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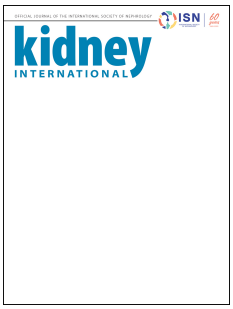

Population-based reference values for kidney function and kidney function decline in 25- to 95-year-old Germans without and with diabetes.

Janina M. Herold, M.Sc., Simon Wiegrebe, M.Sc., Jana Nano, MD, PhD, Bettina Jung, MD, Mathias Gorski, PhD, Barbara Thorand, PhD, Wolfgang Koenig, MD, Tanja Zeller, PhD, Martina E. Zimmermann, PhD, Ralph Burkhardt, MD, Bernhard Banas, MD, Helmut Küchenhoff, PhD, Klaus J. Stark, PhD, Annette Peters, PhD, Carsten A. Böger, MD, Iris M. Heid, PhD

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

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Aim

80 year-old

eGFR=58ml/min/1.73m²

1. Is this an age-appropriate eGFR value?

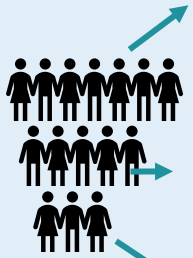
2. What is the expected range of eGFR decline based on their risk profile?

Data

Cross-sectional and longitudinal data

>12 000 individuals aged 25-95 years

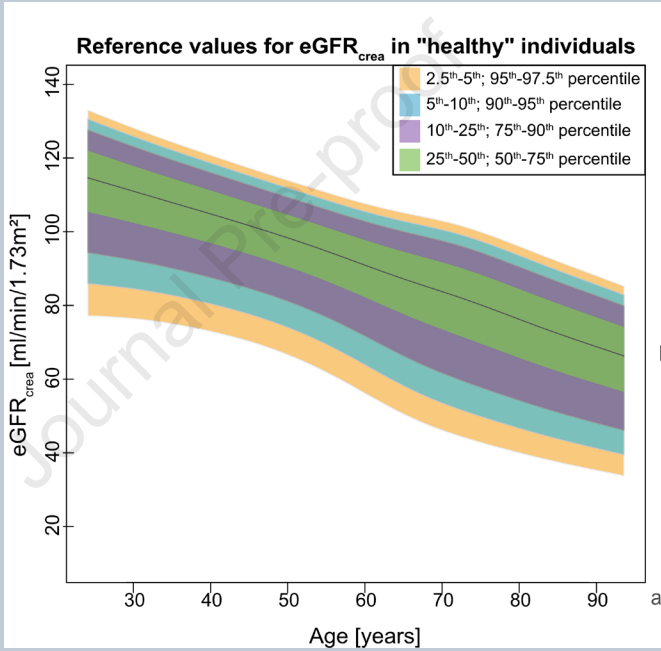
>26 000 eGFR assessments



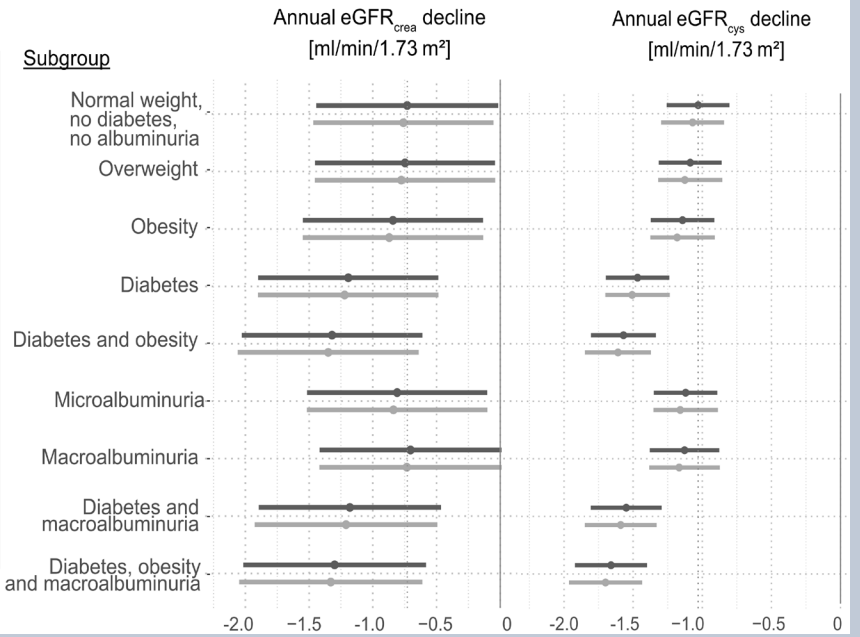
- General population
- "Healthy" group
- Diabetes population

Findings

1. Reference values for eGFR



2. Reference values for eGFR decline



3. Revisiting CKD prevalence (eGFR cut-off without/with age-dependency)

Herold, 2024

CONCLUSION Our reference values help clinicians to judge eGFR values in individuals according to their age and to understand the expected range of annual eGFR decline based on their risk profile.

[QUERY TO AUTHOR: title and abstract rewritten by Editorial Office – not subject to change]

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

Running Head: Reference values for kidney function and kidney function decline

Word count: 4,224 (incl. abstract)

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Abstract

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/1.73m² [-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.

Keywords: Reference values, kidney function, kidney function decline, general population, chronic kidney disease, diabetes

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. While chronic kidney disease is defined as eGFR<60 ml/min/1.73m², the question arises whether a value of, e.g., 58 ml/min/1.73m² 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.

Introduction

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 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/1.73m² define chronic kidney disease (CKD).[2,3] About 10% of the world´s population[4] and 10-13% in Germany[5] are affected by CKD.

Elderly individuals often have eGFR<60 mL/min/1.73m² due to natural kidney aging,[6,7] giving rise to a substantial debate whether age-dependent CKD definitions are warranted.[8] Clinicians are typically faced with the question whether an observed eGFR of, e.g. 58 ml/min/1.73m² 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 above the age of 80,[12-15] including two 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 fashion.

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 four 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 four population-based cohorts from South Germany: (i-ii) two studies for the middle-aged adult population (KORA-3, KORA-4), (iii) one study for the old-aged population (AugUR), and (iv) one study on individuals with diabetes (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 were assessed following Clinical & Laboratory Standards Institute (CLSI) guidelines. Serum creatinine concentrations were measured by enzymatic assays or modified Jaffé (if applicable, corrected by factor 0.95[23]) and standardized to IDMS (Information Display Measurements Standard). Since 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

136 considered, KORA-F3 “baseline” for analyses using creatinine. Cystatin C was measured via
137 nephelometric methods or immunoassays and standardized according to IFCC (International
138 Federation of Clinical Chemistry). Glycated hemoglobin (HbA1c) was measured from EDTA
139 anticoagulated whole blood via ion-exchange high performance liquid chromatographic assay
140 (KORA, AugUR) or immunoassay (DIACORE). Urine albumin and creatinine were measured
141 in each study and at each timepoint, except KORA-S4, KORA-Fit3, KORA-Fit4. A detailed
142 overview of blood processing and biomarker measurements is provided in **Supplementary**
143 **Table S1**.
144
145 **Variable assessment**
146 The outcome of interest was GFR and various formulas estimate GFR from creatinine and/or
147 cystatin to fit eGFR as closely as possible to measured GFR (mGFR). For our primary
148 analyses, we derived $eGFR_{crea}$, $eGFR_{cys}$ and $eGFR_{crea\text{-}cys}$ using the Chronic Kidney Disease
149 Epidemiology Collaboration (CKD-EPI) 2021 equation,[24] the CKD-EPI 2012 equation,[25] or the
150 combined equation from 2021,[24] respectively. CKD-EPI 2021 includes sex-specific coefficients
151 and an age-term (e.g. 0.9938^{age}) and avoids the race-term from CKD-EPI 2009.[26] CKD-EPI
152 2021 was used by the recent KDIGO guidelines.[27] However, most European laboratories still
153 derive $eGFR_{crea}$ by CKD-EPI 2009,[26] and European societies recommended to stall the update
154 to CKD-EPI 2021 due to limited advantages for European populations.[28] As potential update,
155 alternative equations for $eGFR_{crea}$[29] and $eGFR_{cys}$[30] are suggested by the European Kidney
156 Function Consortium (EKFC; sex-specific coefficients, no age term until 40, e.g. 0.990^{age-40} for
157 age>40). We thus applied also CKD-EPI 2009 and EKFC for sensitivity analyses.
158 From each study center visit, time-dependent covariables were obtained in a very
159 similar fashion across studies. Albuminuria was derived from urinary albumin to urinary
160 creatinine ratio (UACR) as microalbuminuria (UACR ≥30 and <300mg/g) or macroalbuminuria
161 (UACR ≥300mg/g).[31] Diabetes was defined via self-report, intake of antidiabetic medication
162 (using Anatomical Therapeutic Chemical classification[32]), or HbA1c ≥6.5%. DIACORE was
163 restricted to individuals with diabetes assessed via health insurance provider. History of

