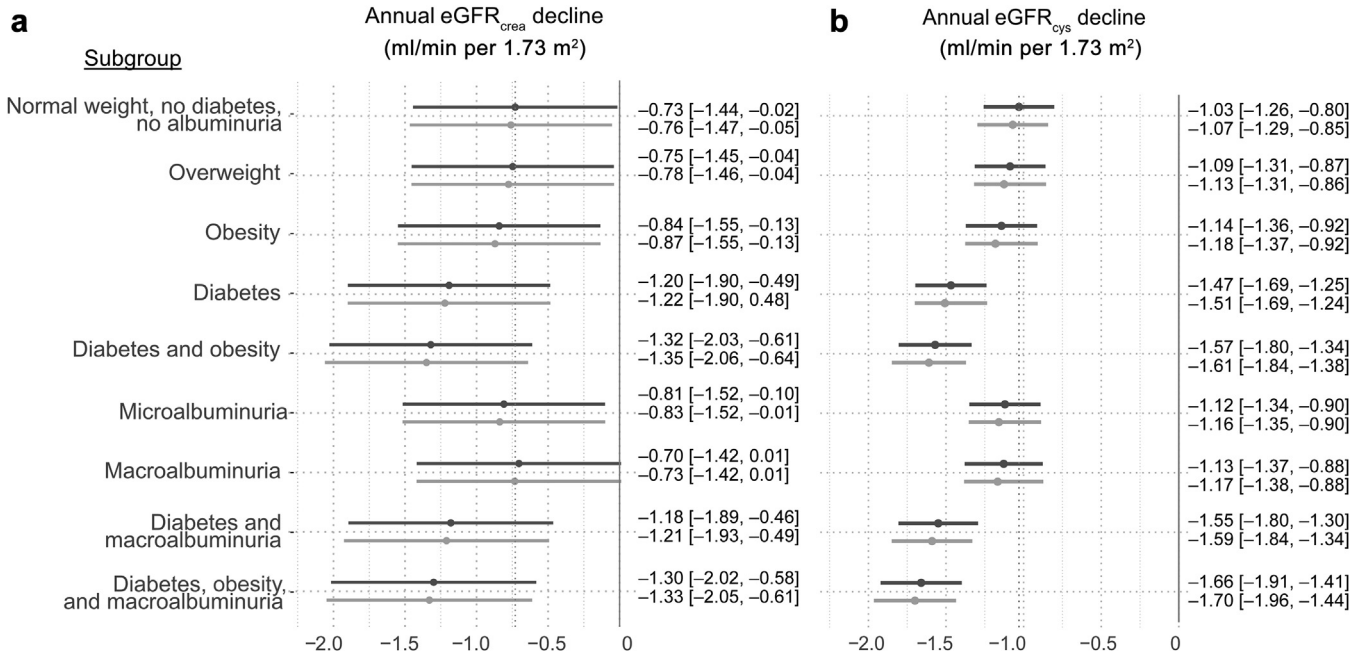

Figure 4 | Reference values for estimated glomerular filtration rate (eGFR) decline in longitudinal data. The analyzed sample consisted of individuals with at least 1 eGFR value available at any time point and with available information on diabetes, body mass index (BMI), and urinary albumin-to-creatinine ratio. Shown are reference values for annual eGFR decline for different subgroups of individuals for (**a**) eGFR based on creatinine ($eGFR_{crea}$) and (**b**) eGFR based on cystatin C ($eGFR_{cys}$). For each outcome, a multivariable linear mixed model was applied ($n_{eGFRcrea}$ = 10,800, $m_{eGFRcrea}$ = 19,173 and $n_{eGFRcys}$ = 9725, $m_{eGFRcys}$ = 18,165): random intercept + random slope (RS) model with age (centered at 50 years), sex, diabetes, BMI category, albuminuria category, and their interactions with age as covariables. Reference values for annual decline were derived from combining β estimates for age and the age interaction with the respective risk factor (Supplementary Table S8) with the respective 95% prediction interval including the variability of RS ($SD_{eGFRcrea}$ = 0.36, $SD_{eGFRcys}$ = 0.11). Reference values are color coded by sex (dark gray: women; light gray: men). The dashed vertical line indicates the value for eGFR decline for the reference group (women, normal weight, no diabetes, and no albuminuria). The stated values next to the bars indicate sex-specific estimates with the respective 95% prediction intervals.