cardiovascular disease (CVD) was defined as self-report of any prior myocardial infarction, or stroke (or interventional revascularization in AugUR and DIACORE). Body-mass index (BMI) was computed using measured weight (from each visit) divided by squared height [kg/m^2] (from baseline visit). BMI ≥25 and <30kg/m² was defined as "overweight" and BMI ≥30kg/m² as "obese". Blood pressure was measured three times at each study center visit and the mean of 2nd and 3rd measurements was used for analyses.

Inclusion and exclusion criteria

For our analyses, we included participants aged ≥25 years (minimum age in KORA studies), with neither renal replacement therapy (dialysis or kidney transplantation) nor history of severe kidney disease (end-stage kidney disease, acute kidney injury, 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/1.73m² or after onset of renal replacement therapy or severe kidney disease; we excluded individuals without any available measurement of $eGFR_{crea}$ at any timepoint (**Supplementary Figure S2b**).

We analyzed the data focused on general population individuals (i.e. KORA-3, KORA-4, 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 CVD, systolic/diastolic blood pressure ≥140/90 mmHg, or UACR≥30 mg/g at baseline (cross-sectional analyses) or at the respective timepoint (longitudinal analyses); the "healthy"-defining variables were non-missing in >99% individuals at baseline or any timepoint 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 one timepoint (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/1.73m²). While 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 (CI) 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 (RI), sex, interaction of sex with f(age) or age, respectively, 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 one eGFR value while accounting for intra-subject 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, micro- and macroalbuminuria), their interaction with age, 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 2.5^{th}, 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th},

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 $eGFR_{crea-cys}$, since 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 which 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 cut-off values for eGFR

There is a substantial debate on the use of age-independent versus age-dependent eGFR cut-off values to define CKD.[8] We derived the proportion of CKD by age-group based on $eGFR_{crea}$<60 mL/min/1.73m², UACR≥30 mg/g, or their combination. We contrasted these with CKD proportions that would be yielded if age-specific cut-off values for eGFR were based on our GALMSS-derived reference values (using midpoint age per age-group and corresponding modelled 2.5th percentile).

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, AugUR) covered a baseline age of 25-95 years, and 8%, 5%, or 24% had diabetes,

247 respectively; individuals from the diabetes study (DIACORE) were aged 27-92 years (**Table 1**;
248 by sex, **Supplementary Table S2**).

249 First, we evaluated the comparability between studies in the cross-sectional data. We
250 observed comparable age-group specific mean eGFR between studies, except slightly lower
251 mean at older age for DIACORE in line with lower eGFR in diabetes (**Supplementary Figure**
252 **S3a & S3b**). Second, we derived mean values by age-group and sex in the joint cross-sectional
253 data focused on general population (KORA-3, KORA-4, AugUR; n=5,732), their "healthy"
254 subgroup (n=3,042), or individuals with diabetes (including DIACORE: n=3,890;). We found (i)
255 a predominant impact of age on $eGFR_{crea}$ and $eGFR_{cys}$, (ii) little difference by sex, (iii) an
256 approximately linear decrease in eGFR by age, even for younger individuals aged 25-39 years
257 compared to 40-49 years, and (iv) lower mean values for $eGFR_{cys}$ than for $eGFR_{crea}$ at older
258 age (**Figure 1**, **Supplementary Table S3).** The pattern was similar for general population,
259 "healthy", and diabetes - with slightly higher mean for "healthy" and lower mean for diabetes
260 at older age.

261

262 **Longitudinal data: participants characteristics and estimates of eGFR-decline**

263 Our longitudinal analyses included 12,076 or 12,638 individuals with up to 5 assessments of
264 $eGFR_{crea}$ or $eGFR_{cys}$, respectively, covering an age range of 25-98 years ($m_{eGFRcrea}$= 26,179 or
265 $m_{eGFRcys}$= 24,507, respectively; **Table 2**). Study-specific analyses showed comparable course
266 of eGFR (using GAM; **Supplementary Figure S4**) and annual decline estimates (using LMM;
267 **Supplementary Table S4**) across KORA-3, KORA-4, AugUR ($eGFR_{crea}$: -0.8 to -1.0
268 mL/min/1.73m² per year) and slightly steep decline in DIACORE (-1.5 mL/min/1.73m²). We
269 also found similar results in meta-analysis versus joint analyses or when adding random slopes
270 (**Supplementary Tables S4 & S5**). We thus continued to analyze the longitudinal data jointly
271 adjusting for study membership and without random slopes, if not indicated otherwise.

272 We analyzed the longitudinal data for general population, "healthy" individuals, or
273 individuals with diabetes, ($n_{eGFRcrea}$=9,082, 4,545, or 4,323, $n_{eGFRcys}$=9,644, 6,126, or 4,304,
274 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, -0.77], -0.79 [-0.83, -0.76], or -1.20 [-1.33, -1.08] mL/min/1.73m² 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 age² 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, micro-, and macroalbuminuria, and their interactions with age as covariables; $n_{eGFRcrea}$=10,815, $n_{eGFRcys}$=9,725). Annual $eGFR_{crea}$-decline for the reference group (50-year-old normal-weight women without diabetes or albuminuria) was -0.73 mL/min/1.73m² [95%-CI=-0.77, -0.69] (**Table 4**, "Age effect"), similar to the above stated estimate in "healthy" individuals. Most 95%-CIs excluded zero, indicative of a well-powered analysis, and overlapped for $eGFR_{crea}$ and $eGFR_{cys}$, suggesting similar associations for both biomarkers. Compared to 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/1.73m² 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" 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, $n_{eGFRcrea}$=4,984, $n_{eGFRcrea-cys}$=3,042). A person's $eGFR_{crea}$ value measured in clinical practice – or, if cystatin is also available, $eGFR_{crea-cys}$ – can be judged against these reference value diagrams (**Figure 3a & 3c, Supplementary Table S7**): e.g. $eGFR_{crea}$=62 mL/min/1.73m² is way below the 5th percentile for a 60-year-old healthy individual, but near the 25th percentile if the person is 80-year-old. Age-group specific eGFR percentiles were highly comparable to previously reported mGFR percentiles[34] (**Supplementary Table S7**).

Since many patients in the nephrologists' practice have diabetes, we also generated reference values for individuals with diabetes ($n_{eGFRcrea}$=3,172, $n_{eGFRcrea-cys}$=3,890): a person with diabetes and $eGFR_{crea}$=62 mL/min/1.73m² will be above the 5th or 25th percentile when the patient is 60-year-old or 80-year-old, respectively (**Figure 3b & 3d, 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 to persons without risk factors. We derived 95%-prediction intervals for individuals without and with overweight/obesity, diabetes, or micro-/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/1.73m² per year. (ii) Due to the linearity assumption, this is the same when the woman is 70-year-old. (iii) If the person is a man, this interval is very similar (-0.05 to -1.47 mL/min/1.73m² 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/1.73m² per year, respectively (independent of age, very similar for men). For $eGFR_{cys}$, these intervals were smaller due to 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=5,732), 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 & S5b**): while 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 versus 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 & S7**), but two aspects differed: In cross-sectional data, mean levels differed between $eGFR_{cys}$ and $eGFR_{crea}$ in young individuals (**Supplementary Figure S6a-S6c**); in longitudinal data, no eGFR-decline was observed in general population individuals until the age of 40 (**Supplementary Figure S6d**). Reference values for $eGFR_{crea}$ based on 2.5th percentiles in "healthy" individuals were similar for EKFC compared to CKD-EPI for individuals aged <70 years (**Supplementary Table S9**).

CKD proportions with age-independent and age-dependent cut-off 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 ≥30mg/g or eGFR <60 mL/min/1.73m²), we yielded the following CKD proportions: 4%, 4%, 7%, 14%, 30%, or 48% for age-groups 30-40, 40-50, 60-70, 70-80, or 80+ years, respectively (**Figure 5a**). While almost no-one in the young age-group had CKD via the eGFR criterion, about 1/3 of the individuals aged 70+ 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 is needed to develop age-dependent cut-off values, we were interested in the impact of age-

dependent cut-offs 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, 30 mL/min/1.73m² for the age-groups 30-40, 40-50, 50-60, 60-70, 70-80, 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 three 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/1.73m² 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 intra-person variability, are readily interpretable, and fill an important gap of epidemiological 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, 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. While there have been reported differences in mGFR between men and women,[13] our data showed very little sex differences in eGFR accounting for age. Lower levels of $eGFR_{cys}$ compared to $eGFR_{crea}$ levels in elderly shown in cross-sectional data were also in line with longitudinal data results that $eGFR_{cys}$-decline was steeper than $eGFR_{crea}$-decline. Both is an indication of overestimated GFR by $eGFR_{crea}$ and underestimated eGFR-decline in the older age range due to muscle mass loss described

previously.[37] While 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 mGFR.[34]

Our reference values from population-based cross-sectional data are unique for Germany due to their wide age range and smooth percentile curves. European reference 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/1.73m² was well within the norm for "healthy" elderly, but would result in a CKD classification according to the established definition.[2] There is a substantial debate on whether this age-independent cut-off value of 60 mL/min/1.73m² appropriately distinguishes the healthy aging kidney from kidney disease. Based on the risk of kidney failure and mortality of ~100,000 individuals,[40] age-specific eGFR cut-off values for CKD have been proposed previously (75, 60, or 45 mL/min/1.73m² for age-groups 18-54, 55-64, or 65+ years, respectively.[8] We evaluated similar, but more refined age-specific cut-off values based on our age-specific 2.5th percentiles in "healthy" individuals (75, 70, 60, 50, 40, 35 mL/min/1.73m² for <40, 40-50, 50-60, 60-70, 70-80, 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 cut-off values for their predictive ability of severe endpoints.

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 two 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 utilized 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, e.g. 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/1.73m² 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 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 non-participants.[17-19] Due to this participation bias and exclusion of individuals with severe kidney disease or renal 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 straight-forward 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 timepoints. While 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: due to excluding individuals with renal replacement therapy, end-stage kidney disease, 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]

While the data is from one country, reference values on eGFR and eGFR-decline can be generalized to other countries of similar life-style and health care systems; generalizability

443 to non-Caucasian populations is limited due to the study population being mostly White
444 Caucasian.[17,19,22] A challenge derives from the different equations to estimate GFR from
445 creatinine: reference values should be based on the equation used by laboratories in clinical
446 practice. KDIGO guidelines[27] (CKD-Epi 2021) differ to European laboratory practice (mostly
447 CKD-Epi 2009), and European societies recommend to stall the update.[28,42] In our data,
448 individual $eGFR_{crea}$ values were very similar for CKD-EPI 2009 compared to CKD-Epi 2021,
449 making our reference values applicable when laboratory reports are based on CKD-EPI 2009.
450 EKFC-derived $eGFR_{crea}$ values[29] differed, prompting us to present reference values also for
451 this alternative equation that is currently being discussed as potential update to CKD-EPI 2009
452 in Europe.

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

Disclosure statement

J.M.H., S.W., J.N., B.J., M.G., B.T., M.E.Z., R.B., B.B., H.K., K.J.S., A.P., and C.A.B. declare no conflicts of interest. W.K. 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, Genentech; lecture fees from Bristol-Myers Squibb, Novartis, Amgen, Berlin-Chemie, Sanofi and AstraZeneca; grants and non-financial support from Abbott, Roche Diagnostics, Beckmann, and Singulex, outside the submitted work. T.Z. is listed as co-inventor of an international patent on the use of a computing device to estimate the probability of myocardial infarction (International Publication Number WO2022043229A1). T.Z. is shareholder of the ART.EMIS GmbH Hamburg. I.M.H. has received support from Roche Diagnostics for a biomarker project, but unrelated to the work presented here. The results presented in this paper have not yet been published, either in whole or in part.

Data Sharing 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 due to the data protection requirements of study participants. Data are available upon reasonable request.

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Author Contributions Statement

J.M.H.: Statistical analyses, manuscript writing

S.W.: Statistical analyses, interpretation of results

J.N.: Scientific coordinator of kidney variables (KORA)

B.J.: Study data management, Study Co-PI (DIACORE)

M.G.: Data preparation, quality control

B.T.: Study data management (KORA)

W.K.: Biomarker measurement (KORA)

T.Z.: Biomarker measurement (KORA)

M.E.Z.: Data management (AugUR)

R.B.: Laboratory analysis and biomarker measurements

B.B.: Study PI (DIACORE)

H.K.: Statistical expertise, interpretation of results

K.J.S.: Study coordination (AugUR), data management (DIACORE)

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C.A.B.: Study PI (DIACORE), project initiation, manuscript design

I.M.H.: Study PI, project initiation, supervision of statistical analyses, manuscript design and writing

All authors contributed to the reviewing and editing of the manuscript and approved the final version.

Ethics 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 Helsinki declaration 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 WHO MONICA project. All other KORA studies were approved by the Ethics Committee of the Bavarian Chamber of Physicians (KORA-F3 EC No 03097, KORA-S4 EC No 99186, KORA-F4 / FF4 EC No 06068,

KORA-Fit EC No 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 Helsinki declaration and its later amendments and all participants provided written informed consent.

Supplementary Material

Supplementary Note S1. Study specific information

Supplementary Note S1.1. Study design

Supplementary Note S1.2. Processing of biomaterial and biomarker measurements

Supplementary Note S2. Statistical approaches

Supplementary Note S2.1. Cross-sectional and longitudinal analyses to derive the course of eGFR over age

Supplementary Note S2.2. Risk factor association analyses in longitudinal data

Supplementary Note S2.3. Reference values for eGFR in cross-sectional data

Supplementary Note S2.4. Reference values for eGFR-decline for individuals without and with risk factors in longitudinal data

Supplementary Table S1. Overview of biomarker measurement in each of the studies. Shown are available details for serum creatinine and serum cystatin C timepoint of blood sampling and sample processing, assay name and underlying method as well as details available for sample storage and location information of measurement. Shown are respective details for urine creatinine and urine albumin measurements for all studies.

Supplementary Table S2. Sex-specific characteristics of cross-sectionally analyzed sample separated by study. The analyzed sample was restricted to individuals with available eGFR values from baseline study assessment. Shown are demographic characteristics, information on diseases and medication intake, laboratory measurements with focus on established risk factors previously reported for kidney function decline.[S4] Estimated glomerular filtration rate was deviated from serum creatinine[S5] or serum cystatin.[S6] Continuous variables are given as mean values with standard deviation (SD). Categorical variables are shown in percent and absolute number of affected individuals. Relative frequency is calculated based on non-missing values of each categorical variable.

Supplementary Table S3. **Mean values per age-group with respective number of individuals in cross-sectional data.** The analyzed sample consisted of individuals with available $eGFR_{crea}$ and $eGFR_{cys}$. Shown are age-group specific sample sizes, mean values and standard errors for $eGFR_{crea}$ and $eGFR_{cys}$ for the general population individuals (KORA-3,

KORA-4, AugUR), "healthy" individuals (excluding individuals with diabetes, CVD, HbA1c≥6.5%, blood pressure ≥ 140/90 mmHg, or UACR ≥30 mg/g; selected from KORA-3, KORA-4, AugUR), and individuals with diabetes (DIACORE, extended with respective individuals from KORA-3, KORA-4, AugUR).