values were previously provided for a limited age range[15,16] or limited to eGFR using an outdated formula.[11,15,26,38] Previous statistical methods to display reference values from cross-sectional data used median values, percentiles per age group connected by a line, or quantile regression assuming linear decrease.[9,11,15]

Our reference values indicate, as shown by others,[39] that an eGFR of 60 ml/min per 1.73 m^2 was well within the norm for *healthy* elderly individuals but would result in a CKD classification according to the established definition.[2] There is a substantial debate on whether this age-independent cutoff value of 60 ml/min per 1.73 m^2 appropriately distinguishes the healthy aging kidney from kidney disease. On the basis of the risk of kidney failure and mortality of ∼100,000 individuals,[40] age-specific eGFR cutoff values for CKD have been proposed previously (75, 60, or 45 ml/min per 1.73 m^2 for age groups 18–54, 55–64, or ≥65 years, respectively).[8] We evaluated similar, but more refined, age-specific cutoff values based on our age-specific 2.5th percentiles in *healthy* individuals (75, 70, 60, 50, 40, and 35 ml/min per 1.73 m^2 for <40, 40–50, 50–60, 60–70, 70–80, and ≥80 years, respectively) and demonstrated a substantial impact on the proportion of CKD. Large longitudinal data on kidney failure and mortality will be needed to evaluate such alternative eGFR cutoff values for their predictive ability of severe end points.

It was not clear how to present reference values for eGFR decline given the current nephrological literature. Longitudinal data and reference values for eGFR decline have been scarce in Germany and internationally. Previous work generated reference values for $eGFR_{crea}$ decline as quantiles for the $eGFR_{crea}$ difference between 2 assessments[11] or as mean slopes by age group.[41] However, reference values should give a sense of what to expect regarding the eGFR decline when a person of a certain risk profile regarding obesity, diabetes, or albuminuria appears in clinical practice. For this, we used risk factor association estimates from multivariable LMM with random slopes that accounted for the uncertainty in the association estimate and the variability of person-specific slopes. Importantly, the resulting 95% prediction intervals have an intuitive interpretation: for a person seen in clinical practice, with diabetes and obesity but without albuminuria, the clinician can use these intervals to say that 95% of such individuals have an annual decline of –2.03 to –0.61 ml/min per 1.73 m^2 per year.

There are some strengths and limitations that should be mentioned. A strength of our data is that the studies are random population-level cohorts: individuals were drawn