Supplementary Table S4. Longitudinal analysis of annual decline of eGFR by study and combined. The analyzed sample consisted of individuals with at least one available $eGFR_{crea}$ value at any timepoint. For each study and outcome $eGFR_{crea}$ and $eGFR_{cys}$, we applied a linear mixed model (LMM, RI-only model; age centered at 50 years, sex, and their interaction as covariables). Sensitivity analyses in a subset of elderly individuals (AugUR: n= 1,898, m=2,784) and individuals with diabetes (DIACORE: n=2,586, m= 8,592) restricted to individuals survived follow-up yielded the same annual decline estimates (-1.08 [-1.22, -0.90] and -1.44 [-1.50, -1.32] ml/min/1.73m² for AugUR and DIACORE, respectively). Joint data results are compared to an analysis adjusting for study membership ("joint-study") and to a meta-analysis of beta- estimates ("meta"; inverse-variance-fixed effect, $\beta = \sum_i \beta_i w_i / \sum_i w_i$, with $w_i = 1/SE_i^2$. Beta-estimates with respective 95%-CI are given.

Supplementary Table S5. Alternative model results for annual eGFR-decline by study in longitudinal analyses using random slopes. The analyzed sample consisted of individuals with at least one eGFR value available at any timepoint. For each study and outcome, a linear mixed model was fitted (LMM, RI+RS model; age centered at 50 years, sex, and their interaction as covariables). Shown is also the standard deviation of random slopes (SD_{RS}). Results are very similar to the results from LMM RI-only shown in Supplementary Table S4).

Supplementary Table S6. Stepwise analyses of albuminuria association with eGFR levels and eGFR-decline in longitudinal data. The analyzed sample consisted of individuals with at least one eGFR value available at any timepoint and with available information on diabetes, body-mass index (BMI) and urinary-to-creatinine ratio (UACR). For each outcome, $eGFR_{crea}$ or $eGFR_{cys}$, three multivariable linear regression models were fitted (LMM, RI-only, model 1: age centered at 50 years, sex, and micro-, and macroalbuminuria, and their interactions with age, and study membership as covariables, model 2: adding diabetes and its interaction with age, model 3: adding overweight and obesity, and their interactions with age. Beta estimates are shown in mL/min/1.73 m² with 95%-CI.

Supplementary Table S7. Percentile values for $eGFR_{crea}$ and $eGFR_{crea\text{-}cys}$ based on CKD-EPI 2021 equations[S5,S6] in cross-sectional data. The analyzed sample was restricted to individuals with available eGFR values at baseline. Shown are modelled percentiles for the midpoint of each age interval resulting from GAMLSS for "healthy" individuals ($n_{eGFRcrea}$=4,984, $n_{eGFRcrea\text{-}cys}$=3,042) and individuals with diabetes ($n_{eGFRcrea}$=3,172, $n_{eGFRcrea\text{-}cys}$=3,890). Percentile values correspond to reference curves in Figure 3. Percentiles of measured GR (mGFR) based on 1,983 living kidney donors[S7]are provided for comparison.

Supplementary Table S8. Longitudinal analyses for risk factor association with eGFR-levels and eGFR-decline. Table is analogous to Table 4 except for the random slopes included in the model (RI+RS; age centered at 50 years, sex, diabetes, overweight, obesity, micro-, and macroalbuminuria, their interactions with age, and study membership as covariables). Beta estimates are shown in mL/min/1.73m² with 95%-CI. Results are very similar to results shown in Table 4 for the RI-only model.

Supplementary Table S9. Percentile values for $eGFR_{crea}$ based on EKFC 2021 equation[S9] in cross-sectional data. The analyzed sample was restricted to individuals with available $eGFR_{crea}$ value at baseline. Shown are modelled percentiles for the midpoint of each age interval resulting from GAMLSS for "healthy" individuals ($n_{eGFRcrea}$=4,984) and individuals with diabetes ($n_{eGFRcrea}$=3,172). Percentile values correspond to reference curves in

Supplementary Figure S1. Comparability of mean eGFR in KORA. Shown are mean values of **(A)** $eGFR_{crea}$ and **(B)** $eGFR_{cys}$ per age-group in the two KORA surveys S3 and S4 with the respective follow-up data. Mean values of $eGFR_{cys}$ in KORA-F4 are based on only 234 individuals with available $eGFR_{cys}$ and thus, not interpretable. For KORA-S3, the CREA assay (Boehringer Mannheim) was used, for which documentation regarding comparability with other assays, e.g. with the next generation assay CREA PLUS, was lacking (personal communication: Koenig Lab, Ulm, Roche Diagnostics, Burkhard Lab, Regensburg).

Supplementary Figure S2. Overview of study data. Shown are the number of included individuals (n) and number of measurements (m) in the analysis of $eGFR_{crea}$, $eGFR_{cys}$, or $eGFR_{crea\text{-}cys}$ for **(a)** cross-sectional and **(b)** longitudinal analyses. Exclusion criteria for individuals and measurements of eGFR are described stating the numbers of individuals or numbers of measurements that are excluded in each step.

Supplementary Figure S3. Age-group specific mean values of eGFR in cross-sectional data. The analyzed sample consisted of individuals with available eGFR value at baseline. Shown are study-specific mean values of **(a)** creatinine- or **(b)** cystatin-based eGFR by age-groups. Color code was used to differentiate between the studies. Whiskers represent the 95%- CIs.

Supplementary Figure S4. Decline of eGFR over age per study in longitudinal data. The analyzed sample consisted of individuals with at least one available $eGFR_{crea}$ value at any timepoint. Shown are predicted values of $eGFR_{crea}$ and $eGFR_{cys}$ over the full age range (25-98 years). General additive models (GAM) were fitted on longitudinal data in each study separately (RI-only) with age modelled as function by splines, *f(age),* and sex and sex**f(age)* as covariables. Values on the y-axis are the **(a)** $eGFR_{crea}$ or **(b)** $eGFR_{cys}$ values predicted by the model fitted for each study. Color code differentiates between the studies and bands represent the 95%-CI.

Supplementary Figure S5. Comparison of eGFR in the general population using different equations. The analyzed sample consisted of general population individuals with eGFR available at baseline (n=5,732). Shown are individuals´ values of $eGFR_{crea}$ based on CKD-EPI 2021 equation[S6] (y-axis) compared to (a) CKD-EPI 2009[S9] (x-axis) and (b) EKFC 2021[S10] (x-axis). Also shown are individuals´ values for $eGFR_{cys}$ based on CKD-EPI 2012[S7] (y-axis) compared to EKFC 2023[S11] (x-axis).

Supplementary Figure S6. Sex- and age-group specific eGFR mean values and eGFR decline over age using EKFC equations. The analyzed sample consisted of (a-c) individuals with both $eGFR_{crea}$ and $eGFR_{cys}$ values available at baseline (cross-sectional data) or (d-f) individuals with at least one eGFR value at any timepoint (longitudinal data). Color code differentiates between $eGFR_{crea}$ (blue) based on EKFC 2021[S10] and $eGFR_{cys}$ (orange) based on EKFC 2023.[S11] Shown are cross-sectional mean values 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%-CIs. Also shown are predicted values of $eGFR_{crea}$ and $eGFR_{cys}$ over the full age range (25-98 years) for (d) the general population ($n_{eGFRcrea}$= 9,082, $m_{eGFRcrea}$= 16,835, $n_{eGFRcys}$= 9,644, $m_{eGFRcys}$= 15,188), (e) "healthy" individuals ($n_{eGFRcrea}$= 4,545, $m_{eGFRcrea}$= 5,848, $n_{eGFRcys}$= 3,896, $m_{eGFRcys}$= 5,188) and (f) individuals with diabetes from all studies ($n_{eGFRcrea}$= 4,323, $m_{eGFRcrea}$= 11,179, $n_{eGFRcys}$= 4,304, $m_{eGFRcys}$= 11,091). Prediction values were derived from a generalized additive model fitted for each outcome $eGFR_{crea}$ or $eGFR_{cys}$ (GAM, RI-only; f(age), sex, their interaction, and study membership as covariables). Line type between men (dashed) and women (solid). Bands represent the 95%-CIs.