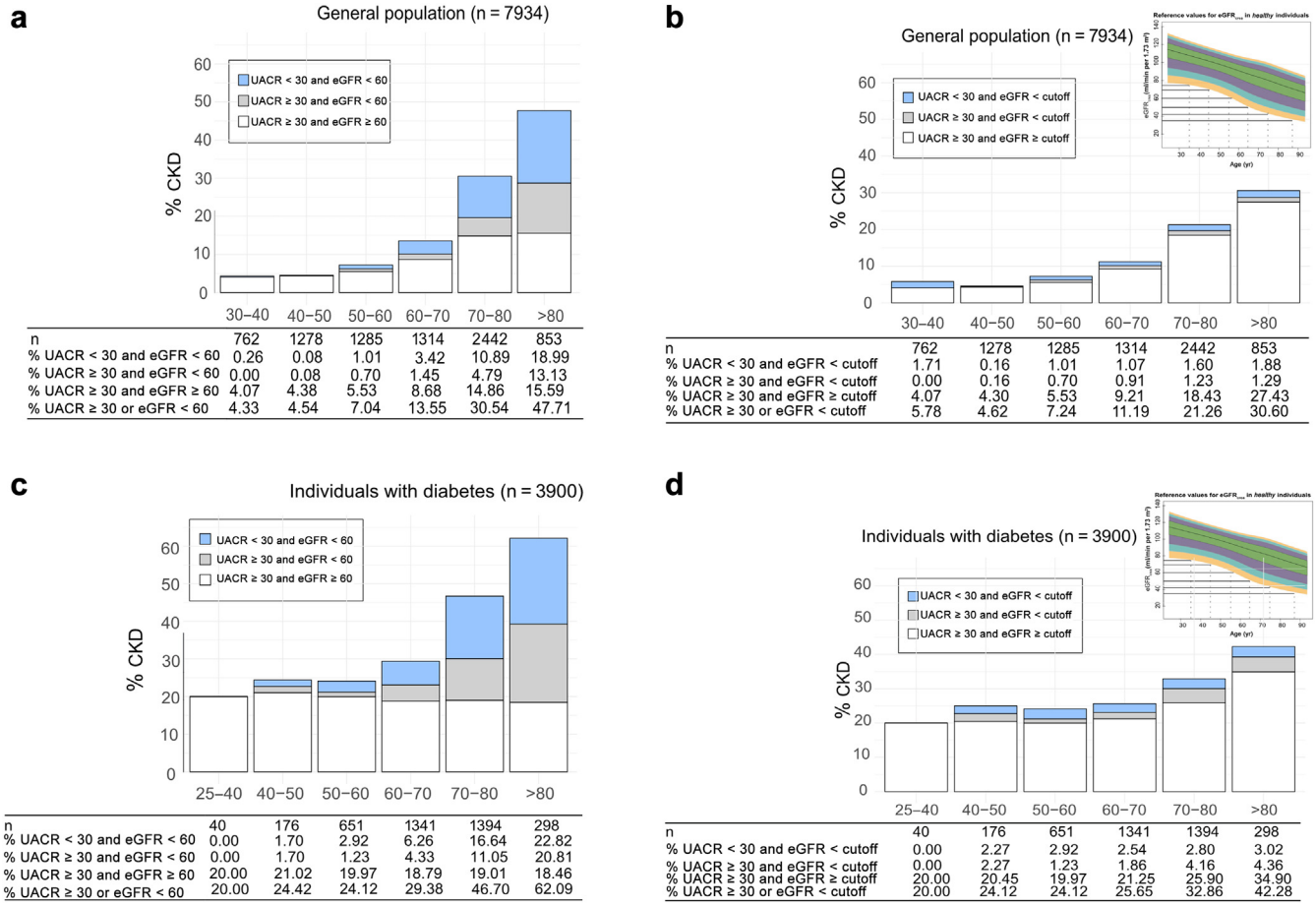

Figure 5 | Revisiting chronic kidney disease (CKD) prevalence in the general population and individuals with diabetes in cross-sectional data. The analyzed sample consisted of individuals with both estimated glomerular filtration rate based on creatinine ($eGFR_{crea}$) and urinary albumin-to-creatinine ratio (UACR) assessments available at baseline. Shown are percentages of individuals with CKD, defined by albuminuria (UACR ≥30 mg/g) or $eGFR_{crea}$ <60 ml/min per 1.73 m^2, in (**a,b**) the general population and (**c,d**) individuals with diabetes derived. (**a,c**) The percentage of CKD resulting from cutoff defined by Kidney Disease: Improving Global Outcomes (KDIGO). The white and gray bars show percentage of individuals with albuminuria ($eGFR$ ≥60 ml/min per 1.73 m^2 or cutoff or $eGFR$ <60 ml/min per 1.73 m^2 or cutoff, respectively); blue bar shows the percentage of individuals without albuminuria but low $eGFR_{crea}$ values. (**b,d**) The percentage of CKD resulting from age-dependent cutoffs (30–40 years: 75 ml/min per 1.73 m^2; 40–50 years: 70 ml/min per 1.73 m^2; 50–60 years: 60 ml/min per 1.73 m^2; 60–70 years: 50 ml/min per 1.73 m^2; 70–80 years: 40 ml/min per 1.73 m^2; >80 years: 35 ml/min per 1.73 m^2), for $eGFR_{crea}$ in *healthy* individuals (rounded 2.5th percentile for midpoint age of respective age group).