Supplementary Figure S7. Reference values for eGFR and eGFR decline based on EKFC equation[S10] in cross-sectional data. The analyzed sample consisted of individuals with (a&b) available eGFR values at baseline (cross-sectional data) or (c&d) at least one eGFR value available at any timepoint (longitudinal data) and with available information on diabetes, body-mass index (BMI) and urinary-to creatinine ratio (UACR). Shown are percentiles curves of $eGFR_{crea}$ based on cross-sectional data (GAMLSS) from (a) "healthy" individuals ($n_{eGFRcrea}$=4,984, $n_{eGFRcrea\text{-}cys}$=3,042) and (b) individuals with diabetes ($n_{eGFRcrea}$=3,172, $n_{eGFRcrea\text{-}cys}$=3,890). Age-group-specific percentiles are shown in Supplementary Table S8. Also shown are reference values for annual eGFR-decline for different subgroups of individuals for (c) $eGFR_{crea}$ and (d) $eGFR_{cys}$ based on longitudinal data (LMM, RI+RS, $n_{eGFRcrea}$= 10,800, $m_{eGFRcrea}$= 19,173 and $n_{eGFRcys}$= 9,725, $m_{eGFRcys}$= 18,165). Reference values for women (dark grey) and men (light grey) are displayed as 95% prediction interval including the variability of RS ($SD_{eGFRcrea}$= 0.23, $SD_{eGFRcys}$= 0.25). The dashed vertical line indicates the estimate of 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.

References

1. Denic A, Lieske JC, Chakkera HA, Poggio ED, et al. The Substantial Loss of Nephrons in Healthy Human Kidneys with Aging. J Am Soc Nephrol. 2017;28(1):313-320.
2. KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). 2009.
3. Andrew S. Levey, Josef Coresh, Kline Bolton, Bruce Culleton, et al. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1-266.
4. Cockwell P, Fisher L-A. The global burden of chronic kidney disease. Lancet. 2020;395(10225):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(44):745-751.
6. Jha V, Garcia-Garcia G, Iseki K, Li Z, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):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(12):1258-1270.
8. Delanaye P, Jager KJ, Bökenkamp A, Christensson A, et al. CKD: A Call for an Age-Adapted Definition. J Am Soc Nephrol. 2019;30(10):1785-1805.
9. Wetzels JFM, Kiemeney LALM, Swinkels DW, Willems HL, et al. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. Kidney Int. 2007;72(5):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(9):2577-2582.
11. Waas T, Schulz A, Lotz J, Rossmann H, 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(1):10165.
12. Ebert N, Jakob O, Gaedeke J, van der Giet M, et al. Prevalence of reduced kidney function and albuminuria in older adults: the Berlin Initiative Study. Nephrol Dial Transplant. 2017;32(6):997-1005.
13. Eriksen BO, Palsson R, Ebert N, Melsom T, 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(7):1602-1615.
14. Hemmelgarn BR, Zhang J, Manns BJ, Tonelli M, et al. Progression of kidney dysfunction in the community-dwelling elderly. Kidney Int. 2006;69(12):2155-2161.
15. Schaeffner ES, Ebert N, Kuhlmann MK, Martus P, et al. Age and the Course of GFR in Persons Aged 70 and Above. Clin J Am Soc Nephrol. 2022;17(8):1119-1128.

16. Potok OA, Rifkin DE, Ix JH, Shlipak MG, et al. Estimated GFR Accuracy When Cystatin C- and Creatinine-Based Estimates Are Discrepant in Older Adults. Kidney Med. 2023;5(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:S19-25.
18. Dörhöfer L, Lammert A, Krane V, Gorski M, 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, Dietl A, 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, Meisinger 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(6):847-853.
21. Rheinberger M, Jung B, Segiet T, Nusser J, et al. Poor risk factor control in outpatients with diabetes mellitus type 2 in Germany: The DIAbetes COhoRtE (DIACORE) study. PLoS One. 2019;14(3):e0213157.
22. Donhauser FJ, Zimmermann ME, Steinkirchner AB, Wiegrebe S, 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(6).
23. Goek O-N, Prehn C, Sekula P, Römisch-Margl W, et al. Metabolites associate with kidney function decline and incident chronic kidney disease in the general population. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association:2131-2138.
24. Inker LA, Eneanya ND, Coresh J, Tighiouart H, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737-1749.
25. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20-29.
26. Levey AS, Stevens LA, Schmid CH, Zhang YL, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.
27. 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, Langlois 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(1):44-47.

29. Pottel H, Björk J, Courbebaisse M, Couzi L, 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(2):183-191.
30. Pottel H, Björk J, Rule AD, Ebert N, et al. Cystatin C-Based Equation to Estimate GFR without the Inclusion of Race and Sex. N Engl J Med. 2023;388(4):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(11):825-830.
32. 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(4):e231870.
34. Delanaye P, Gaillard F, van der Weijden J, Mjøen G, 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(3):401-407.
35. Warren B, Rebholz CM, Sang Y, Lee AK, 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(8):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(11):1979-1988.
38. Levey AS, Coresh J, Greene T, Marsh J, 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(4):766-772.
39. Glassock RJ, Rule AD. Aging and the Kidneys: Anatomy, Physiology and Consequences for Defining Chronic Kidney Disease. Nephron. 2016;134(1):25-29. doi:10.1159/000445450
40. Matsushita K, van der Velde M, Astor BC, Woodward M, 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(9731):2073-2081.
41. Baba M, Shimbo T, Horio M, Ando M, et al. Longitudinal Study of the Decline in Renal Function in Healthy Subjects. PLoS One. 2015;10(6):e0129036.
42. Gansevoort RT, Anders H-J, Cozzolino M, Fliser D, et al. What should European nephrology do with the new CKD-EPI equation? Nephrol Dial Transplant. 2023;38(1):1-6.

Figure legend

Figure 1. Sex and age-group specific mean values of eGFR in cross-sectional data. The analyzed sample consisted of individuals with both $eGFR_{crea}$ and $eGFR_{cys}$ values available at baseline. Shown are mean values of creatinine- or cystatin-based eGFR ($eGFR_{crea}$ (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%-CIs. Numbers are shown in **Supplementary Table S3**.

Figure 2. Longitudinal analysis of decline of eGFR over age. The analyzed sample consisted of individuals with at least one eGFR value available at any timepoint. Shown are predicted values of $eGFR_{crea}$ and $eGFR_{cys}$ over the full age range (25-98 years) for (a) the general population ($n_{eGFRcrea}$= 9,082, $m_{eGFRcrea}$= 16,835, $n_{eGFRcys}$= 9,644, $m_{eGFRcys}$= 15,188), (b) a subset of "healthy" individuals ($n_{eGFRcrea}$= 4,545, $m_{eGFRcrea}$= 5,848, $n_{eGFRcys}$= 3,896, $m_{eGFRcys}$= 5,188) and (c) individuals with diabetes from all studies ($n_{eGFRcrea}$= 4,323, $m_{eGFRcrea}$= 11,179, $n_{eGFRcys}$= 4,304, $m_{eGFRcys}$= 11,091). Data of all studies were analyzed jointly for the outcome $eGFR_{crea}$ and $eGFR_{cys}$ (Generalized additive model (GAM), RI-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%-CIs.

Figure 3. Reference values for $eGFR_{crea}$ and $eGFR_{crea\text{-}cys}$ 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 $eGFR_{crea\text{-}cys}$ based on data from (a&c) "healthy" individuals ($n_{eGFRcrea}$=4,984, $n_{eGFRcrea\text{-}cys}$=3,042) and (b&d) individuals with diabetes ($n_{eGFRcrea}$=3,172, $neGFR_{crea\text{-}cys}$=3,890). The color code was used to differentiate areas between selected percentiles (grey: 2.5^{th}-5^{th} and 95^{th}-97.5^{th}; blue: 5^{th}-10^{th} and 90^{th}-95^{th} percentile; purple: 10^{th}-25^{th} and 75^{th}-90^{th} percentile; green: 25^{th}-50^{th} and 50^{th}-75^{th} percentile). Age-group-specific percentiles are shown in **Supplementary Table S7**.

Figure 4. Reference values for eGFR-decline in longitudinal data. The analyzed sample consisted of individuals with at least one eGFR value available at any timepoint and with available information on diabetes, body-mass index (BMI) and urinary-to creatinine ratio (UACR). Shown are reference values for annual eGFR-decline for different subgroups of individuals for (a) $eGFR_{crea}$ and (b) $eGFR_{cys}$. For each outcome, a multivariable linear mixed model (LMM) was applied ($n_{eGFRcrea}$= 10,800, $m_{eGFRcrea}$= 19,173 and $n_{eGFRcys}$= 9,725, $m_{eGFRcys}$= 18,165): random intercept (RI)+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 beta 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 grey: women, light grey: 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 correspond next to the bars indicate sex-specific estimates with the respective 95% prediction intervals.

Figure 5. Revisiting CKD prevalence in the general population and individuals with diabetes in cross-sectional data. The analyzed sample consisted of individuals with both $eGFR_{crea}$ and UACR assessments available at baseline. Shown are percentages of individuals with CKD, defined by albuminuria (UACR ≥30mg/g) or $eGFR_{crea}$ <60 mL/min/1.73m², in (a&b) the general population and (c&d) individuals with diabetes derived. a&c show the percentage of CKD resulting from cutoff defined by KDIGO. The white and grey bars show percentage of individuals with albuminuria (eGFR≥60 or cut-off or eGFR<60 or cut-off, respectively); blue bar shows the percentage of individuals without albuminuria but low $eGFR_{crea}$ values. b&d show the percentage of CKD resulting from age-dependent cut-offs (30-40 years: 75; 40- 50 years: 70; 50-60 years: 60; 60-70 years: 50; 70-80 years: 40; >80: 35mL/min/1.73m²), for $eGFR_{crea}$ in "healthy" individuals (rounded 2.5th percentile for midpoint age of respective age-group).

Tables

Table 1. Characteristics of cross-sectionally analyzed individuals by study. 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, laboratory measurements with focus on established risk factors previously reported for kidney function decline.[33] Estimated glomerular filtration rate (eGFR) was derived from serum creatinine via CKD-EPI 2021 equation,[24] serum cystatin or both via CKD-EPI 2012 equation.[25]

	KORA 3	KORA 4	AugUR	DIACORE
n	2,906	3,732	2,385	2,991
Demographic characteristics				
Age, mean (SD), y	57 (13)	50 (14)	78 (5)	65 (9)
Men % (n)	48 (1,422)	48 (1,823)	48 (1,151)	60 (1,795)
never smoked % (n)	44 (1,282)	41 (1,539)	55 (1,311)	42 (1,260)
ever smoked % (n)	37 (1,075)	33 (1,240)	38 (921)	45 (1,342)
BMI, mean (SD), kg/m²	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 (1,623)
Overweight % (n)	44 (1,255)	43 (1,609)	46 (1,091)	35 (1,032)
Diabetes % (n)	8 (241)	5 (197)	24 (534)	100 (2,991)
Time since diabetes [years]	10 (10)	10 (8)	*NA*	10 (8)
Systolic BP mean (SD), mmHg	130 (20)	128 (19)	132 (18)	139 (18)
Diastolic BP mean (SD), mmHg	82 (11)	80 (10)	76 (11)	77 (11)
Hypertension % (n)	34 (979)	29 (1068)	31 (739)	45 (1,329)
CVD % (n)	5 (137)	0.2 (7)	22 (516)	26 (773)
Medication intake				
Glucose-lowering % (n)	6 (182)	3 (122)	16 (385)	88 (2616)
Blood pressure-lowering % (n)	32 (916)	18 (674)	68 (1,609)	78 (2,324)
Lipid-lowering % (n)	11 (318)	6 (224)	35 (828)	50 (1,477)
Laboratory measurements				
HbA1c, mean (SD), %	5.4 (0.5)	5.6 (0.6)	5.8 (0.7)	6.9 (1.1)
LDL cholesterol, mean (SD), mg/dL	128.1 (32.8)	137.3 (41.4)	141.2 (34.9)	118.1 (37.0)
HDL cholesterol, mean (SD), mg/dL	58.6 (17.1)	57. 9 (17.0)	61.3 (15.5)	52.9 (15.3)
Hemoglobin, mean (SD), g/dL	14.2 (1.2)	14.3 (1.3)	13.8 (1.3)	14.2 (1.3)
UACR**, mean (SD), mg/g	17.5 (137.1)	25.5 (199.3)	42.9 (127.8)	75.8 (342.4)
Creatinine, mean (SD), mg/dL	0.88 (0.28)	0.85 (0.24)	0.97 (0.31)	0.96 (0.36)
Cystatin C*, mean (SD), mg/L	0.93 (0.24)	0.86 (0.23)	1.20 (0.31)	1.10 (0.39)
Kidney function				
$eGFR_{crea}$, mean (SD), mL/min/1.73 m²	90.6 (17.2)	96.6 (16.0)	72.6 (16.7)	82.5 (20.6)
$eGFR_{cys}$*, mean (SD), mL/min/1.73 m²	90.0 (19.9)	97.2 (19.5)	61.1 (16.9)	74.6 (22.5)
$eGFR_{crea\text{-}cys}$, mean (SD), mL/min/1.73 m²	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)

NA: not available; BMI: body-mass index, BP: blood pressure, HbA1c: glycated hemoglobin A1c, UACR: urinary-albumin-to-creatinine-ratio, eGFR in mL/min/1.73m². Microalbuminuria: UACR ≥30 and <300mg/g; macroalbuminuria: UACR ≥300mg/g. "Overweight": BMI ≥25 and <30kg/m²; "Obese": BMI ≥30kg/m². Non-missing data used to calculate percentages (KORA3, KORA4, AugUR, DIACORE, respectively: Smoking: 2,898, 3,728, 2,373, 2,979; BMI: 2,882, 3,705, 2,370, 2,976; diabetes: 2,899, 3,719, 2,260, 2,991; blood pressure: 2,893, 3,719, 2,379, 2,989; CVD: 2,899, 3,724, 2,363, 2,985; intake of glucose-/lipid lowering medication: 2,900, 3,724, 2,378, 2,970; intake blood pressure-lowering medication: 2,900, 3,724, 2,378, 2,991; UACR: 2,701, 2,894, 2,310, 2,908. The "healthy"-defining variables were non-missing in >99% individuals at baseline or any timepoint (except for UACR in KORA). *Cystatin C and $eGFR_{cys}$ are shown for KORA-S3. **UACR and albuminuria is shown for KORA-F4.

Table 2. Descriptive statistics for longitudinal data. For longitudinal data analyses, the analyzed sample consisted of individuals with at least one eGFR value available at any timepoint. Shown are age and follow-up time per study and overall. Numbers of individuals and respective number of measurements are given for each biomarker.

	KORA3	KORA4	AugUR	DIACORE	Overall
Age, min-max, years	34-85	25-88	70-98	27-93	25-98
FU-time, 75th percentile (max), years	11 (25)	9 (20)	3.3 (10)	9 (12)	5 (25)
Measurement intervals median (max) years	10 (11)	7 (9)	3.2 (5.5)	2.3 (5.2)	2.8 (11)
Individuals					
$n_{eGFRcrea}$	2,933	3,752	2,397	2,994	12,076
$n_{eGFRcys}$	3,641	3,614	2,389	2,994	12,638
$n_{eGFRcrea-cys}$	231	3,614	2,388	2,994	9,227
eGFR assessments					
$m_{eGFRcrea}$	3,749	9,644	3,442	9,344	26,179
$m_{eGFRcys}$	3,866	8,116	3,206	9,319	24,507
$m_{eGFRcrea-cys}$	231	8,112	3,196	9,319	20,858

FU: follow-up

Table 3. Annual decline of eGFR in longitudinal analyses for the general, the "healthy", and diabetes individuals. Longitudinal data of all studies were analyzed jointly in individuals with at least one available eGFR value available at any timepoint. For each outcome $eGFR_{crea}$ and $eGFR_{cys}$, a linear mixed model (LMM, RI-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, AugUR), their subgroup of "healthy" individuals (excluding individuals with diabetes, CVD, HbA1c≥6.5%, UACR≥ 30 mg/g, or blood pressure ≥140/90 mmHg; from KORA-3, KORA-4, AugUR), and individuals with diabetes (DIACORE, diabetes individuals from KORA-3, KORA-4, AugUR). Beta estimates with respective 95%-CI are given. There was no evidence for interaction of age with sex (except for a small agexsex interaction for $eGFR_{cys}$ in "healthy").