randomly from population registries or, for the diabetes study, health care providers. However, participants are typically not hospitalized and more mobile, healthier, and more health interested than nonparticipants.[17–19] Because of this participation bias and exclusion of individuals with severe kidney disease or kidney replacement therapy, mean levels of eGFR in cross-sectional and longitudinal analyses might be overestimated in the general or diabetes population. Furthermore, it is not fully straightforward how to define *healthy* individuals; we tried to capture the most relevant factors known to influence the health status in view of kidney function.[9,41] Another limitation is the various assays used for biomarker measurements across studies and time points. Although we ascertained comparability of age-group–specific mean values across arrays with little evidence of systematic error, the different assays can be expected to have increased the random noise. Still, various assays will also be used in clinical routine, and our data might thus provide a more realistic scenario than standardized centralized measurements. Finally, the potential of survival bias warrants consideration: because of excluding individuals with kidney replacement therapy, kidney failure, acute kidney injury, or nephrectomy, we expect negligible loss to follow-up due to kidney-related death; sensitivity analyses suggested no impact of survival status on annual decline estimates, in line with previous work using bivariate analysis.[15]

Although the data are from 1 country, reference values on eGFR and eGFR decline can be generalized to other countries of similar lifestyle and health care systems; generalizability to non-Caucasian populations is limited because the study population was mostly White Caucasian.[17,19,22] A challenge derives from the different equations to estimate GFR from creatinine: reference values should be based on the equation used by laboratories in clinical practice. KDIGO guidelines[27]

(CKD-EPI 2021) differ from European laboratory practice (mostly CKD-EPI 2009), and European societies recommend stalling the update.[28,42] In our data, individual $eGFR_{crea}$ values were similar for CKD-EPI 2009 compared with CKD-EPI 2021, making our reference values applicable when laboratory reports are based on CKD-EPI 2009. EKFC-derived $eGFR_{crea}$ values[29] differed, prompting us to present reference values also for this alternative equation that is currently being discussed as a potential update to CKD-EPI 2009 in Europe.

In conclusion, we provided age-specific reference values for eGFR in healthy individuals and reference values for eGFR decline by subgroups of special interest in clinical routine. These reference values can help guide clinicians in judging their patient's eGFR against the normal range and in predicting annual eGFR decline in general and in high-risk subgroups. Our findings support the pledge for an age-adapted CKD definition and motivate further analyses to investigate the benefit of age-specific thresholds.

DISCLOSURE

WK reports advisory board fees from AstraZeneca, Novartis, Amgen, Pfizer, The Medicines Company, DalCor, Kowa, Corvidia, OMEICOS, Daiichi-Sankyo, Novo Nordisk, New Amsterdam Pharma, TenSixteen Bio, Esperion, and Genentech; lecture fees from Bristol-Myers Squibb, Novartis, Amgen, Berlin-Chemie, Sanofi, and AstraZeneca; and grants and nonfinancial support from Abbott, Roche Diagnostics, Beckmann, and Singulex, outside the submitted work. TZ is listed as coinventor of an international patent on the use of a computing device to estimate the probability of myocardial infarction (international publication number WO2022043229A1). TZ is shareholder of the ART.EMIS GmbH Hamburg. IMH has received support from Roche Diagnostics for a biomarker project, but unrelated to the work presented here. The results presented in this article have not yet been published, either in whole or in part. All the other authors declared no competing interests.

DATA STATEMENT

Mean values and percentiles are provided in detail in Supplementary Tables S3 and S7. The individual participant data of the studies cannot be shared openly because of the data protection requirements of study participants. Data are available on reasonable request.

ACKNOWLEDGMENTS

This work was funded by the Deutsche Forschungsgemeinschaft (DFG; German Research Foundation) project identifier 387509280, SFB1350 (subproject C6 to IMH) and project identifier 509149993, TRR 374. The AugUR (Altersbezogene Untersuchungen zur Gesundheit der Universität Regensburg) study was supported by the German Federal Ministry of Education and Research (grant numbers BMBF 01ER1206 and BMBF 01ER1507 to IMH) and by the German Research Foundation (grant number HE 3690/7-1 to IMH). The KORA (Cooperative Health Research in the Region of Augsburg) study was initiated and financed by the Helmholtz Zentrum München–German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Data collection in the KORA study is done in cooperation with the University Hospital of Augsburg. Cystatin C measurements in KORA have been partly funded through the EU project BiomarCaRE (grant agreement no. HEALTH-F2-2011-278913) under the Seventh Framework Programme (FP7/2007-2013). TZ is funded by the German Research Foundation, the EU Horizon 2020 programme, the EU ERANet and ERAPreMed Programmes, the German Centre for Cardiovascular Research (DZHK; 81Z0710102), and the German Ministry of Education and Research. The DIACORE (DIAbetes COhoRtE) study was supported by a grant from the KFH Foundation for Preventive Medicine (CAB). This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement no. 115974 (BEAt-DKD). This Joint Undertaking (JU) receives the support from the European Union's Horizon 2020 research and innovation programme and EFPIA with JDRF. Any dissemination of results reflects only the author's view; the JU is not responsible for any use that may be made of the information it contains.