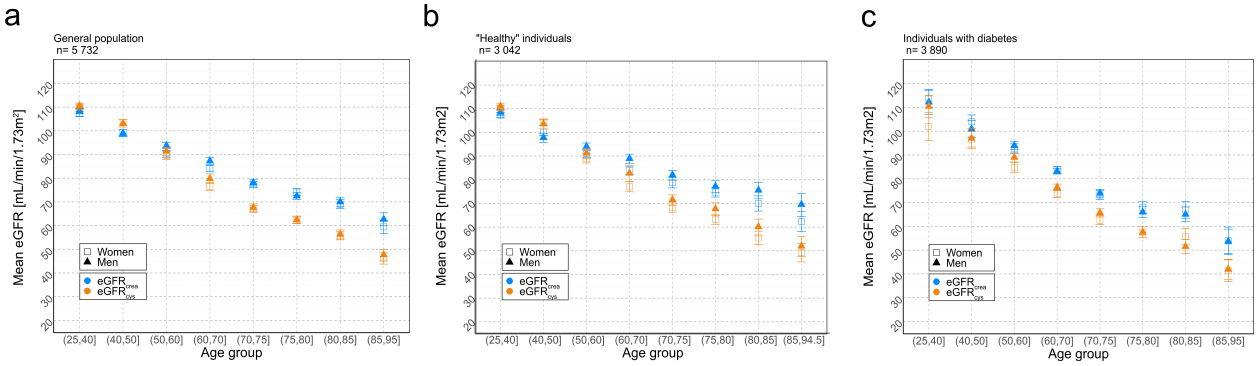
	General population	"Healthy" individuals	Individuals with diabetes
$eGFR_{crea}$			
n	9 082	4 545	4 323
m	16 835	5 848	11 179
Intercept	95.1 [94.6, 95.7]	95.9 [95.3, 96.4]	100.4 [97.7, 103.1]
Age	-0.80 [-0.82, -0.77]	-0.79 [-0.83, -0.76]	-1.20 [-1.33, -1.08]
Sex	1.35 [0.70, 2.01]	1.14 [0.29, 1.99]	0.28 [-1.58, 2.14]
Age x sex	0.00 [-0.03, 0.03]	0.05 [-0.003, 0.10]	-0.00 [-0.08, 0.08]
$eGFR_{cys}$			
n	9 644	6 126	4 304
m	15 188	9 127	11 091
Intercept	95.7 [95.2, 96.3]	92.9 [92.4, 93.4]	94.2 [91.1, 97.3]
Age	-1.1 [-1.10, -1.04]	-1.09 [-1.13, -1.06]	-1.29 [-1.44, -1.14]
Sex	0.38 [-0.25, 1.01]	0.92 [-0.05, 1.90]	6.95 [5.00, 8.89]
Age x sex	0.021 [-0.01, 0.051]	0.07 [0.02, 0.13]	-0.26 [-0.33, 0.11]

n: number of individuals included in analysis, m: number of measurements.

Table 4. Longitudinal analyses for risk factor association with eGFR-levels and eGFR-decline. The analyzed sample consisted of individuals with at least one eGFR value available at any timepoint and with available information on diabetes, body-mass index (BMI) and urinary-to-creatinine ratio (UACR). For each outcome, $eGFR_{crea}$ or $eGFR_{cys,}$ a multivariable linear regression model (LMM) was fitted (RI-only; age centered at 50 years, sex, diabetes, overweight, obesity, micro-, and macroalbuminuria, their interactions with age, and study membership as covariables). Beta estimates are shown in mL/min/1.73m² with 95%-CI. 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 nor 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/1.73m² lower $eGFR_{crea}$ than 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/1.73m² steeper annual $eGFR_{crea}$ decline (average decline of (-0.73) + (-0.12) = -0.85 mL/min/1.73m² per year) than without obesity.

	$eGFR_{crea}$	**$eGFR_{cys}$**
n	10,815	9,725
m	19,183	18,165
Main effects		
Intercept	97.09 [96.4,97.8]	95.1[94.3,95.9]
Age	-0.73 [-0.77,-0.69]	-1.03 [-1.07,-0.99]
Men	1.46 [0.66,2.26]	2.15 [1.25,3.05]
Diabetes	5.64 [4.62,6.66]	5.33 [4.25,6.41]
Overweight	-1.77 [-2.59,-0.95]	-0.76 [-1.64,0.12]
Obesity	-2.50 [-3.50,-1.50]	-3.73 [-4.81,-2.65]
Microalbuminuria	0.96 [-0.14,2.06]	0.16 [-0.96,1.28]
Macroalbuminuria	-3.65 [-6.20,-1.10]	-3.92 [-6.55,-1.29]
Interaction effects		
Age x Men	-0.03 [-0.07,0.01]	-0.04 [-0.08,-0.00]
Age x Diabetes	-0.45 [-0.49,-0.41]	-0.43 [-0.49,-0.37]
Age x Overweight	-0.03 [-0.07,0.01]	-0.05 [-0.09,-0.01]
Age x Obesity	-0.12 [-0.16,-0.08]	-0.11 [-0.17,-0.05]
Age x Microalbuminuria	-0.09 [-0.13,-0.05]	-0.09 [-0.15,-0.03]
Age x Macroalbuminuria	-0.08 [-0.20,0.04]	-0.10 [-0.22,0.02]

Microalbuminuria was defined as UACR ≥30 and <300mg/g and macroalbuminuria as UACR ≥300mg/g. BMI ≥25 and <30kg/m² was defined as "overweight" and BMI ≥30kg/m² as "obese".



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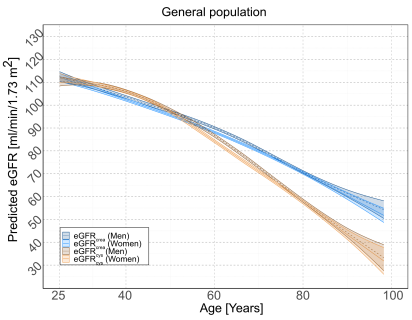

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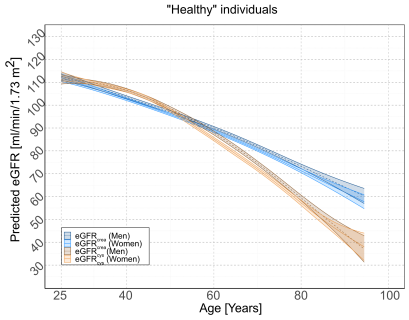

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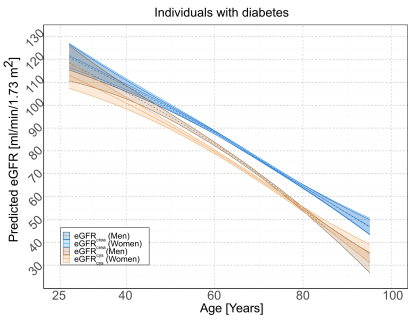

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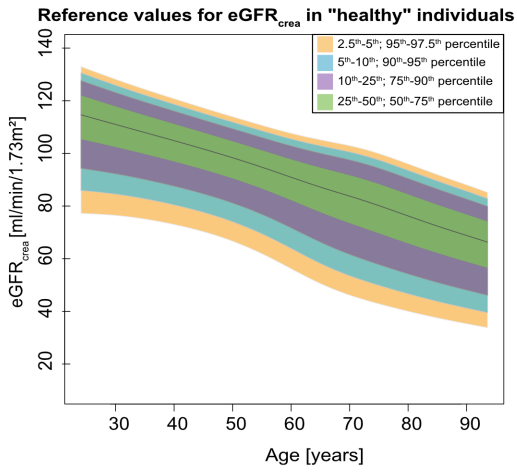

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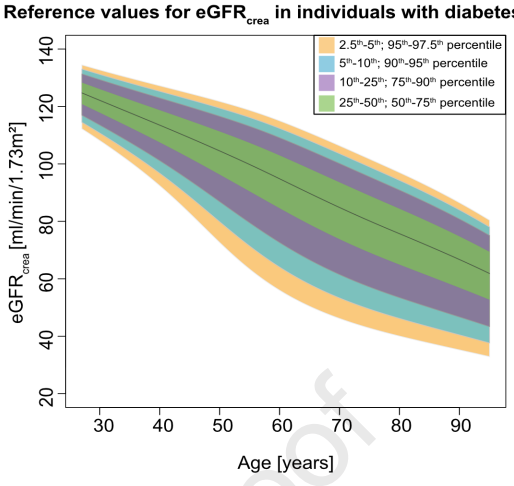