We would like to thank all AugUR, KORA, and DIACORE study participants for taking part in the studies. We further thank the physicians and health insurance companies supporting the studies and all study nurses for their expert work in performing the study visits.

AUTHOR CONTRIBUTIONS

JMH performed statistical analyses and manuscript writing; SW performed statistical analyses and interpretation of results; JN was the scientific coordinator of kidney variables (KORA [Cooperative Health Research in the Region of Augsburg]); BJ performed study data management and was the study co–principal investigator (PI) (DIACORE [DIAbetes COhoRtE]); MG performed data preparation and quality control; BT: studied the data management (KORA); WK performed biomarker measurements (KORA); TZ performed biomarker measurements (KORA); MEZ performed data management (AugUR [Altersbezogene Untersuchungen zur Gesundheit der Universität Regensburg]); RB performed laboratory analysis and biomarker measurements; BB was the study PI (DIACORE); HK performed statistical expertise and interpreted the results; KJS: was the study coordination (AugUR) and performed data management (DIACORE); AP: was the study PI (KORA); CAB: was the study PI (DIACORE), initiated the project, and designed the manuscript; and IMH: was the study PI, initiated the project, supervised statistical analyses, and designed and wrote the manuscript. All authors contributed to the reviewing and editing of the manuscript and approved the final version.

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

REFERENCES

1. Denic A, Lieske JC, Chakkera HA, et al. The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol*. 2017;28:313–320.
2. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2009;113:S1–S130.
3. Levey AS, Coresh J, Bolton K, et al. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(suppl 1):S1–S266.
4. Cockwell P, Fisher L-A. The global burden of chronic kidney disease. *Lancet*. 2020;395:662–664.
5. Weckmann G, Chenot J-F, Stracke S. The management of non-dialysis-dependent chronic kidney disease in primary care. *Dtsch Arztebl Int*. 2020;117:745–751.
6. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet*. 2013;382:260–272.

7. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int*. 2011;80:1258–1270.
8. Delanaye P, Jager KJ, Bökenkamp A, et al. CKD: a call for an age-adapted definition. *J Am Soc Nephrol*. 2019;30:1785–1805.
9. Wetzels JFM, Kiemeney LALM, Swinkels DW, et al. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. *Kidney Int*. 2007;72:632–637.
10. Berg UB. Differences in decline in GFR with age between males and females: reference data on clearances of inulin and PAH in potential kidney donors. *Nephrol Dial Transplant*. 2006;21:2577–2582.
11. Waas T, Schulz A, Lotz J, et al. Distribution of estimated glomerular filtration rate and determinants of its age dependent loss in a German population-based study. *Sci Rep*. 2021;11:10165.
12. Ebert N, Jakob O, Gaedeke J, et al. Prevalence of reduced kidney function and albuminuria in older adults: the Berlin Initiative Study. *Nephrol Dial Transplant*. 2017;32:997–1005.
13. Eriksen BO, Palsson R, Ebert N, et al. GFR in healthy aging: an individual participant data meta-analysis of iohexol clearance in European population-based cohorts. *J Am Soc Nephrol*. 2020;31:1602–1615.
14. Hemmelgarn BR, Zhang J, Manns BJ, et al. Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int*. 2006;69:2155–2161.
15. Schaeffner ES, Ebert N, Kuhlmann MK, et al. Age and the course of GFR in persons aged 70 and above. *Clin J Am Soc Nephrol*. 2022;17:1119–1128.
16. Potok OA, Rifkin DE, Ix JH, et al. Estimated GFR accuracy when cystatin C- and creatinine-based estimates are discrepant in older adults. *Kidney Med*. 2023;5:100628.
17. Holle R, Happich M, Löwel H, Wichmann HE. KORA–a research platform for population based health research. *Gesundheitswesen*. 2005;67(suppl 1):S19–S25.
18. Dörhöfer L, Lammert A, Krane V, et al. Study design of DIACORE (DIAbetes COhoRtE) - a cohort study of patients with diabetes mellitus type 2. *BMC Med Genet*. 2013;14:25.
19. Stark K, Olden M, Brandl C, et al. The German AugUR study: study protocol of a prospective study to investigate chronic diseases in the elderly. *BMC Geriatr*. 2015;15:130.
20. Seissler J, Feghelm N, Then C, et al. Vasoregulatory peptides pro-endothelin-1 and pro-adrenomedullin are associated with metabolic syndrome in the population-based KORA F4 study. *Eur J Endocrinol*. 2012;167:847–853.
21. Rheinberger M, Jung B, Segiet T, et al. Poor risk factor control in outpatients with diabetes mellitus type 2 in Germany: the DIAbetes COhoRtE (DIACORE) study. *PLoS One*. 2019;14:e0213157.
22. Donhauser FJ, Zimmermann ME, Steinkirchner AB, et al. Cardiovascular risk factor control in 70- to 95-year-old individuals: cross-sectional results from the population-based AugUR study. *J Clin Med*. 2023;12:2102.
23. Goek O-N, Prehn C, Sekula P, et al. Metabolites associate with kidney function decline and incident chronic kidney disease in the general population. *Nephrol Dial Transplant*. 2013;28:2131–2138.
24. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. 2021;385:1737–1749.
25. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367:20–29.
26. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
27. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024;105(4S):S117–S314.
28. Delanaye P, Schaeffner E, Cozzolino M, et al. The new, race-free, Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation to estimate glomerular filtration rate: is it applicable in Europe? a position statement by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM). *Clin Chem Lab Med*. 2023;61:44–47.
29. Pottel H, Björk J, Courbebaisse M, et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate: a cross-sectional analysis of pooled data. *Ann Intern Med*. 2021;174:183–191.
30. Pottel H, Björk J, Rule AD, et al. Cystatin C-based equation to estimate GFR without the inclusion of race and sex. *N Engl J Med*. 2023;388:333–343.
31. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158:825–830.
32. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2013. 2012.
33. Gregorich M, Kammer M, Heinzel A, et al. Development and validation of a prediction model for future estimated glomerular filtration rate in people with type 2 diabetes and chronic kidney disease. *JAMA Netw Open*. 2023;6:e231870.
34. Delanaye P, Gaillard F, van der Weijden J, et al. Age-adapted percentiles of measured glomerular filtration in healthy individuals: extrapolation to living kidney donors over 65 years. *Clin Chem Lab Med*. 2022;60:401–407.
35. Warren B, Rebholz CM, Sang Y, et al. Diabetes and trajectories of estimated glomerular filtration rate: a prospective cohort analysis of the Atherosclerosis Risk in Communities Study. *Diabetes Care*. 2018;41:1646–1653.
36. Verbeke G. Linear mixed models for longitudinal data. In: Neal RM, ed. *Bayesian Learning for Neural Networks*. Springer; 1996:63–153.
37. Raman M, Middleton RJ, Kalra PA, Green D. Estimating renal function in old people: an in-depth review. *Int Urol Nephrol*. 2017;49:1979–1988.
38. Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007;53:766–772.
39. Glassock RJ, Rule AD. Aging and the kidneys: anatomy, physiology and consequences for defining chronic kidney disease. *Nephron*. 2016;134:25–29.
40. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2081.
41. Baba M, Shimbo T, Horio M, et al. Longitudinal study of the decline in renal function in healthy subjects. *PLoS One*. 2015;10:e0129036.
42. Gansevoort RT, Anders H-J, Cozzolino M, et al. What should European nephrology do with the new CKD-EPI equation? *Nephrol Dial Transplant*. 2023;38:1–6.