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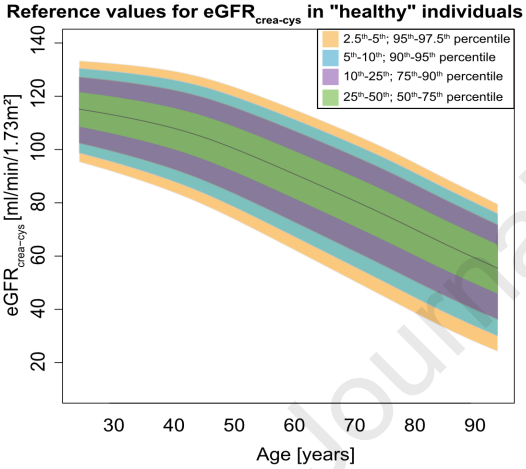

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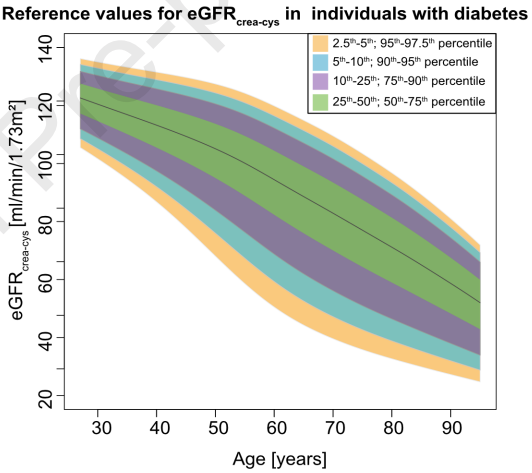

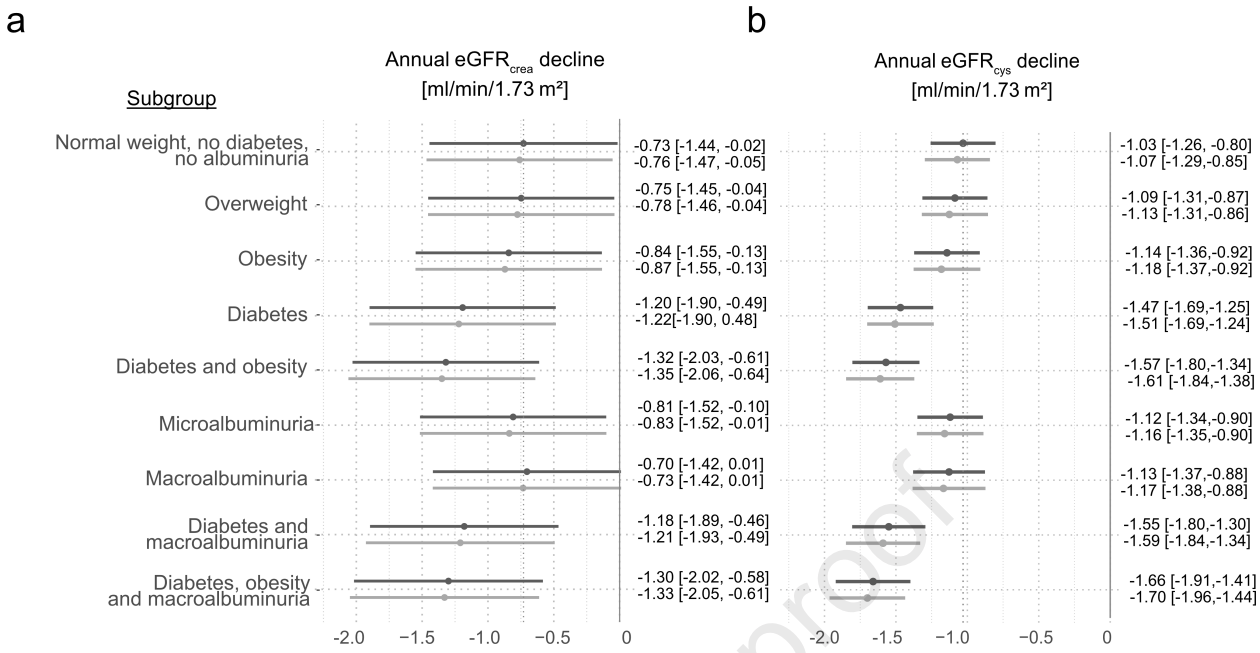

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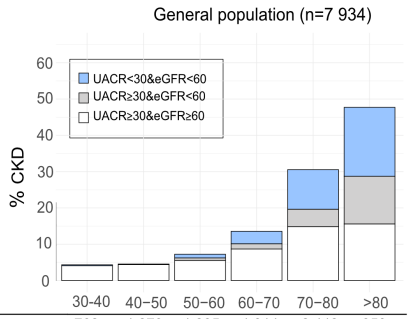
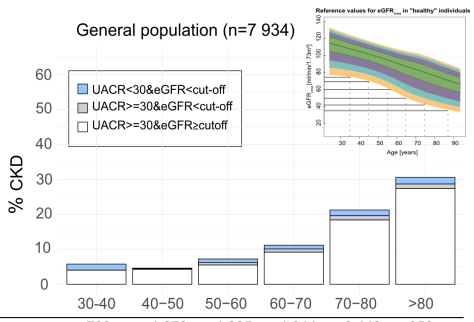


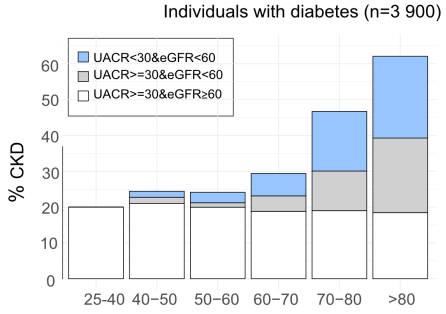
n	762	1 278	1 285	1 314	2 442	853
%UACR<30&eGFR<60	0.26	0.08	1.01	3.42	10.89	18.99
%UACR≥30&eGFR<60	0.00	0.08	0.70	1.45	4.79	13.13
%UACR≥30 &eGFR ≥60	4.07	4.38	5.53	8.68	14.86	15.59
%UACR≥30 or eGFR<60	4.33	4.54	7.04	13.55	30.54	47.71

b



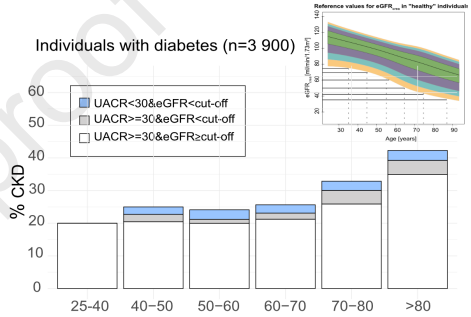
n	762	1 278	1 285	1 314	2 442	853
%UACR<30&eGFR< cut-off	1.71	0.16	1.01	1.07	1.60	1.88
%UACR≥30&eGFR< cut-off	0.00	0.16	0.70	0.91	1.23	1.29
%UACR≥30&eGFR ≥ cut-off	4.07	4.30	5.53	9.21	18.43	27.43
%UACR≥30 or eGFR< cut-off	5.78	4.62	7.24	11.19	21.26	30.60

c



n	40	176	651	1 341	1 394	298
%UACR<30&eGFR<60	0.00	1.70	2.92	6.26	16.64	22.82
%UACR≥30&eGFR<60	0.00	1.70	1.23	4.33	11.05	20.81
%UACR≥30&eGFR≥60	20.00	21.02	19.97	18.79	19.01	18.46
%UACR≥30 or eGFR<60	20.00	24.42	24.12	29.38	46.70	62.09

d



n	40	176	651	1341	1394	298
%UACR<30&eGFR<cut-off	0.00	2.27	2.92	2.54	2.80	3.02
%UACR≥30&eGFR<cut-off	0.00	2.27	1.23	1.86	4.16	4.36
%UACR≥30&eGFR ≥ cut-off	20.00	20.45	19.97	21.25	25.90	34.90
%UACR≥30or eGFR<cut-off	20.00	24.12	24.12	25.65	32.86	42.28